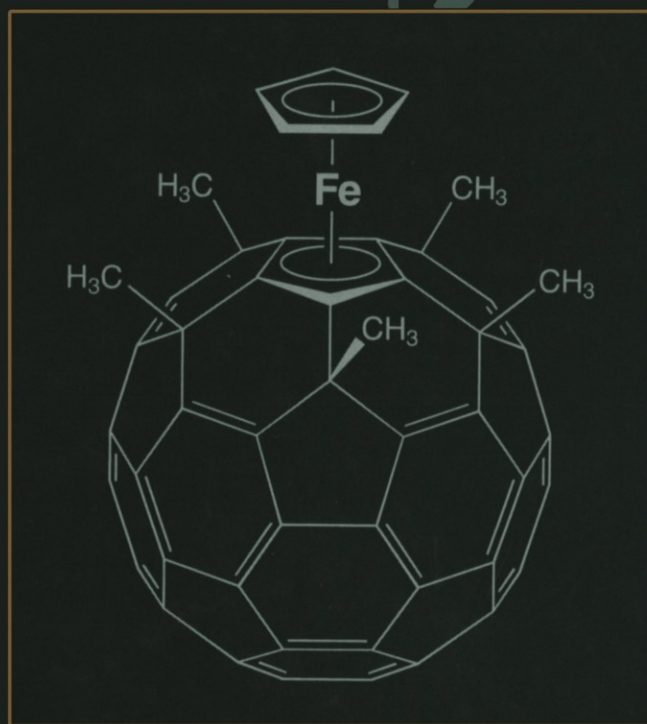


CHEMICAL KINETICS AND INORGANIC REACTION MECHANISMS

SECOND EDITION



Smiljko Ašperger

Chemical Kinetics and
Inorganic Reaction Mechanisms
Second Edition

Chemical Kinetics and Inorganic Reaction Mechanisms Second Edition

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*To my wife Ema
our son Miroslav
and our grandson Lovro*

FOREWORD

The serious study of the reaction mechanisms of transition metal complexes began some five decades ago. Work was initiated in the United States and Great Britain; the pioneers of that era were, in alphabetical order, F. Basolo, R. E. Connick, J. O. Edwards, C. S. Garner, G. P. Haight, W. C. E. Higginson, E. L. King, R. G. Pearson, H. Taube, M. L. Tobe, and R. G. Wilkins. A larger community of research scientists then entered the field, many of them students of those just mentioned. Interest spread elsewhere as well, principally to Asia, Canada, and Europe.

Before long, the results of individual studies were being consolidated into models, many of which traced their origins to the better-established field of mechanistic organic chemistry. For a time this sufficed, but major revisions and new assignments of mechanism became necessary for both ligand substitution and oxidation-reduction reactions. Mechanistic inorganic chemistry thus took on a shape of its own.

This process has brought us to the present time. Interests have expanded both to include new and more complex species (*e.g.*, metalloproteins) and a wealth of new experimental techniques that have developed mechanisms in ever-finer detail. This is the story the author tells, and in so doing he weaves in the identities of the investigators with the story he has to tell. This makes an enjoyable as well as informative reading.

Professor Ašperger is to be commended for preparing an authoritative and contemporary volume in the field. Modern studies are emphasized, and the readers are led straight to the frontier after the fundamentals are presented. The final chapter, *Some Recent Publications in the Scientific Spotlight*, is innovative. Eleven contemporary metal systems are shown, most in terms of synthesis and structure. Challenges can be found here for the mechanistic chemist.

James H. Espenson

Iowa State University
Ames, Iowa, USA
January 2003

PREFACE

This book is the thoroughly revised English version of the first Croatian edition published in 1999 by the Croatian Academy of Sciences and Arts in Zagreb under the title *Kemijska kinetika i anorganski reakcijski mehanizmi* (*Chemical Kinetics and Inorganic Reaction Mechanisms*). Since three years have passed from the appearance of the Croatian edition, the entire text has been rewritten. Thus, the thermodynamic and kinetic chapters have been raised to a higher level. New material has been added in an effort to make the English edition “up-to-date.” For instance, Ahmed Zewail’s laser technique for observation of the motions of atoms and molecules during chemical changes (Nobel Prize for chemistry, 1999) is now described. The thermally induced spin crossover phenomenon found in the solid state, as well as in solutions of the complexes of iron(II), iron(III) and cobalt(II), is presented. The molecular bistability leading to metal complexes with short memory effects has been depicted. Special attention has been paid to platinum complexes as antitumor agents. The antitumor activity of germanium complexes and of metallocenes is described and the mechanism of the antitumor activity is discussed. The second generation of cisplatin analogs is presented. Attention has been also paid to the antitumor activity of metallocenes. Metallocene chemistry is presently a very promising field of inorganic chemistry. Metallocene complexes of titanium and zirconium are mentioned and their important role in the manufacture of polymers is stressed. The role of ferrocene derivatives as effective nucleophilic catalysts in kinetic resolutions of many useful organic reactions is included in the text. New achievements in the chemistry of dendrimers (cascade molecules) are described.

During the writing of the book several papers relevant to the book’s subject were published. Although a time distance is usually needed for proper appreciation of recent papers, the author discusses a few of them in Chapter 15 – “Recent publications in the scientific spotlight”. The selection of these papers is very arbitrary, and limited to the author’s own interest and judgement, and the available space. The first initiative in this respect came from the author’s regular reading of the *Chemical & Engineering News*, and he acknowledges this incentive.

The book is a monograph aimed primarily at young researchers (graduate students) in the field of inorganic reaction mechanisms. The first part of the book (about 110 pages) is devoted to chemical kinetics necessary for the study

of any reaction mechanism, whether inorganic or organic. Understanding of this part requires a knowledge of inorganic, organic and physical chemistry at the undergraduate level. Graduate students of any chemical subject, as well as graduate students of chemical engineering, pharmaceutical and even medical sciences might find this part useful. It is written in a way easily acceptable to graduate students of various basic interests. The remaining part of the book is devoted to the study of reaction mechanisms of transition metal complexes. These compounds contain metals such as iron, copper, cobalt, *etc.*; their reactions are not only the domain of inorganic, but also of organic chemists and biochemists (hemin, hemoglobin, cytochromes, chlorophylls, cobalamins, *etc.*), so the interest in the subject of the book should actually be much broader than one would expect from its title.

The idea of writing such a book was born after I taught at a graduate course in inorganic reaction mechanisms at Northwestern University, Evanston, Illinois, in 1970. The majority of my students were inorganic chemists, but some declared themselves as organic chemists, interested in reaction mechanisms in general. With pleasure I adjusted my course to such an audience, because I have never appreciated the 19th century division into chemistry of “dead matter” (inorganic) and chemistry of substances isolated from living organisms (organic).

Since then, many years passed until in 1997 I started to work on the Croatian version of the book, having in mind that Croatian chemists should publish also in Croatian, otherwise further development of the Croatian chemical terminology would be seriously impeded, a problem that is faced by many small nations. When the book appeared in 1999, I received several suggestions to prepare its English version, which has now been done.

I am greatly obliged to Professor Vladimir Simeon for suggesting numerous improvements and for editing the manuscript. Besides, Professors Vl. Simeon and Tomislav Cvitaš, contributed several pages to Chapter 1 (mostly pertaining to quantum mechanics and to statistical thermodynamics), and conformed the definitions and usage of physical quantities, symbols and terminology to the current standards recommended by IUPAC. Thanks are due to my colleagues, Professors Zlatko Mihalić, Leo Klasinc and Nenad Trinajstić, who read the manuscript and gave many useful remarks and suggestions. Professor N. Trinajstić was the editor of the first (Croatian) edition. I am also grateful to Mrs. Greta Prajdić, BSc, for careful technical editing and to Mrs. Tamara Jovanović, BA, who corrected my English.

Smiljko Ašperger

Zagreb, October 2002

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INTRODUCTION

The term reaction mechanism refers to the specific sequence of elementary reactions leading to an overall chemical change. Inorganic chemistry has always lagged behind organic chemistry in determination of reaction mechanisms. The first ideas of the mechanisms of organic reactions started to develop around 1920. The mechanistic considerations of organic reactions in solutions were primarily applied to the reactions of tetrahedral and trigonal planar carbon atoms. This is because organic compounds often undergo reactions at one center, while the other bonds suffer minor changes or practically do not change at all. Organic reactions are very versatile. Their rates can be easily varied by changing the reaction conditions in order to get rates that can be followed by conventional kinetic techniques available at the time.

On the other hand, inorganic reactions are often very fast and therefore less favorable for kinetic studies, although discussions about the mechanisms of inorganic reactions, with ideas not very far from those of the present day, are already found in the publications of Alfred Werner.*

In 1891 Werner put forward his coordination theory, which permitted a simple classification of inorganic compounds and extended the concept of isomerism. His views have remained fundamental to modern inorganic chemistry and have paved the way for modern concepts of chemical bonding. Werner received the Nobel Prize for Chemistry in 1913 "in recognition of his work on the linkage of atoms and molecules by which he has thrown new light on earlier investigations and opened up new fields of research especially in inorganic chemistry".

The progress of chemistry of metal complexes, notably the development of metallo-organic and bioinorganic chemistry, enabled the kinetic studies of octahedral complexes of cobalt(III), for instance $[\text{Co}(\text{NH}_3)_6]^{3+}$, and of square-planar complexes, such as $[\text{PtCl}_4]^{2-}$, and also of tetrahedral complexes, for instance $[\text{CuBr}_4]^{2-}$, and several others.

Physical and theoretical chemistry started to penetrate equally into organic and inorganic chemistry, and the borders between these two fields began to disappear. Thus, organic and inorganic chemistry are nowadays equally meritorious for the broadening of our knowledge of reaction mechanisms in general.

* ALFRED WERNER, 1866–1919, professor of chemistry at the University of Zürich.

Chapter 1

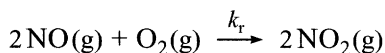
CHEMICAL KINETICS AND REACTION MECHANISMS

1.1. INTRODUCTION

One of the important reasons why chemists study rates of chemical reactions is a practical one. They want to determine the rate at which a reaction mixture approaches the state of its equilibrium, yielding a certain reaction product. This rate can be enhanced by changing the concentration of reactants and the pressure, by temperature increase, or by various catalysts. A more sophisticated reason, which is presently of our primary interest, is the study of reaction mechanisms, that is, the determination of those elementary reaction steps which finally lead to the reaction product.

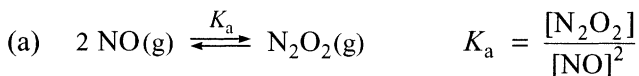
But, under reaction mechanism we also have in mind the detailed analysis of how the chemical bonds break and form anew, that is to say how the atomic nuclei and electrons regroup in forming the activated complex (or transition state). At the same time, we must bear in mind that each of the mentioned elementary reactions has its own reaction mechanism, so that complete knowledge of a reaction mechanism is a goal that is very rarely attained.

A pragmatic criterion for testing a reaction mechanism is the question: does it work in the sense that experimental data support it, does it make useful predictions about experiments not yet done. When it no longer works, the proposed mechanism must be abandoned. In this respect, several examples are quoted in books on kinetics and mechanisms.^{1,2} An often quoted example is the third order gas reaction:

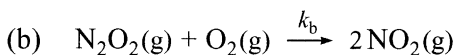


Its rate depends on the concentration of NO to the power of two and on the concentration of oxygen to the power of one. According to the above equa-

tion, the reaction appears to be trimolecular, but this is very unlikely. Trimolecular collisions are rare, because the probability of three molecules colliding simultaneously with adequate energies and proper steric orientations is small indeed. It appears that the first step is the quickly established pre-equilibrium, in which a dimer, N_2O_2 , (or $(\text{NO})_2$), is formed:



In the bimolecular reaction that follows, NO_2 will be formed by oxidation of the dimer:

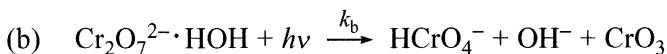
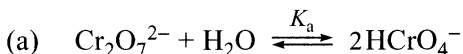


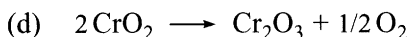
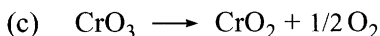
The rate law according to which the product is formed is therefore given by the equation:

$$\frac{d[\text{NO}_2]}{dt} = k_b[\text{N}_2\text{O}_2][\text{O}_2] = k_b K_a [\text{NO}]^2 [\text{O}_2] = k_t [\text{NO}]^2 [\text{O}_2]$$

The negative temperature coefficient of the reaction ($\partial k / \partial T < 0$), that is, the temperature quotient $Q_{10} = (k_{T+10\text{K}} / k_T) < 1$ (the rate of the reaction diminishes with increasing temperature) speaks in favor of the above mechanism. Since the rate constant of the overall reaction, k_t , is the product of two constants, k_b and K_a , the reaction rate can diminish with increasing temperature if the assumed pre-equilibrium is exothermic and the decrease of the equilibrium constant K_a with temperature increase is larger than the increase of the rate constant k_b . It is reasonable to assume that the dimer N_2O_2 (or $(\text{NO})_2$) is destabilized at elevated temperatures. This is exactly what is observed. Such cases are extremely rare because the rate constant most often exhibits a temperature increase larger than the temperature decrease of the equilibrium constant.

On the other hand, a negative temperature dependence of the reaction rate is more often met in photoreactions. Thus, the rate of photooxidation of glycerol and ethylene glycol with dichromate decreases with increasing temperature.^{3,4} Dichromate is in equilibrium (a) with hydrogenchromate. Since the pre-equilibrium is endothermic ($\Delta_a H^\circ = 5060 \text{ J mol}^{-1}$), the equilibrium constant (K_a) increases with increasing temperature, causing a lowering of the concentration of $\text{Cr}_2\text{O}_7^{2-} \cdot \text{HOH}$, which is the photoactive component.

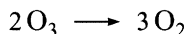




The reaction kinetics can be easily followed spectrophotometrically because the dichromate solutions are orange and Cr_2O_3 is green. Photoreaction (b) is the slowest process and therefore the rate-determining step. This step is practically independent of temperature because photoreactions proceed on account of light energy rather than thermal energy. Therefore, the overall reaction rate must decrease with increasing temperature, as observed. The rate constant of the overall process is now a product of two constants, the equilibrium constant K_a and the rate constant k_b . Of these two constants only K_a is affected by temperature change, while k_b is almost insensitive to the change of temperature. Therefore, the Arrhenius plot $\ln k_{\text{obs}}$ vs. $1/T$ becomes in fact the plot of van't Hoff's equation, enabling determination of the reaction enthalpy of (a) as 5060 J mol^{-1} . The enthalpy determined from the measurements of the heat of neutralization of sodium hydrogen chromate by sodium hydroxide⁵ was found to be 57070 J mol^{-1} , a value ten times higher than that determined by the mentioned plot of van't Hoff's equation. This disagreement prompted a recalculation of the enthalpy of the reaction (a) using a newly published equilibrium constant.⁴ The new value of the reaction enthalpy amounted to 4960 J mol^{-1} , in reasonable agreement with the caloric effect of the temperature function of the overall reaction rate (5060 J mol^{-1}).

The reaction mechanism required the existence of tetravalent Cr in CrO_2 , which was shortly afterwards proven to exist by other authors. The proposed mechanism might still be corrected by newer facts, nevertheless it was very useful in broadening our knowledge of chromium chemistry.

A reaction with quickly established pre-equilibrium, also often cited,⁶ is the conversion of ozone to molecular oxygen:



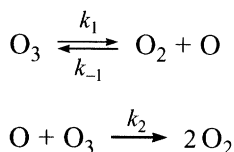
If the reaction were bimolecular, *i.e.*, the result of $\text{O}_3 + \text{O}_3$ collisions, the rate law would be:

$$-\frac{d[\text{O}_3]}{dt} = k[\text{O}_3]^2$$

But the kinetic measurements show that the reaction rate follows the expression:

$$-\frac{d[\text{O}_3]}{dt} = k \frac{[\text{O}_3]^2}{[\text{O}_2]}$$

Therefore, the probable mechanism involves a pre-equilibrium:



If it is assumed that the above pre-equilibrium is quickly established, the equilibrium concentration of atomic oxygen is then given by the expression:

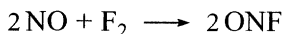
$$[\text{O}] = K \frac{[\text{O}_3]}{[\text{O}_2]} \quad K = \frac{k_1}{k_{-1}}$$

The overall reaction rate is then determined by the slow bimolecular process, the rate of which is given by the expression:

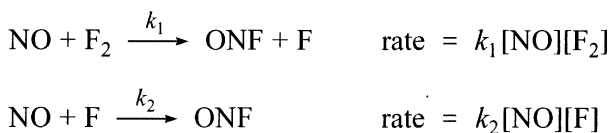
$$-\frac{d[\text{O}_3]}{dt} = k_2[\text{O}][\text{O}_3] = k_2K \frac{[\text{O}_3]^2}{[\text{O}_2]}$$

It can be concluded that the proposed mechanism involving the fast pre-equilibrium is very probable, though not proven.

There are several analogous examples of kinetic support to a proposed reaction mechanism. An instructive example is the formation of nitrosyl fluoride:



According to the equation, the reaction appears to be trimolecular, but, as already discussed, this is not very probable. The much more likely mechanism is the one involving bimolecular collisions:



According to this mechanism, the reaction intermediate is the fluorine atom. It should be expected that the reactions with reactive atoms, as is the fluorine atom, are fast. It is therefore probable that the bimolecular reaction between NO and F₂ is the slowest step, the bottleneck of the reaction, and therefore rate-determining. Thus, the overall reaction rate should be given by the expression:

$$\text{rate} = k_1[\text{NO}][\text{F}_2]$$

which has been confirmed by experiments. Therefore, the proposed reaction mechanism involving fluorine atoms appears likely, but it has not been proven.

From all the mentioned examples we can conclude that there are very few reaction mechanisms that have been determined “beyond reasonable doubt”. In his lecture to the Croatian Chemical Society in Zagreb, the late Professor Ronald S. Nyholm (University College London) commented: “Kinetics are facts, mechanisms are fictions”, but we can add – very interesting and useful fictions.

1.2. CHEMICAL REACTIONS AND ENERGY CHANGES

The potential energy even of the simple H_2 molecule cannot be calculated by classical methods; one must use quantum mechanical methods. But even in the case of this simple molecule, the calculation is very difficult. What makes such calculations feasible is the fact that it is possible to separate the motions of the nuclei from the motions of the electrons. This practical independence of the electronic and nuclear motion is the basis of the Born-Oppenheimer approximation.*

The approximation is based on the idea that the motions of the electrons are practically unaffected by the motions of the nuclei. Hydrogen (^1H) nuclei, being about 1800 times heavier than one electron, and therefore moving much slower, may be considered to be stationary. The purpose of the approximation is to reduce the problem of simultaneous motion of the nuclei and electrons to two much simpler problems, that is, one for the motion of the electrons and the other for the nuclei. The Schrödinger equation** can then be separated into two equations: one for the electrons and the other for the nuclei.

We can then take that the nuclei move in a potential field given by the calculated electronic energy as a function of nuclear coordinates. In this way, it is possible to collect information how the energy of the molecule varies with bond length, or in general, with a change of molecular geometry.

Based on these ideas, the potential energy surface was first computed in 1931 by Henry Eyring and Michael Polanyi.⁷ This is considered one of the great landmarks in the development of chemical kinetics.

* MAX BORN, 1882–1970, a German physicist, shared with Walter Bothe the Nobel Prize for physics for 1954; ROBERT OPPENHEIMER, 1904–1967, American nuclear physicist, worked on production of the atomic bomb.

** ERWIN SCHRÖDINGER, 1887–1962, Austrian physicist, shared with Paul A. M. Dirac (1902–1984) the Nobel Prize for physics for 1933.

Let us consider the H_2 molecule. The nuclei of its atoms are at an equilibrium distance when the potential energy of the molecule is at its minimum. At internuclear distances smaller than the equilibrium distance, the repulsion energy increases substantially. The increase of the internuclear distance above the equilibrium distance also causes a potential energy increase until the breakage of the bond, whereby the potential energy becomes the energy of two separated H-atoms. The energy needed for dissociation of the H_2 molecule into atoms $\text{H} + \text{H}$ is 436 kJ mol^{-1} , the zero-point energy being $\approx 26.4 \text{ kJ mol}^{-1}$ (Figure 1.2.1).⁸

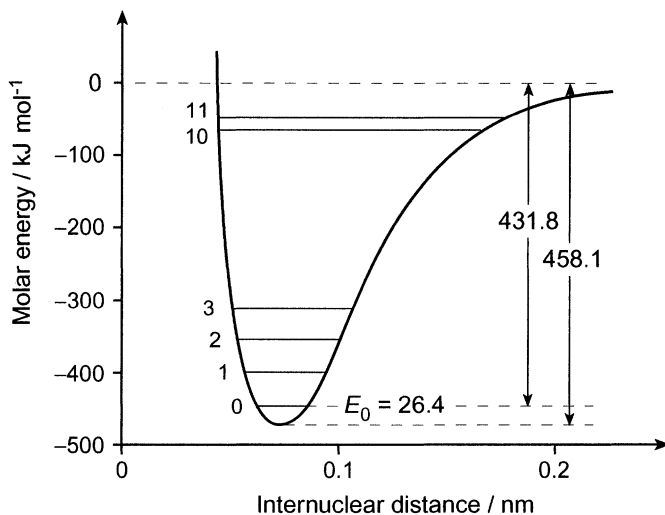


Figure 1.2.1. Potential energy curve for the hydrogen molecule (H_2) with vibrational energy levels, dissociation energy $\approx 431.8 \text{ kJ mol}^{-1}$ and zero-point energy $E_0 \approx 26.4 \text{ kJ mol}^{-1}$ (adapted from refs. 8a and 8b).

Let us also consider the reverse process $\text{H} + \text{H} \longrightarrow \text{H}_2$. When two hydrogen atoms are very far apart, they do not act one upon the other. But when the atoms approach each other, their nuclei undergo repulsion. In addition, the electron clouds undergo repulsion, as well. Concerning the energy change, the attraction between atomic nuclei and electron clouds that surround the nuclei is most important. When atoms approach, the electron clouds are drawn into the region between the nuclei. The combination of two nuclei and two electrons has lower energy (is more stable) than isolated atoms, each with its electron. The exact interpretation can only be given by quantum mechanics showing that the main contribution is from quantum mechanical exchange – a phenomenon which has no equivalent in classical mechanics. When the minimum of the potential energy is reached, the equilibrium internuclear distance

is about 74 pm.⁸ Further decrease of the internuclear distance below this optimal distance starts to increase repulsion forces between the positive nuclei, largely surpassing the attractive forces described.

When we follow the change of potential energy with changing internuclear distance, we have in mind that the energy of rotation is small, compared to vibrational energies, and therefore of minor importance. Since the vibrational levels are quantized, the vibrations can occur at some definite frequencies only. For the diatomic H₂ molecule, the vibrational energy levels E_v are approximately given by the equation of a harmonic oscillator:

$$E_v = (v + \frac{1}{2})h\nu \quad (1.2.1)$$

where ν is the frequency of vibration of the bonded atoms and v is the vibrational quantum number ($= 0, 1, 2, 3, \dots$). The separation between adjacent energy levels of a harmonic oscillator is:

$$E_{v+1} - E_v = h\nu \quad (1.2.2)$$

and it is equal for all adjacent energy levels.

At absolute zero, all molecules are at the lowest energy level ($v = 0$) and the vibrational energy called “zero-point energy” (E_0) is $h\nu/2$; for the hydrogen molecule, $E_{0,m}$ amounts to 26.4 kJ mol⁻¹ (6.3 kcal mol⁻¹).

The frequency of vibration is:

$$\nu = \frac{1}{2\pi} \sqrt{\frac{f}{\mu}} \quad (1.2.3)$$

where f denotes the force constant and μ is the reduced mass:

$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

For the H₂ molecule, the reduced mass is:

$$\mu_{H_2} = \frac{m_H^2}{2m_H} = \frac{m_H}{2}$$

While the classical mechanics would allow two atomic nuclei at absolute zero to be entirely motionless, quantum mechanics sees the zero-point state as the state in which two nuclei continuously fluctuate around their equilibrium position, even at absolute zero. The situation is analogous to that of a particle

confined to a square well, so its position is not entirely certain. No molecule can exist in a stationary position at the potential minimum because then its position and its momentum would be precisely known, which would violate the Heisenberg uncertainty principle: It is impossible to specify simultaneously with arbitrary precision both the momentum and the position of a particle.

As it is done in Figure 1.2.1 for molecular hydrogen, it is possible to construct potential energy curves for different molecules. If the molecules consist of several atoms, this becomes a very complicated problem, but the general shape of the potential energy curves remains similar to that for molecular hydrogen.

It is interesting to note that in the mid of the 18th century RUGJER JOSIP BOŠKOVIĆ (Rogerius Josephus Boscovich) (1711–1787), astronomer and mathematician, developed ideas about the nature of matter that are very close to those of today. Bošković was born in Dubrovnik (Croatia). As a Jesuit, he was schooled in Dubrovnik (*Collegium Ragusinum*) and in Rome (*Collegium Romanum*). He taught mathematics at the University of Rome and at the University of Pavia. His ideas on the nature of matter were published in books: “*Theoria philosophiae naturalis redacta ad unicam legem virium in natura existentium*”, Vienna 1758, and in “*Theoria Philosophiae Naturalis*”, Venice 1763. According to Bošković, matter consists of material (physical) points.^{9,10} Bošković distinguishes material dots from mathematical dots: material dots exhibit inertia, they are simple, impenetrable, cannot be divided, have no structure, and are the origin of forces which depend upon distances. The force is repulsive when the distance between material dots is small. The smaller the distance, the larger is the repulsive force. By increasing the distance, the force diminishes until it is annulled, converted into an attractive force, acquires a maximum, falls to zero, becomes repulsive again, and so on. In this way, there is a steady change of repulsive and attractive forces, so that various stable interatomic distances must exist.

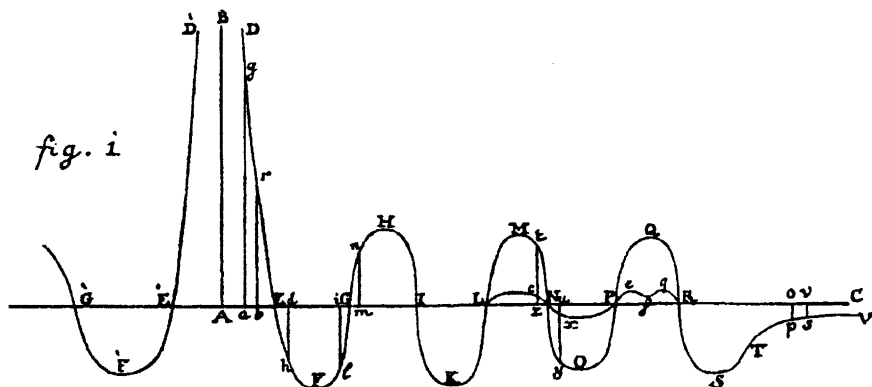


Figure 1.2.2. Curva Boscovichiana.

Because of the continuity of the curve, he excluded the possibility of direct contact between the material dots, due to the repulsive force, which rises to infinity, and therefore two atoms cannot occupy the same space. Until then nobody had excluded this possibility. At that time, there was no way of determining the heights to which the curves rise, or the distances at which they cut the axis, so the model was a qualitative one. Bošković's force is very similar to the force between atoms in a molecule or in solids, or to the force between nucleons (protons and neutrons). Bošković tried to define a unique law of forces in nature (*lex unica virium in natura existentium*). This idea could be felt in Albert Einstein's and Werner Heisenberg's work and in today's still unsuccessful efforts to describe four forces in nature: gravitation, electromagnetic, weak and strong nuclear forces, by a unique law. Bošković's atomic model introduced the idea of "allowed" and "forbidden" tracks for particles, putting forward the idea of the quantized structure of matter. J. J. Thomson directly accepted these ideas in 1907, which later on were the basis for Niels Bohr's atom. Bošković found support for his ideas in England (J. Priestley, J. Robinson, H. Davy, M. Faraday, and Lord Kelvin). It is no wonder that Heisenberg saw in Bošković "a great visionary".

1.3. COLLISION THEORY

The starting point of the collision theory is the notion that reactions occur by collisions between molecules.

Reactions in solutions have been studied most extensively because their kinetics are relatively easy to study, compared to reactions in the gaseous phase. Nevertheless, gas reactions were the main substrate for the study of reaction rates, based on the kinetic theory of gases.

1.3.1. Calculation of rate constants

Chemical reactions include unimolecular, bimolecular and termolecular reactions. Collisions involving four molecules are improbable and even ternuclear processes are rare.

Gaseous reactants collide but most collisions do not yield a chemical reaction. The nonreactive collisions of molecules with one another and with the walls of the vessel cause the high energy molecules to lose some of their energy, but the Maxwell distribution of molecular velocities* is rapidly restored and maintained.

The distribution of molecules to the stationary states of different energies was derived at the end of 1900 by Boltzmann.** According to Boltzmann, the

* JAMES CLERK MAXWELL, Scottish physicist, 1831–1879.

** LUDWIG BOLTZMANN, 1844–1906, Austrian physicist.

ratio of the numbers of molecules in states with energies E_1 and E_2 is given by the equation:

$$\frac{N_1}{N_2} = e^{-(E_1 - E_2)/k_B T} \quad (1.3.1)$$

where k_B is the Boltzmann constant, *i.e.*, the gas constant per molecule.

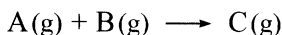
It was soon realized that at the moment of collision only a small fraction of molecules has enough energy and the correct geometry to react. If the total number of molecules is N , then the number of molecules with sufficient energy to react, N^* , is approximately given by the expression:

$$N^* = N e^{-E_A/RT} \quad (1.3.2)$$

where E_A is the molar energy of activation of the reaction, *i.e.*, the minimum energy that reactants must have in order to form products, which will be discussed in more detail in the next section.

By inserting a certain typical value for E_A , it can be shown that only a very small fraction of the total number of molecules has enough energy to react. Thus, if a reaction has an energy of activation of 100 kJ mol^{-1} (an often met value), then at 300 K, the ratio $N^*/N \approx 10^{-15.6}$, and thus, approximately, only one molecule out of 10^{16} molecules has the sufficient energy for reaction.

Let us consider a simple bimolecular reaction taking place in a dilute gas phase:



whose rate is defined as:

$$v = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = \frac{d[C]}{dt}$$

In the simple classical collision theory, the molecules A, B and C are represented as hard spheres characterized by their masses and radii. The frequency of collisions (divided by volume), *i.e.*, the collision number, is given by:

$$Z = \sigma \sqrt{\frac{8k_B T}{\pi \mu}} (N_A)^2 [A][B] \quad (1.3.3)$$

Z being proportional to the concentrations of the reactants and to the collision cross-section,

$$\sigma = \pi(r_A + r_B)^2$$

defined as the squared sum of molecular radii. Further, Z is proportional to the square root of temperature and to the reciprocal reduced mass of two colliding molecules,

$$\mu = \frac{m_A m_B}{m_A + m_B}$$

As already pointed out, only a tiny fraction of collisions can be 'productive' (*i.e.*, yield C), because only a few molecules have energies higher than the 'threshold', E_A (eq. 1.3.2). The fraction of succesful collisions can be calculated by applying the Boltzmann formula (1.3.1), and eq. (1.3.3) becomes:

$$Z^* = \left(\sigma \sqrt{\frac{8k_B T}{\pi \mu}} (N_A)^2 [A][B] \right) e^{-E_A/RT} \quad (1.3.4)$$

Z^* denoting the frequency of successful collisions. From an elementary stoichiometric consideration, it is readily seen that the reaction rate is directly proportional to Z^* :

$$v = \frac{Z^*}{N_A}$$

Now, it is possible to write the final expression for the reaction rate:

$$v = \left(\sigma \sqrt{\frac{8k_B T}{\pi \mu}} N_A e^{-E_A/RT} \right) [A][B] \quad (1.3.5)$$

which is completely analogous to the rate law for a bimolecular process:

$$v = {}^2k[A][B] \quad (1.3.6)$$

Accordingly, the collision-theoretical expression for the rate constant of a bimolecular reaction is:

$${}^2k = \sigma \sqrt{\frac{8k_B T}{\pi \mu}} N_A e^{-E_A/RT} \quad (1.3.7)$$

(reaction molecularity is indicated in the left superscript: 2k).

1.3.2. Arrhenius equation

In order to explain the observed kinetic behavior, Arrhenius* expressed the view that, in a reacting system, there is only a certain number of “active” molecules that can undergo reaction. Arrhenius claimed that the nonreactive molecules could be activated by absorption of the heat of “normal” molecules. He found that the effect of temperature on the reaction rate could be represented by the equation:

$$\frac{d \ln k}{dT} = \frac{\text{constant}}{RT^2} \quad (1.3.8)$$

Arrhenius believed that there was an equilibrium between “active” and “inert” molecules at any given temperature and that this equilibrium is shifted in favor of “active” molecules with temperature rise. It has been found for many chemical reactions that a plot of $\ln k$ against $1/T$ gives a straight line.

The next most important idea was that the temperature dependence of the reaction rate constant must be a function similar to the temperature dependence of the reaction equilibrium constant, because the equilibrium constant is equal to the ratio of forward and reverse rate constants ($K_c = k_{\rightarrow}/k_{\leftarrow}$). Since van't Hoff's** differential equation:

$$\frac{d \ln K_c}{dT} = \frac{\Delta_r H^\circ}{RT^2} \quad (1.3.9)$$

where K_c is the reaction equilibrium constant and $\Delta_r H^\circ$ the reaction enthalpy, was known at that time, Arrhenius replaced the equilibrium constant K_c with the rate constant k and concluded that he also had to replace the reaction enthalpy, $\Delta_r H^\circ$, with the energy of activation E_a . He thought that a reasonable

* SVANTE AUGUST ARRHENIUS, 1859–1927, Swedish physicist and chemist, was a professor of chemistry in Stockholm. His electrolytic theory of dissociation was advanced in 1884–87. In 1903 he was awarded the Nobel Prize for chemistry “in recognition of the extraordinary services he has rendered to the advancement of chemistry by his electrolytic theory of dissociation.” In 1909 he was elected director of the Nobel Institute in Stockholm. Together with PAUL EHRLICH, he studied the toxins and antitoxins. Paul Ehrlich and Sahachiro Hata discovered salvarsan; Ehrlich (1854–1938) shared with ILJA ILJIĆ MEČNIKOV (1845–1916) the Nobel Prize for medicine in 1908.

** JACOBUS HENDRICUS VAN'T HOFF, 1852–1911, Dutch chemist, was awarded in 1901 the first Nobel Prize for chemistry “in recognition of the extraordinary services he has rendered by the discovery of the laws of chemical dynamics and osmotic pressure in solution.” At that time he was a professor at the University of Berlin. He was especially concerned with the dynamics of chemical equilibria. His famous equation (van't Hoff's equation) was, at that time, called the reaction isochore. The equation expresses the variation of equilibrium constant with temperature. Van't Hoff died of tuberculosis at Steglitz near Berlin.

equation for the variation of rate constant with temperature might be:

$$\frac{d \ln k}{dT} = \frac{E_a}{RT^2} \quad (1.3.10)$$

i.e.,

$$E_a = RT^2 \frac{d \ln k}{dT} \quad (1.3.11)$$

The Arrhenius equation is usually written as:

$$k = Ae^{-E_a/RT} \quad (1.3.12)$$

where A is commonly known as the pre-exponential factor. Arrhenius defined the activation energy as the minimum energy that reactants must have in excess of the mean energy of all reactant molecules in order to form products. He understood that only a very small fraction of the total number of molecules can have the energy $E \geq E_a$, and that the portion of these molecules is determined by the Boltzmann distribution law (1.3.1).

Arrhenius could not define the physico-chemical meaning of his pre-exponential factor A . Nevertheless, the Arrhenius equation contributed substantially to the development of the theory of reaction rates.

Discrepancies between the results predicted by the collision theory (equation 1.3.7) and the experimental values were corrected by introducing the so-called steric factor P ; hence the equation (1.3.12) assumed the form (1.3.13):

$$^2k = Ae^{-E_a/RT} = PZe^{-E_a/RT} \quad (1.3.13)$$

where Z is the collision number (see Table 1.3.1).

Table 1.3.1. Arrhenius parameters for some bimolecular gas reactions

	$E_a/\text{kJ mol}^{-1}$	$A/\text{dm}^3\text{mol}^{-1}\text{s}^{-1}$		Steric factor (P)	Ref.
		Collision theory	Observed		
$2\text{NOCl} \longrightarrow 2\text{NO} + \text{Cl}_2$	103.0	5.9×10^{10}	9.4×10^9	0.16	a
$2\text{NO}_2 \longrightarrow 2\text{NO} + \text{O}_2$	111.0	4.0×10^{10}	2.0×10^9	5.0×10^{-2}	b
$\text{H}_2 + \text{C}_2\text{H}_4 \longrightarrow \text{C}_2\text{H}_6$	180	7.3×10^{11}	1.24×10^6	1.7×10^{-6}	c
$\text{K} + \text{Br}_2 \longrightarrow \text{KBr} + \text{Br}$	0	2.1×10^{11}	1.0×10^{12}	4.8	c

(a) G. Waddington and R. C. Tolman, *J. Am. Chem. Soc.* **1935**, 57, 689.

(b) M. Bodenstein and H. Ramstetter, *Z. Phys. Chem.* (Munich), **1922**, 100, 106.

(c) M. J. Pilling, *Reaction Kinetics*, Clarendon Press, Oxford 1974.

It was necessary to introduce the steric factor P because it was obvious that, for steric reasons, not all collisions would be equally successful. Indeed, pre-exponential factors calculated on the basis of the collision theory were generally too high, so that the actual values of 2k were usually obtained by steric factors of 1 to 0.001, as shown in Table 1.3.2 (steric factors as low as 10^{-6} have been also published – see also Table 1.3.1).

Table 1.3.2. Steric factors for some bimolecular reactions¹¹

	P
$\text{H} + \text{H}_2 \longrightarrow \text{H}_2 + \text{H}$	1
$\text{H} + \text{Br}_2 \longrightarrow \text{HBr} + \text{Br}$	1
$\text{Cl} + \text{H}_2 \longrightarrow \text{HCl} + \text{H}$	1
$\text{Br} + \text{H}_2 \longrightarrow \text{HBr} + \text{H}$	0.1
$\text{H} + \text{HBr} \longrightarrow \text{H}_2 + \text{Br}$	0.1
$\text{CF}_3 + \text{H}_2 \longrightarrow \text{CF}_3\text{H} + \text{H}$	0.001

The steric factor $P = 1$ suggests that the reaction takes place always when two very simple molecules collide with an energy in the approaching direction that is by E_A larger than the average energy of the reactants. On the other hand, if collisions occur simultaneously and in the presence of several “correctly” oriented molecules (“ n -body collision”), a very small value of P can be expected.

In spite of the fact that the introduction of the steric factor into the collision theory appeared reasonable, it was useless in theoretical calculations of bimolecular rate constants because no successful procedure for the calculation of steric factors from the characteristics of the reacting molecules was yet found. In fact, the steric factor can be considered a numerical measure for the indeterminacy of the collision theory, because rate constants calculated by the collision theory are not only too high, but which is even worse, all values of calculated rate constants for different reactions are practically equal. It may be concluded that the collision theory cannot predict variations in A , which may amount to several orders of magnitude. It should be added that the simple collision theory is not able to predict the value of the activation energy.

1.4. TRANSITION STATE THEORY

The transition state theory, also called the theory of the activated complex, was known as the “theory of absolute reaction rates” in its early days. According to Henry Eyring (American chemist, 1901–1981) and Michael Polanyi (1891–1976) (see section 1.2), many reactions proceed *via* a pre-equilibrium mechanism. For instance, a bimolecular reaction



can be represented by the equation:



where $(AB)^\ddagger$ denotes a transient intermediate known as “activated complex”. Its structure bears some similarities to both the reactants and the products: for example, in the reaction



the “bond” lengths in the colinear activated complex are longer than covalent bonds in either H_2 or HD , but still shorter than the non-bonding distances.

The nature of the assumed transient species can be better understood by considering the reaction system to be an assembly of atoms, *e.g.*, $2H$ and D in the above example. Potential energy of this assembly is a function of relative positions (“internal coordinates”) of its atoms. When the system contains only the molecules of the reactants ($H-H + D$) – which are chemically stable – its potential energy is obviously at a minimum. Likewise, when the system contains only the products ($H + H-D$), the potential energy is also at a minimum, different from the previous one. Consequently, any of the many reaction paths leading from one minimum of potential energy to the other must pass through a maximum – a potential barrier. However, this maximum is the lowest of all near-by maxima; it is a kind of a saddle point in a mountain pass. Therefore, the constellation of atoms represented by this saddle point is not a stable chemical species. Nevertheless, in Eyring’s theory, it is treated as a chemical species in equilibrium with the reactants (some prefer to call it *quasi-equilibrium*). Eyring maintained that there was an essential difference between the activated complex and the transition state. He regarded the activated com-

plex as a real chemical entity of very short life, while the transition state was more of a useful mathematical artefact to him.*

Nowadays, there is a tendency to define the transition state more broadly. The definition of the transition state (TS) used recently by John C. Polanyi** and Ahmed H. Zewail¹¹ is the “full family of configurations through which the reacting particles evolve *en route* from reactants to products.” They believe that this definition of the TS (usual symbol $\ddagger$, displayed at the crest of the energy barrier to reaction) is likely to prove most enduring.

The potential energy, E_p , of the (2H, D) system mentioned above in a collinear approach is a function of two variables (“internal coordinates”), viz. the distances $r_{H,H}$ and $r_{H,D}$. Therefore, the function $E_p(r_{H,H}, r_{H,D})$ can be represented by a surface in a three-dimensional diagram, having two minima (corresponding to two stable states, H–H + D and H + H–D) and a maximum (corresponding to the transition states H $\cdots$ H $\cdots$ D). Orthogonal projection of the minimum energy path onto the coordinate plane ($r_{H,H}, r_{H,D}$) is called reaction coordinate. No such visualization is possible for systems containing more than three atoms, but the concept of the reaction coordinate, though abstract, can still be used (see section 1.6 and Figure 1.6.1).

The assumption of a pre-equilibrium mechanism implies that the rate constant 2k of the overall second order reaction (eq. 1.4.1a) should be much lower than either k_1 or k_{-1} , (eq. 1.4.1b), the rate-determining step being the unimolecular decay of (AB) ‡ . Thus, the concentration of (AB) ‡ is determined by the equilibrium constant of the formation of the activated complex:

$$K_c = \frac{[(AB)^\ddagger]}{[A][B]} \quad (1.4.3a)$$

$$[(AB)^\ddagger] = K_c[A][B] \quad (1.4.3b)$$

The rate of the product formation is:

$$\frac{d[P]}{dt} = {}^2k[A][B] = k^\ddagger[(AB)^\ddagger] = k^\ddagger K_c[A][B] \quad (1.4.4)$$

* Private communication by Professor Maurice M. Kreevoy who collaborated with Eyring and knew his views.

** JOHN C. POLANYI, son of the famous chemist M. Polanyi, born in Berlin in 1929, professor at the University of Toronto, shared the 1986 Nobel Prize for chemistry with Dudley R. Herschbach, American chemist, and Yuan T. Lee, Taiwanese-American chemist, for their contributions to the dynamics of chemical elementary processes; AHMED ZEWAİL, born in Egypt, professor of chemical physics at the California Institute of Technology in Pasadena, obtained the Nobel Prize for chemistry in 1999 for his studies of the transition states of chemical reactions using femtosecond spectroscopy.

where 2k is the rate constant of the overall second order reaction, and $k^\ddagger$ is the unimolecular rate constant for the decomposition of the transition state $(A\cdots B)^\ddagger$. We see that

$$^2k = k^\ddagger K_c \quad (1.4.5)$$

Hence, the task of the theory is to calculate the rate constant $k^\ddagger$ of the unimolecular decay of $(AB)^\ddagger$ and the activation equilibrium constant K_c .

One of the vibrational modes of the activated complex leads to the $A\cdots B$ bond cleavage (in the above H_2/HD example: asymmetric stretching of $H\cdots H\cdots D$ complex). The frequency of this vibration is closely related to the $(AB)^\ddagger$ decay frequency:

$$k^\ddagger = \kappa \nu^\ddagger \quad (1.4.6)$$

where κ is the so-called transmission coefficient, *i.e.*, the ratio of probabilities of the two modes of $(AB)^\ddagger$ decay – into the products ($k^\ddagger$) or back to the reactants (k_{-1}). In most cases, κ is close to 1 (say, within ± 0.1).

In favorable cases, notably for dilute (nearly ideal) gaseous systems, a slightly different equilibrium constant of activation, $K_c^\ddagger$, can be estimated by the methods of statistical thermodynamics.

Thermodynamic properties of an assembly of many mutually independent molecules of the same kind are determined by one single quantity, the so called molecular partition function. The partition function is a statistical mechanics concept representing a link between microscopic and macroscopic thermodynamic properties. It enables the expression of the equilibrium constant in terms of energies of individual degrees of freedom for the molecules. The molecular partition function is defined as the sum over stationary quantum states of the molecules (numerated by $i = 1, 2, 3, \dots$):

$$q = \sum_i e^{-\epsilon_i/k_B T}$$

(ϵ_i denotes the energy of the i -th state). If the individual molecular motions are also mutually independent (a reasonably good approximation), q can be factorized into partition functions for individual molecular motions:

$$q = q_t q_r q_v q_e$$

(subscripts t, r, v, e refer to translational, rotational, vibrational and electronic motions, respectively). The details of the calculation can be found elsewhere.

The equilibrium constant for the activation reaction (1.4.1b) can be written in terms of partition functions divided by volume, $\tilde{q} = q/V$, in the following way:

$$K_c^\ddagger = N_A \frac{\tilde{q}_{AB}^\ddagger}{\tilde{q}_A \tilde{q}_B} e^{-\Delta\epsilon_0/k_B T}$$

Unlike the equilibrium constant K_c from eq. (1.4.3a), the vibrational partition function in $\tilde{q}_{AB}^\ddagger$ in the above formula is computed by taking out the “critical” vibration leading to the product(s). The difference between the ground state energies of reactants and of the activated complex, denoted as $\Delta\epsilon_0$, is approximately equal to the height of the potential barrier or – hypothetically speaking – to the activation energy at zero thermodynamic temperature (0 K).

It can be shown that the two equilibrium constants are related by the expression:

$$K_c = \frac{k_B T}{h\nu^\ddagger} K_c^\ddagger \quad (1.4.7)$$

If $k^\ddagger$ (1.4.6) and K_c (1.4.7) are inserted into (1.4.5), the well known Eyring equation is obtained:

$$^2k = \kappa \frac{k_B T}{h} K_c^\ddagger \quad (1.4.8)$$

Except for the reactions between small molecules, the theoretical computation of $K_c^\ddagger$ is a difficult or even unsolvable task and, because of the short life of the activated complex, the experimental determination of $K_c^\ddagger$ is hardly imaginable. Fortunately, there is a way out of this frustrating situation, viz. applying a well-known formula of chemical thermodynamics to the activation equilibrium constant (*NB*: the notation used follows the recommendations of IUPAC’s “Green Book”¹⁶⁸):

$$\Delta^\ddagger G^\circ = -RT \ln K^{\ddagger\circ} \quad (1.4.9)$$

which can be written as:

$$K^{\ddagger\circ} = e^{-\Delta^\ddagger G^\circ/RT} \quad (1.4.10)$$

Here, $\Delta^\ddagger G^\circ$ denotes the standard Gibbs energy of activation and $K^{\ddagger\circ}$ is the thermodynamic (standard) equilibrium constant of activation, defined in terms of (relative) activities of A, B and (AB) ‡ :

$$K^{\ddagger\circ} = \frac{a_{AB}^\ddagger}{a_A a_B} \quad (1.4.11)$$

(note that the contribution of “critical” vibration, $k_B T/h$, is not included into $K^\ddagger$). The well-known thermodynamic relation

$$\Delta_r G^\circ = \Delta_r H^\circ - T \Delta_r S^\circ$$

can also be applied to the formation of the activated complex:

$$\Delta^\ddagger G^\circ = \Delta^\ddagger H^\circ - T \Delta^\ddagger S^\circ \quad (1.4.12)$$

$\Delta^\ddagger H^\circ$ and $\Delta^\ddagger S^\circ$ denoting the enthalpy of activation and the entropy of activation, respectively.

However, the values of standard thermodynamic quantities ($K^\ddagger$, $\Delta^\ddagger G^\circ$, $\Delta^\ddagger H^\circ$ and $\Delta^\ddagger S^\circ$) depend not only on temperature but also on the choice of standard (reference) state. Therefore, reactions taking place in the gas phase have to be considered in a different way than those among the solutes in a dilute solution.

Gases. – By convention, the activity of the i -th component of a dilute (nearly ideal) gas mixture is defined as

$$a_i = \frac{p_i}{p^\circ} \quad (1.4.13)$$

(usually, but not necessarily, $p^\circ = 1 \text{ bar} = 100 \text{ kPa}$). Assuming that $\kappa \approx 1$ and combining (1.4.8) with eqs. (1.4.10) to (1.4.13), the following formulas for the rate constant of a bimolecular reaction can be derived:

$$^2k = \frac{k_B T}{h} \frac{RT}{p^\circ} e^{-\Delta^\ddagger G^\circ / RT} \quad (1.4.14)$$

$$^2k = \frac{k_B T}{h} \frac{RT}{p^\circ} e^{\Delta^\ddagger S^\circ / R} e^{-\Delta^\ddagger H^\circ / RT} \quad (1.4.15)$$

Transition state theory can be applied to the reactions other than bimolecular. For m -molecular reactions of the n -th order, eq. (1.4.15)* can be generalized into:

$$^n k = \frac{k_B T}{h} \left(\frac{RT}{p^\circ} \right)^{m-1} e^{\Delta^\ddagger S^\circ / R} e^{-\Delta^\ddagger H^\circ / RT} \quad (1.4.16)$$

* In order to avoid confusion, it may be necessary to specify either the number of molecules participating in the reaction, *i.e.*, the molecularity, m , or the phenomenological order of the reaction, n (for elementary reactions $m = n$). It may be advantageous to write m (or n) as a left superscript to the rate constant symbol [T. Cvitaš, University of Zagreb, Croatia, personal communication (2000).]

By substituting (1.4.16) into the empirical definition of activation energy (1.3.11), one gets:

$$E_a = RT^2 \frac{d \ln^l k}{dT} = \Delta^\ddagger H^\circ + lRT \quad (1.4.17)$$

where l stands for either m or n , whichever applicable, and E_a is the Arrhenius energy of activation.

Solutions. – The relative activity of the i -th solute in a solution is defined by a different relation:

$$a_i = \frac{c_i \gamma_i}{c^0} \quad (1.4.18a)$$

(usually, but not necessarily, $c^0 = 1 \text{ mol dm}^{-3}$). For nearly ideal dilute solutions, the activity coefficients, γ_i , are close to 1 and the formula reduces to:

$$a_i = \frac{c_i}{c^0} \quad (1.4.18b)$$

Now, by making use of (1.3.11), the general formula for the rate constant of an m -molecular reaction of the n -th order in solution can be derived:

$$^n k = \frac{k_B T}{h} \left(\frac{1}{c^0} \right)^{m-1} e^{\Delta^\ddagger S^\circ/R} e^{-\Delta^\ddagger H^\circ/RT} \quad (1.4.19)$$

For reactions in solution, the relation of activation enthalpy and Arrhenius energy of activation can be obtained in an analogous manner as (1.4.17) above, viz. from eqs. (1.4.19) and (1.3.11):

$$E_a = \Delta^\ddagger H^\circ + RT \quad (1.4.20)$$

In the special case of bimolecular reactions in solution, formula (1.4.19) reads:

$$^2 k = \frac{k_B T}{h c^0} e^{\Delta^\ddagger S^\circ/R} e^{-\Delta^\ddagger H^\circ/RT} \quad (1.4.21)$$

By taking logarithms, this expression can be recast into the form

$$\ln \frac{k}{T} = -\frac{\Delta^\ddagger H^\circ}{R} \frac{1}{T} + \ln \frac{k_B}{h c^0} + \frac{\Delta^\ddagger S^\circ}{R} \quad (1.4.22)$$

which permits an easy estimation of $\Delta^\ddagger H^\circ$ and $\Delta^\ddagger S^\circ$ from empirical values of the rate constants determined at varied temperatures. Provided $\Delta^\ddagger H^\circ$ does not change in the scanned temperature range, the plot of $\ln(k/T)$ vs. $1/T$ should be linear, with the slope of $-\Delta^\ddagger H^\circ/R$ and the intercept $\ln(k_B/hc^\circ) + \Delta^\ddagger S^\circ/R$. Where applicable, this method is a useful alternative to the use of eq. (1.4.20).

Since the Arrhenius activation energy is closely related to the enthalpy of activation, formulas (1.4.17) and (1.4.20) can be used to express the pre-exponential factor $A = PZ$, defined by eq. (1.3.13), in terms of activation entropy. From eq. (1.4.16) for the reactions in gaseous phase one obtains:

$$PZ = \frac{k_B T}{h} \left(\frac{RT}{p^\circ} \right)^{m-1} e^m e^{\Delta^\ddagger S^\circ/R} \quad (1.4.23)$$

while eq. (1.4.19) for solution reactions yields:

$$PZ = \frac{k_B T}{h} \left(\frac{1}{c^\circ} \right)^{m-1} e e^{\Delta^\ddagger S^\circ/R} \quad (1.4.24)$$

The last two equations show that, by experimentally determining the pre-exponential factors, the value of the entropy of activation can be obtained. In this way, one can get a qualitative idea of the structure of the activated complex.

For unimolecular reactions, (1.4.24) reduces to:

$$PZ = \frac{k_B T}{h} e e^{\Delta^\ddagger S^\circ/R} \quad (1.4.25)$$

This special case is particularly important because the kinetics of bimolecular reactions are often studied under pseudo-first order conditions (*i.e.*, in excess of one of the two reactants). Eq. (1.4.25) is directly applicable to non-electrolytes in dilute solutions but it can be also adapted to electrolyte solutions (*e.g.*, to kinetic salt effect – see section 1.9.2).

It can be shown that $\Delta^\ddagger H^\circ = E_a - RT = E_A - RT/2$, where E_a is the Arrhenius (empirical) energy of activation and E_A is the threshold molar energy of activation derived from the collision theory. Since RT is comparatively small (at room temperature $RT = 2.5 \text{ kJ mol}^{-1} = 0.6 \text{ kcal mol}^{-1}$), all the three values, *viz.* $\Delta^\ddagger H^\circ$, E_a and E_A , are nearly equal and represent the energy barrier that the reactants must pass on their way to products.

Since the quantity $k_B T e/h$ in eq. (1.4.25) amounts roughly to 10^{13} (at room temperature), it can be taken as a 'normal' value of Z , so that $\Delta^\ddagger S^\circ$ can be identified with the steric factor, P :

$$P \approx e^{\Delta^\ddagger S^\circ/R} \quad (1.4.26)$$

Nevertheless, as $\Delta^\ddagger S^\circ$ depends on the choice of standard states, one should be careful with the relation of P to $\Delta^\ddagger S^\circ$ and consult specialized monographs on chemical kinetics. According to eq. (1.4.26), the value of steric factor $P = 1$ corresponds to $\Delta^\ddagger S^\circ = 0$ and the reaction proceeds at a 'normal' rate. If $P > 1$, the entropy of activation is greater than zero, *i.e.*, positive, and the reaction proceeds faster than "normal". If the steric factor is less than 1, the entropy of activation is negative, and the reaction proceeds slower than "normal".

If we take the ratio of equations (1.4.21) for two rate constants, k_1 i k_2 , and supposing that both reactions have equal energies of activation, we get:

$$\frac{k_1}{k_2} = \frac{e^{\Delta^\ddagger S_1^\circ/R}}{e^{\Delta^\ddagger S_2^\circ/R}} \quad (1.4.27)$$

Assuming that $k_1/k_2 = 10$, then $\Delta(\Delta^\ddagger S^\circ) \approx 19 \text{ JK}^{-1} \text{ mol}^{-1}$ ($4.58 \text{ cal K}^{-1} \text{ mol}^{-1}$). We can see that an increase of the entropy of activation of $19 \text{ JK}^{-1} \text{ mol}^{-1}$ causes a rate acceleration by one order of magnitude.

In the same way, using the Arrhenius equation (1.3.12), it can be shown that, assuming equal Arrhenius pre-exponential factors and equal temperatures (about 300 K), an increase of the energy of activation of 5.86 kJ mol^{-1} ($= 1.4 \text{ kcal mol}^{-1}$) will cause a decrease in the rate by a factor of 10.

For a reaction with a steric factor $P = 1$, the entropy of activation $\Delta^\ddagger S = 0$, because it has been shown that $P \approx \exp(\Delta^\ddagger S^\circ/R)$. This means that the degrees of order (or disorder) in the transition state and in the reactants are equal, and so the difference of their entropies is zero.

Very small steric factors (P down to 10^{-9} , $\Delta^\ddagger S$ as low as $-175 \text{ JK}^{-1} \text{ mol}^{-1}$) are found in reactions in which ions are produced. In such reactions, the polar transition state is well solvated, which means that in the transition state a relative increase of order is established (relative to the ground state), leading to a negative entropy of activation.

1.5. STERIC EFFECTS AND REACTIVITY OF STRICTLY ORIENTED MOLECULES

One should bear in mind that in typical collisions the molecules freely rotate and assume random mutual orientations. Until recently, there was no way of forcing the molecules to react under a strictly defined geometric orientation, the effect of which on reactivity could then be studied. The main information on the reactants' steric orientation stemmed from indirect studies

of reactions in solutions where the complications caused by solvent interference were always present. Therefore, kinetic studies in the gaseous phase were, in principle, favored. The most fascinating example of a steric effect is certainly that in bimolecular nucleophilic substitutions (S_N2), like the reaction $Cl^- + CR_3I \longrightarrow CR_3Cl + I^-$. Experiments have shown that if $R = H$, the reaction proceeds with the inversion of configuration at the central carbon atom (the well known Walden inversion). It was concluded that the Cl^- attack is the “back-side attack”, later renamed “*trans*-attack” (for aesthetic reasons, as once Sir Christopher Ingold commented to the author with a hardly noticeable smile). On the other hand, bulky groups R prevent inversion, due to the steric effect, simultaneously reducing the reaction rate.

1.5.1. Molecular beams studies

An important advance in the experimental study of intermolecular forces has resulted from the development of molecular beams. A molecular beam is a narrow beam of molecules traveling through an evacuated space. Using these beams, it is possible to study chemical reactions between pairs of molecules with exactly defined energies and directions of approach. At sufficiently low pressures, the mean free path of gas molecules becomes so large that the molecules follow the laws of geometric optics and can be collimated into beams. The beam is directed towards other molecules, and the scattering that occurs is related to intermolecular interactions. The molecules in a molecular beam do not change their geometric configuration because they do not collide. An important condition is that a molecule once oriented ought not to be oriented again by collisions, but it must collide with a reactive atom or molecule retaining its initial orientation.

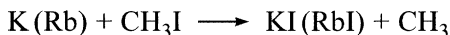
1.5.2. Symmetric top molecules

The first important breakthrough in kinetic studies with molecular beams was made in 1966. Bernstein *et al.*¹³ and Brooks *et al.*¹⁴ developed independently a technique for isolation of oriented symmetric top molecules. These molecules have a unique symmetry axis of the third or higher order (*e.g.*, $CHCl_3$, NH_3 , PH_3 , point group C_{3v}). A polar symmetric top has a dipole moment along the unique symmetry axis. If we try to rotate an irregular stone, as we rotate a spinning top, it will tumble very soon because there is no symmetry axis. Most molecules tumble when they rotate. But symmetric top molecules rotate as a child's spinning top and do not tumble. The dipoles of such

molecules assume a definite orientation in space and do not cancel out by rotation, as is the case with molecules having lower symmetry.^{15,16} The applied technique uses an electric field to focus the symmetric top molecules whose dipole vectors were oriented so that they pointed in the electric field direction. In fact, the technique did not orient symmetric top molecules, but it only selected those molecules, which were already “correctly” oriented.

Consider a gas whose symmetric top molecules, in an electric field, are partly oriented “upward”, partly “downward”, and some “sideward”. The number of molecules oriented “upward” equalizes with molecules oriented “downward” so that, on average, the gas is not oriented. Nevertheless, each single molecule is oriented and it will stay so until collision. In a molecular beam, under reduced pressure, it is possible to eliminate random collisions, so a beam of oriented molecules can be obtained either by using an electric field or by elimination of undesired molecules by “filtration”. Filtration can be achieved because molecules of different orientations have different energies in an electric field, a phenomenon called the Stark effect (the degeneracy associated with the orientation of the rotation in space is partly removed when an electric field is applied to a polar molecule, causing splitting of the states).

Bernstein *et al.*¹³ and Brooks *et al.*¹⁴ applied the mentioned technique to direct studies of steric effects of oriented symmetric top molecules in reactions of CH₃I with potassium and rubidium atoms, respectively:



They observed that the product is formed with higher probability if the potassium atoms approach the iodine from the front side (*cis*-attack) than if they approach the CH₃I molecule from the CH₃ side (*trans*-attack). This is considered the first direct evidence for the influence of orientation on reactivity.

Since the first experiments of Bernstein and Brooks and co-workers with oriented molecules almost up to recent times, it was believed that the symmetric top molecules are the only molecules whose axes of symmetry can be selected and oriented in the electric field. The advance in the field was very slow because the number of symmetric top molecules is rather limited, and there are not too many symmetric tops that could be involved in chemically interesting reactions. During the past thirty years quite a few experiments were done with adsorption and desorption of symmetric top molecules on silver and graphite surfaces. It was established^{17,18} that oriented CF₃H molecules exhibit an unambiguous steric effect in adsorption and subsequent desorption on silver surfaces: at 620 K, about 27% molecules are adsorbed more

readily if the hydrogen atoms are oriented towards the surface and the fluorine atoms are oriented away from the surface. The experiments with oriented molecules on graphite surfaces showed that the most important factor that enables adsorption of oriented molecules is the possibility of energy transfer from the oriented molecules into other degrees of freedom available during the collision.

It may be concluded that the studies of steric effects using beams of oriented spinning top molecules have shown that the reactivity depends mainly on molecular orientation, which directly indicates the importance of steric effects. In some reactions, the results were in accord with our traditional expectations, but in others our intuition led us to wrong conclusions, as seen from the experiments performed on solid surfaces. An excellent review article written by P. R. Brooks, one of the main investigators in the field, is often cited.¹⁹

As already mentioned, people thought that molecules (which are not symmetric tops) tumble too fast to be oriented in an electric field.²⁰⁻²³ Progress was made when it was realized that by cooling in a supersonic adiabatic expansion the rotation of a molecule can be slowed down enough to prevent rotation and to turn the molecules into tiny pendula. To stop such rotation, the energy of interaction between an electric field and the dipole moment has to exceed the rotational energy. The electric field required for this purpose is much larger than the experimentally available electric fields.¹⁶ Fortunately, by cooling molecules in a supersonic adiabatic expansion, it is possible to cool them down to 1 K or even lower. At such low temperatures, the molecules occupy a few lowest rotational states. This enables orientation of a significant fraction of molecules without application of the mentioned high electric fields.²⁴⁻²⁶

B. Friedrich and D. R. Herschbach^{25,26} recognized that molecular axis orientation would exhibit characteristic spectra. They used laser-induced fluorescence spectroscopy to measure Stark shifts (splitting of lines by an electric field) in ICl, showing that this technique can be used to orient the ICl molecule, in spite of the fact that it is a nonsymmetric top molecule.

It is quite understandable that the new technique using cooled, oscillating (not rotating), oriented molecules offers much larger and better possibilities of investigating the steric dynamics of symmetric top molecules. Thus, it has been noticed that the oriented collisions in the reaction $\text{H} + \text{ICl}$ yield predominantly HI, not HCl, though the bond of hydrogen with chlorine is much stronger than that with iodine. It can be expected that the new technique with oriented pendular molecules will solve many similar problems.

In conclusion, the problems associated with steric effects are much more complex than one would expect at first glance.

1.6. REACTION ENERGY PROFILES AND THE REACTION COORDINATE

Let us consider a general reaction $AB + C \longrightarrow A + BC$. The total energy of reactants AB and C is the sum of their kinetic and potential energies. Because of collisions, a part of energy is absorbed and transferred into the kinetic energy of vibrations of bonded atoms. Stretching of bonds and bond ruptures will cause an increase of the potential energy while every bond formation causes a lowering of the potential energy. Along the path from the reactants to products, kinetic energy is converted into potential energy by bond stretching, partial bond formation and molecular distortion. As a consequence of these motions, the transition state is the species of maximum potential energy. By the time the transition state is formed all the energetically unfavorable processes have taken place and the subsequent atomic motions and geometric rearrangements yield more stable configurations of atoms. Potential energy is usually plotted on the vertical axis and the horizontal axis is the reaction coordinate. The plot is referred to as the energy profile diagram of the change in energy of the chemical system as the nuclei of the reactants execute their motions (often not quantitatively known). Actually, the atoms or reacting chemical species approach each other from all possible angles and the definition of the reaction coordinate becomes very complicated. The reaction coordinate is generally not specified in detail because the qualitative concept usually suffices, but specifications are also possible. Thus, in the reaction $\text{CH}_3\text{Cl} + \text{OH}^- \rightleftharpoons \text{CH}_3\text{OH} + \text{Cl}^-$, we can specify the changes in distances between C–O and C–Cl atoms during the reaction and thus approximately specify the reaction coordinate. The reaction $\text{CH}_3\text{Cl} + \text{OH}^-$ is reversible and the equilibrium position is shifted to the right. The atomic displacements reverse as the reaction is reversed. This statement is in accordance with the principle of microscopic reversibility. The principle of microscopic reversibility requires that at equilibrium both forward and reverse reactions proceed at equal rates along the reaction coordinate. This means that the mechanism of the entry of the new ligand must be the reverse of that of the loss of the leaving ligand. It is so insofar some other entering ligand Y resembles the leaving ligand X. This is an important limitation of the principle of microscopic reversibility on the mechanism of replacement of X by Y.

More complex reactions than that between $\text{CH}_3\text{Cl} + \text{OH}^-$ are difficult to depict by plotting the potential energy against the relative atomic positions. Nevertheless, whatever mode of presenting the dependence of potential energy on nuclear distances we choose, the reaction energy profile will basically remain unchanged.

The transition state has a defined geometric and electronic structure. Its life-time is close to zero. Its structure, because of its short life, cannot be

experimentally determined. Nevertheless, we can learn a lot about transition state properties, primarily from kinetic data.

Let us consider a relatively simple exchange process taking place in a single step. *i.e.*, involving only one transition state:



(The already mentioned isotope exchange, $\text{H}_2 + \text{D} \longrightarrow \text{H} + \text{HD}$, is obviously an example of such a process; another example is the reaction of chloromethane with hydroxide ion: $\text{CH}_3\text{Cl} + \text{OH}^- \longrightarrow \text{CH}_3\text{OH} + \text{Cl}^-$.)

The dependence of the potential energy of a microscopic system, containing only three particles (A, B, and C), on the reaction coordinate (see section 1.4) is qualitatively depicted in Fig. 1.6.1. Two stable states (*viz.* reactants, $\text{AB} + \text{C}$, and products, $\text{A} + \text{BC}$), correspond to two local minima of potential energy and the transition state, $[\text{A}\cdots\text{B}\cdots\text{C}]^\ddagger$, is represented by the maximum whose high energy is mostly (but not solely) due to the weakening of the A–B bond. The height of the maximum, measured relative to the reactants, nearly equals the activation energy for the forward reaction, $E_{\text{A}}(\rightarrow)$. Analogously, the maximum height measured relative to the product is the activation energy for the reverse reaction, $E_{\text{A}}(\leftarrow)$. Also, it can be seen that the transition state for both forward and reverse reactions is precisely the same, in accordance with the principle of microscopic reversibility.

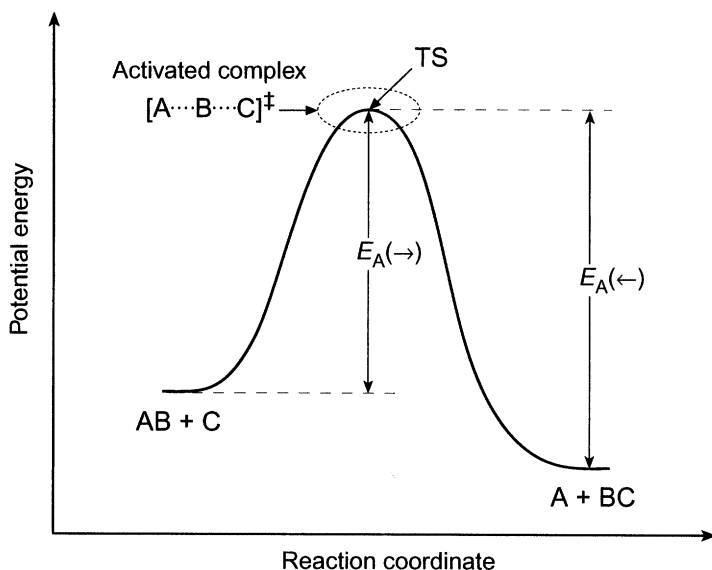
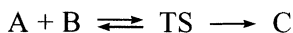


Figure 1.6.1. Energy profile for the reaction $\text{AB} + \text{C} \rightleftharpoons \text{A} + \text{BC}$, with energies of activation (E_{A}) for the forward and backward reactions.

As shown in section 1.4, the reaction coordinate is a highly sophisticated concept, difficult to grasp to many chemists. Besides, there are still comparatively few instances where the theoretical computation of potential energy as a function of atomic coordinates was possible. Therefore, it is advantageous to use another diagram, *viz.* the energy profile of the reaction. In such a diagram, thermodynamic (*i.e.*, macroscopic) properties of the species under consideration are plotted and arranged in a similar way as in the so-called correlation diagrams widely used in quantum chemistry and spectroscopy. For instance, in the energy profile for the reaction



the chemical potentials of the relevant species are plotted (Fig. 1.6.2). The leftmost horizontal line (denoted $A + B$) represents the sum of the chemical potentials of the reactants, *i.e.*, $\mu_A + \mu_B$; the remaining two lines denote μ_{TS} and μ_C , respectively. According to the definition of μ (see below), the ordinate axis is labeled as molar Gibbs* energy, G_m . Note that no abscissa is needed in this kind of diagram.

Reaction energy profiles usually show the dependence of the change of the molar Gibbs free energy, G_m , on the reaction coordinate.

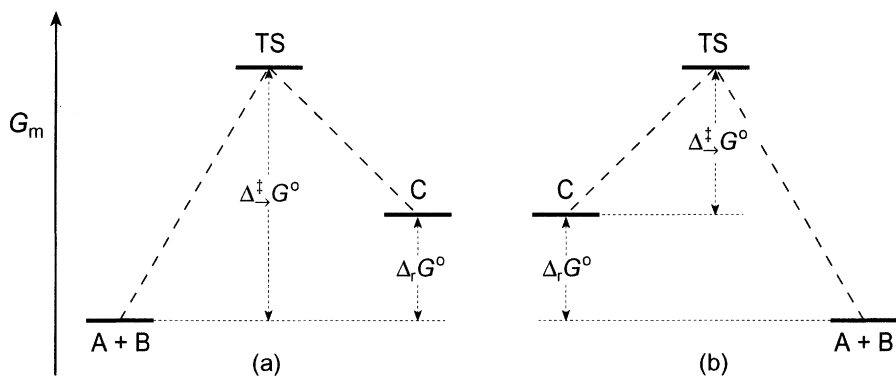


Figure 1.6.2. “Activation profiles” for a single step endergonic reaction ($A + B \rightarrow C$), and its reverse, the exergonic reaction ($C \rightarrow A + B$). The reactions have only one transition state.

* JOSIAH WILLARD GIBBS, 1839–1903, professor of mathematical physics at Yale from 1871 until his death. In 1876 Gibbs published a remarkable paper in the *Transactions of the Connecticut Academy of Sciences* entitled “On the Equilibrium of Heterogeneous Substances.” The paper was completed in 1878 (it amounted to 323 pages) and it laid the foundation for chemical thermodynamics. The concept of free energy appeared for the first time in this paper. Gibbs established a new discipline known today as vector analysis. Nowadays, Gibbs is considered one of the greatest theoreticians in the history of science.

Let us recall: there are two thermodynamic functions whose changes determine the outcomes of processes taking place at constant temperature, viz. Helmholtz* (free) energy:

$$A = U - TS \quad (1.6.1)$$

and Gibbs (free) energy (sometimes called “free enthalpy”):

$$G = U + pV - TS = H - TS \quad (1.6.2)$$

(T , U , H , S denoting thermodynamic temperature, internal energy, enthalpy and entropy, respectively). Work in an isothermal process under constant volume equals the Helmholtz energy change:

$$\Delta A = \Delta U - T\Delta S$$

(for a spontaneous process $(\Delta A)_{TV} < 0$). Work in a process under T , p const. is equal to the Gibbs energy change:

$$\Delta G = \Delta H - T\Delta S = \Delta A + p\Delta V$$

(for a spontaneous process $(\Delta G)_{Tp} < 0$). In processes taking place in condensed systems, ΔV is negligibly small so that $\Delta A \approx \Delta G$.

Chemical potential. – The concept of chemical potential is closely related to the Gibbs energy. It shows how the Gibbs energy of a system is changed when a small amount of one component is added to it. The concept makes it possible to treat equilibria in mixtures and solutions. Chemical potential of a component (say B) in the reaction mixture is defined as

$$\mu_B = \left(\frac{\partial G}{\partial n_B} \right)_{T,p} = \left(\frac{\partial A}{\partial n_B} \right)_{T,V}$$

where n_B stands for the (chemical) amount of B (colloquially called “number of moles”). It can be shown that the Gibbs energy change in reaction $A + B \rightarrow C$ is closely connected with the standard equilibrium constant:

$$\Delta_r G^\circ = -RT \ln K^\circ = \mu_C^\circ - (\mu_A^\circ + \mu_B^\circ) \quad (1.6.3)$$

* HERMANN VON HELMHOLTZ, 1821–1894, German scientist and philosopher, made fundamental contributions to physiology, optics, electrodynamics and meteorology but is best known for his statement of the law of conservation of energy. Helmholtz became professor of physiology at Königsberg in 1849, and in Bonn in 1855. In 1871 he took the chair of physics at the University of Berlin. It is interesting to mention that Helmholtz was completely unaware of Gibbs' work and his concept of free energy.

Analogously, for the activation equilibrium, we can write:

$$\Delta^\ddagger G^\circ = -RT \ln K^\ddagger = \mu_{\text{TS}}^\circ - (\mu_{\text{A}}^\circ + \mu_{\text{B}}^\circ) \quad (1.6.4)$$

The equation (1.4.14) shows that the Gibbs energy of activation determines the rate constant. From the Figure 1.6.2 one could get an impression that the reaction proceeds with a simultaneous increase of free energy. Of course this is not so: the proceeding of a reaction is always followed by a simultaneous decrease of free energy ($-\Delta_r G^\circ = RT \ln K^\circ$), *i.e.*, the larger the decrease in free energy, the larger is the equilibrium constant K° . One should bear in mind that only a very small fraction of molecules acquire enough energy to form the activated complex.

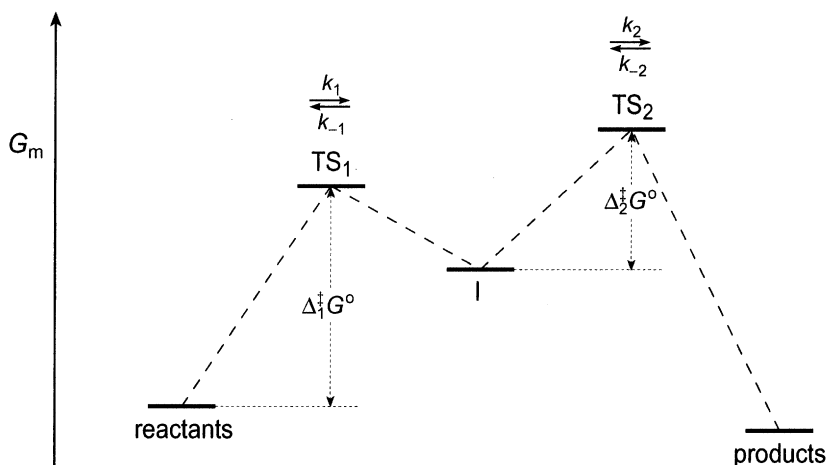
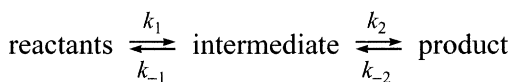


Figure 1.6.3. Activation profiles of a reaction with two transition states and the intermediate I where $\Delta_2^\ddagger G^\circ > \Delta_1^\ddagger G^\circ$.

Figure 1.6.3 is the reaction energy profile for a two-step reaction with two transition states, TS_1 and TS_2 . The overall reaction rate is determined by the step whose transition state has the largest energy. This step is called the rate-limiting (or rate-determining) step and is the “bottleneck” of the overall reaction rate. The letter I denotes the reaction intermediate. The reaction is a composite one, as shown in the scheme:



In Figure 1.6.3, the relative Gibbs energies determine the relations between the rate constants as follows:

$$k_{-1} > k_1 \text{ and } k_2 > k_{-2}$$

The lower the energy barrier, the higher is the rate. We can see that the largest energy barrier in the forward direction is between the intermediate I and the transition state TS_2 ($= \Delta_2^\ddagger G$). This step is therefore the rate-determining or rate-limiting step.

Figure 1.6.4 is an example of a two-step reaction in which the first step is rate determining because $\Delta_1^\ddagger G^\circ > \Delta_2^\ddagger G^\circ$. I is the reaction intermediate and $\Delta_{-1}^\ddagger G^\circ$ is the Gibbs energy of activation for the reverse reaction from the intermediate into reactants A + B.

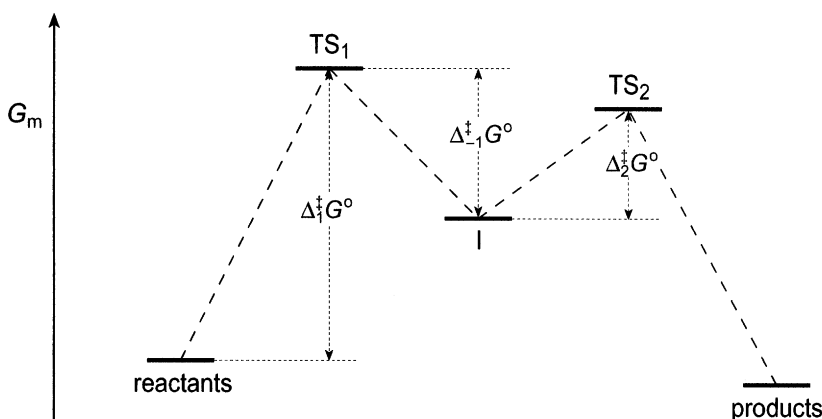


Figure 1.6.4. Activation profiles for a two-step reaction where $\Delta_1^\ddagger G^\circ > \Delta_2^\ddagger G^\circ$; I is the reaction intermediate and $\Delta_{-1}^\ddagger G^\circ$ is the Gibbs energy of activation for the reverse of the intermediate into reactants.

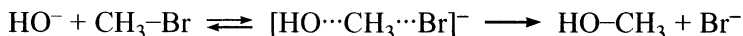
1.7. BIMOLECULAR AND UNIMOLECULAR NUCLEOPHILIC SUBSTITUTIONS (S_N2 AND S_N1 SUBSTITUTIONS)

The ideas of reaction mechanisms of substitution reactions came primarily from organic chemistry. The first notion was that the initial reaction step is the addition of the reactant to the substrate, yielding a new molecular compound from which the group to be replaced is eliminated. This idea was put forward in 1909 but the relevant publications appeared in 1911.²⁷ The same year Le Bel* suggested²⁸ that the entry of the nucleophilic reagent and the departure of the leaving group were two independent events in a simultaneous process.

* ACHILLE LE BEL, 1847–1930, French chemist.

These ideas were further elaborated by Lewis (Gilbert Newton Lewis, 1875–1946), and especially by F. London.²⁹ In this way, bimolecular and monomolecular mechanisms were introduced. C. K. Ingold* *et al.* designated these mechanisms as S_N2 and S_N1.³⁰

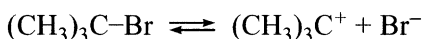
Thus, in an S_N2 reaction (substitution, nucleophilic, bimolecular), such as:



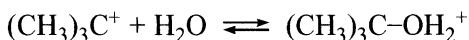
OH[−] participates in the activated complex, which is the reason why the reaction rate depends on the concentration of both reactants, HO[−] and CH₃–Br.

The entry of OH[−] takes place from the opposite side of the bromine atom (*trans*-attack). The mechanism labeled S_N2 covers a wide variety of specific reactions which occur by the common mechanism. They all proceed with inversion of configuration at the reacting carbon, and they all exhibit second-order kinetics. These reactions are affected by several factors, including nucleophilicity of the attacking group (more basic electron pairs tend to be more nucleophilic, *i.e.*, they exhibit larger affinity for the carbon atom), the nature of the leaving group, the structure of the carbon environment where the displacement ensues, and the nature of the solvent.

An example of an S_N1 substitution reaction is the reaction of *t*-butyl bromide with OH[−]. The *trans*-attack is sterically hindered, because the alkyl groups are now on the carbon. The slowest process, which determines the overall reaction rate, is the formation of the carbocation:



Carbocation is a Lewis acid and the reaction with water is fast:



The ionic intermediate dissociates water and with OH[−] yields *t*-butyl alcohol as the final reaction product. In this mechanism the slowest (rate determining or rate limiting) process is the dissociation of bromide; therefore the overall reaction rate does not depend on the methoxide ion concentration. This is the reason why this mechanism is called S_N1 (substitution, nucleophilic, unimolecular). It is obvious that the S_N1 mechanism will be favored in

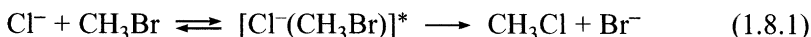
* CHRISTOPHER KELK INGOLD, 1893–1970, professor of chemistry at the University College London. Besides his contributions in the field of organic reaction mechanisms, he is known for taking part in devising the so-called Cahn, Ingold, Prelog priority rules: the configuration about any carbon-carbon double bond can be specified using a set of rules devised in 1964 by the mentioned authors. The rules are incorporated into the IUPAC nomenclature system. When applied to naming alkenes, the rules are known as the E-Z system.

polar solvents, because the rate determining step involves separation of charges (ionization).

1.8. NOVEL VIEWS ON THE MECHANISM OF BIMOLECULAR SUBSTITUTIONS IN THE GAS PHASE

The rate of S_N2 reactions depends on the concentrations of both reactants because both reactants participate in the transition state (see Figure 1.6.1). We say that such a reaction is of the second order, *i.e.*, of the first order with regard to each of the two reactants. The reaction can proceed in one step, which is called the “concerted mechanism”. In Figure 1.6.1, the reaction intermediate is in the vicinity of the transition state. However, it was realized that such a classical energy profile for a S_N2 reaction cannot be applied to all S_N2 reactions. It is characteristic of such an energy profile that the energy of the transition state separates the reactants from the products and that this energy is higher than that of reactants and products. However, this is not always the case, especially not in S_N2 reactions in the gas phase. In 1977, it was anticipated^{31,32} that the S_N2 reactions in gas phase, under certain circumstances, might proceed over two energy minima, the energy of the reactants being higher than that of the transition state. In gas reactions of the S_N2 type, stable intermediates were observed, but they could not be transferred into products.³³ However, this has been recently accomplished and stressed as a great success, offering a new insight into the mechanism of S_N2 gas reactions.

Special attention has been paid to the reaction:



whose energy profile was established, as shown in Figure 1.8.1.³⁴ The energies of the complexes $\text{Cl}^-(\text{CH}_3\text{Br})$, $\text{Br}^-(\text{CH}_3\text{Cl})$ and of the transition state (Figure 1.8.1) were determined experimentally.^{35–38} Relative energies of the reactants $\text{Cl}^- + \text{CH}_3\text{Br}$ and the products $\text{Br}^- + \text{CH}_3\text{Cl}$ are data from the literature.³⁹ Two minima in the figure refer to the ion-dipole complexes, which are stable intermediates on both sides of the transition state.

Under certain circumstances, it has been shown that the S_N2 reactions of such stable intermediates can be initiated using infrared laser light.^{31,32} The reaction can be also activated by collisions with argon atoms.³⁵ The kinetic energy release distribution for metastable dissociation of the $\text{Cl}^-(\text{CH}_3\text{Br})$ species has been measured,³⁴ which may serve as a model for the intermediate in the bimolecular reaction (1.8.1).

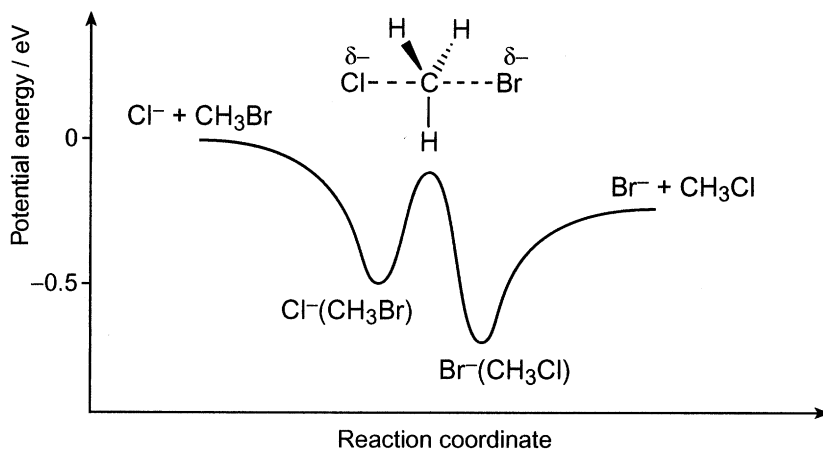


Figure 1.8.1. Schematic potential energy diagram for the S_N2 reaction: $\text{Cl}^- + \text{CH}_3\text{Br} \rightarrow \text{Br}^- + \text{CH}_3\text{Cl}$. (Reproduced by permission from S. T. Graul and M. T. Bowers, and the American Chemical Society.³⁴)

The reaction $\text{Cl}^- + \text{CH}_3\text{Br}$ is exothermic ($\Delta H^\circ = -29.3 \text{ kJ mol}^{-1}$), but only a small fraction of this energy (about 1 kJ mol^{-1}) is released as the energy of translation. The theory predicts that a substantial part of energy remains in CH_3Br , as vibrational excitation, which is significantly larger than one would expect from the statistical energy distribution.

The species $\text{Cl}^-(\text{CH}_3\text{Br})$ were prepared by collisions between the Cl^- ion and CH_3Br at 3000 K. The Cl^- ion was produced in a mass-spectrometer so that CCl_4 absorbed an electron with a simultaneous dissociation of Cl^- . The complex $\text{Cl}^-(\text{CH}_3\text{Br})$, formed in this way, lives too short to be detected (shorter than $20 \mu\text{s}$, which is the time the nascent complex needs to pass the distance between the ion source and the detector). However, at a pressure of 0.1 atm of methyl bromide (collision frequency $\approx 5 \times 10^6 \text{ s}^{-1}$), the short-lived intermediate could be cooled down with third party collisions and its life time increased to more than $20 \mu\text{s}$, which is sufficient to detect the intermediate in a mass-spectrometer and to follow its metastable monomolecular dissociation.

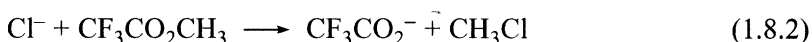
The nascent $\text{Cl}^-(\text{CH}_3\text{Br})$ collision complexes have internal energies of 0.5 eV or greater,⁴⁰ and lifetimes of less than 10^{-6} s .³⁴ The calculations also show³⁷ that the energy barrier of the transition state is by about $4\text{--}8 \text{ kJ mol}^{-1}$ lower than the energy of separated reactants,⁴⁰ which can be also inferred from the kinetic measurements.⁴¹ Reaction (1.8.1) proceeds with about 1% of bimolecular collisions only,⁴² enabling collision stabilization of the $\text{Cl}^-(\text{CH}_3\text{Br})$ reaction complex. The complex was trapped with enough internal excitation³⁴ so that the unimolecular disintegration yielding free Br^- could be successfully followed. The reaction was found practically irreversible,³⁵ in agreement

with its reaction energy profile (high energy barrier for the transition state formation from $\text{Br}^-(\text{CH}_3\text{Cl})$, Figure 1.8.1).

In summary, it is claimed³⁵ that in reaction (1.8.1) the existence of two intermediate complexes, $\text{Cl}^-(\text{CH}_3\text{Br})$ and $\text{Br}^-(\text{CH}_3\text{Cl})$, is observed. From the first intermediate the products can be obtained in about 50% yield, which is much more than the yield of the direct bimolecular reaction; the second intermediate, $\text{Br}^-(\text{CH}_3\text{Cl})$, yields practically only Br^- and CH_3Cl .

It has been shown previously⁴³ that the rates of nucleophilic substitutions in solutions can be as many as 20 orders of magnitude lower than in the gas phase. In aqueous solution, the reacting chloride is substantially stabilized by hydration and cannot react with CH_3Br until the bound water is removed. In the gas phase, Cl^- and CH_3Br connect easily, with a simultaneous potential energy decrease, causing stabilization of the formed intermediate (see Figure 1.8.1). The negative electric charge in $\text{Cl}^-(\text{CH}_3\text{Br})$ is better dispersed than in Cl^- , which facilitates the dissociation of bromide and the formation of the activated complex.

Analogous results were obtained in studying reaction (1.8.2):³⁶



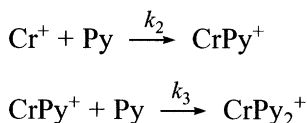
The reaction has an energy profile analogous to reaction (1.8.1).

The investigations described helped overcome the gap between the kinetics of the $\text{S}_{\text{N}}2$ reactions in the gas phase and in the liquid phase, and in this way broaden our knowledge of the mechanism of bimolecular reactions.

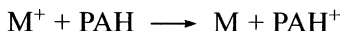
Studies of gas phase reactions of metal ions with organic ligands using mass spectrometry are rather recent;⁴⁴ only relative rates could be deduced because of the difficulties in determining the ligand gas phase concentration. Srzić and co-workers⁴⁵ determined the gas phase concentration of a polycyclic aromatic hydrocarbon (PAH) from the concentration ratio $\text{PAH}_2^+/\text{PAH}^+$ in the equilibrium:



for which the thermodynamic parameters are known. This enabled the calculation of the second order rate constants from the set of pseudo first order rate constants for the ligation reactions of positive metal ions with pyrene (Py). Thus, the rate constants at 25 °C for the reactions:



are 7.8×10^{10} and $6.8 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, respectively, as compared with 3.4×10^{10} and $3.3 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the corresponding reactions of Fe^+ ions. Thus, $k_2(\text{Cr}^+) \approx 2 k_2(\text{Fe}^+)$ and $k_3(\text{CrPy}^+) \approx 2 k_3(\text{FePy}^+)$, whereby $k_1 = 1.3 \times 10^{10} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ is the rate constant for the charge exchange reaction:



which produces the Py^+ necessary for the equilibrium reaction.

1.9. CLASSIFICATION OF REACTION MECHANISMS IN INORGANIC CHEMISTRY INVOLVING METAL COMPLEXES (D, A, I_d AND I_a MECHANISMS)

According to Langford and Gray,⁴⁶ most of the inorganic substitution reactions can be classified as dissociation (D) or association (A) processes. Let us consider a replacement of X by Y in a metal complex where we are concerned with the bond breaking and the bond making between metal M and ligands X and Y, respectively, the remaining ligands being omitted:



The overall reaction (1.9.1) proceeds in two steps, (1.9.2) and (1.9.3). Figure 1.9.1 shows the energy profile for this D or $\text{S}_{\text{N}}1(\text{lim.})$ mechanism. Reaction step (1.9.2) is a slow dissociation. In the transition state TS_1 , the bond $\text{M} \cdots \text{X}$ is practically broken. The entering ligand Y does not participate in the transition state, which is the highest energy barrier. Therefore, the reaction rate does not depend on the nature of the entering ligand (with the exception of effects that might be due to solvation). The reaction intermediate M has a reduced coordination number, and its relative stabilization (lower Gibbs free energy) is due to solvation (formation of bonds with the solvent, stabilizing the chemical species).

Formation of the second transition state (TS_2) requires relatively little energy, primarily needed for elimination of the bound solvent. In this way, the location for new coordination is freed and the weak bond $\text{M} \cdots \text{Y}$ is established. As seen from Figure 1.9.1, the reaction is exothermic. The reaction product M-Y is stable because the reverse reaction requires a relatively high Gibbs free energy.

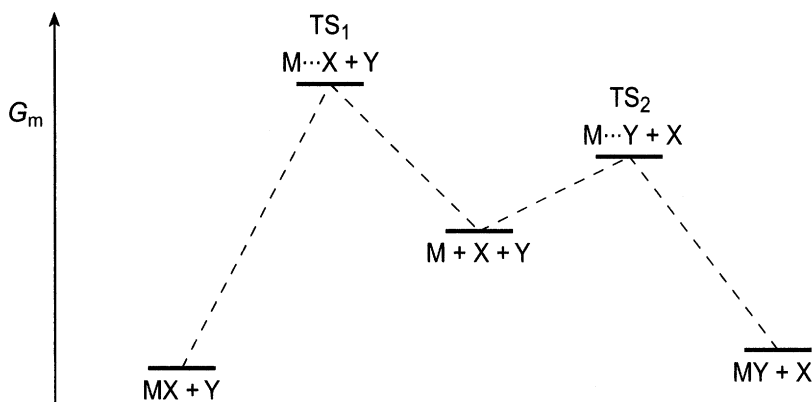


Figure 1.9.1. Activation profile for a D-type reaction [$\equiv S_N1(\text{lim.})$].

We can conclude:

In a D mechanism [$\equiv S_N1(\text{lim.})$], the intermediate has a reduced coordination number. In the transition state, the bond between the metal and the leaving ligand is virtually broken, and the bond with the incoming ligand has not yet been established.

On the other hand, if the overall process (1.9.1) follows an associative (A) mechanism, identical with the $S_N2(\text{lim.})$ mechanism in Ingold's symbolism, then the reaction scheme is:



Figure 1.9.2 shows such a reaction energy profile:

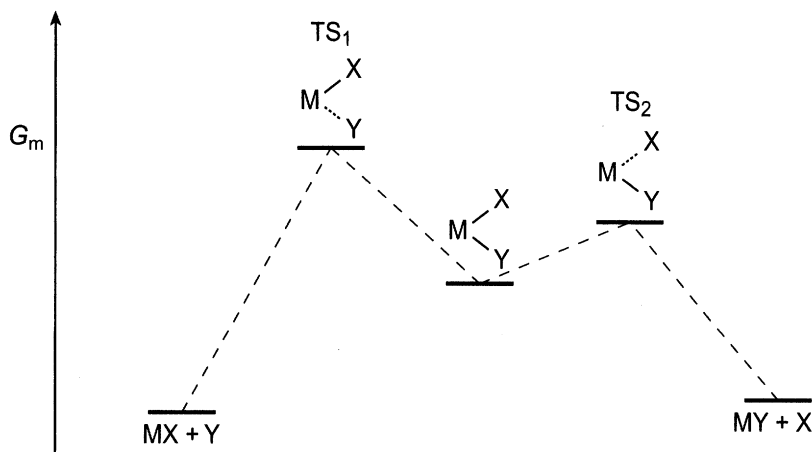


Figure 1.9.2. Activation profile for an A-type reaction [$\equiv S_N2(\text{lim.})$ mechanism].

If reaction (1.9.1) follows an A mechanism, then the intermediate will have an increased coordination number. In the transition state (TS_1), the bond with the entering ligand Y is largely established, while the bond towards the leaving ligand X is not essentially weakened. The reaction rate depends strongly on the nature of the entering ligand Y because Y participates in the transition state.

In case reaction (1.9.1) follows an I mechanism (I stands for “interchange”), then the interchange can be either of the I_d type (interchange, dissociative), or of the I_a type (interchange, associative). The I_d mechanism is identical to Ingold's S_N1 mechanism, and I_a to Ingold's S_N2 mechanism.

It is characteristic of mechanisms $D \equiv S_N1(\text{lim.})$ and $I_d \equiv S_N1$ that their rates are independent of the nature of the entering ligand Y. On the other hand, it is characteristic of mechanisms $A \equiv S_N2(\text{lim.})$ and $I_a \equiv S_N2$ that their rates depend on the concentration of the entering ligands Y, because Y participates in the transition state.

I mechanisms, or “concerted” mechanisms, are the interchanges of ligands X and Y between inner and outer coordination spheres of the metal. These mechanisms can involve different transition states, where I_d and I_a are extreme (border) cases.

The following conclusion can be made:

When the replacement rate of an outgoing ligand depends on the nature (and concentration) of the entering ligand, then A and I_a mechanisms are possible. If the replacement rate is independent of the nature of the entering ligand, then the mechanism is D or I_d .

The D and I_d mechanisms are difficult to distinguish, because the differences depend on the depth of the energy well of the intermediate. If the intermediate is relatively stable and lives long enough (on the time scale probably longer than 10^{-10} s) to be able to discriminate (distinguish) the entering ligands, it will react with them at different rates. This is the condition for a D mechanism. Thus, if two entering ligands Y' and Y'' are present (competition reactions), the products will not be formed statistically (e.g., 50% MY' and 50% MY''), but one of the products will predominate, which strongly indicates that the D mechanism is operative. On the other hand, if the intermediate is exceedingly short-lived (shorter than 10^{-10} s), it cannot discriminate between the entering ligands. The free coordination position is then occupied statistically, namely according to entering ligands' concentrations. This is the so-called “accidental bimolecularity”. Here the reaction rate depends on the entering ligand concentration but not on its nature (this statement disregards the ligands' solvation effects, steric effects, and electric dipole charges effects, which usually ought not to be neglected).

The leaving ligand X leaves the coordination shell and enters the solvation shell. The return from the solvation shell into the coordination shell is

possible, but not if the entering ligand is in great excess and dominates the solvation shell. This is commonly the case because replacements are usually carried out under *pseudo*-first order conditions (*e.g.*, Y is in 10 to 100 fold excess over X). In such an I_d process the reaction rate depends on the entering ligand concentration, but not on its nature.

The distinction between D and I_d mechanisms in polar solvents which can coordinate to the metal is very difficult. Therefore, the replacements of water in $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$ with various anions as entering ligands (anation processes), as well as with uncharged entering ligands, have been extensively investigated.⁴⁷⁻⁵²

1.9.1. The collision theory in solutions

In solutions, the molecules do not move as freely as in the gas phase. Instead, they move in the potential field of neighboring molecules. If two molecules come into contact by random displacements in solution, they will collide a number of times before they separate. This is called an "encounter." If the colliding particles do not react, their encounters are determined by the Brownian movement; they are random and diffusion controlled by Fick's laws. If a bimolecular reaction occurs in every collision, it is said that the reaction is diffusion controlled. The rate of such reactions is the maximum rate attainable in a liquid medium. Most reactions have large energy barriers and steric requirements; therefore, very many collisions are needed before a reaction will take place. An example of a reaction that probably occurs in every collision is the recombination of two methyl radicals to ethane in aqueous solution:



The rate constant of the disappearance of $\text{CH}_3^{\cdot}(\text{aq})$ radicals is $3.2 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 25 °C. The activation energy is 16 kJ mol^{-1} . The rate constant in the gas phase is $2.0 \times 10^{10} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and the activation energy is zero.⁴⁷

The theory predicts the Arrhenius frequency factors for bimolecular reactions to be somewhat larger in solutions than in the gas phase, but there is not much evidence to support this prediction. The average value of the frequency factor for the second order reactions in solutions is $10^{11} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, the same as in the gas phase.⁴⁷

In gases, encounter frequency is much larger than in a solvent. On the other hand, in the solvent the reacting molecules stay longer in each other's vicinity, because the migration of molecules is slow in media of high viscosity. During an encounter, the two molecules may attain enough energy for a

successful encounter. The activation energy in solution is now a composite quantity due to the interaction of the solvent with the activated complex. Therefore, the energy of the entire activated structure must be considered. This is the reason why the statistical treatment is very complicated and difficult to perform.

1.9.2. Primary kinetic salt effect

The thermodynamic approach to the theory of the activated complex enables a relatively simple treatment of the reactions in solutions. An example is the well-known thermodynamic treatment of the primary kinetic salt effect, also known as the kinetic salt effect. This is a variation of the rate constant of the reaction between ions with the ionic strength of the solution. If the reacting ions have the same charge sign (*e.g.*, reactions between two cations or two anions), then increasing the ionic strength (addition of an inert salt) will increase the reaction rate constant. On the other hand, ions of opposite charge will react more slowly in solutions of increased ionic strength.

Quantitative relations of the primary kinetic salt effect are well explained by the Debye-Hückel* theory of strong electrolytes and the transition state theory.

The reaction rate is sensitive to the net force between the reacting ions, and the interionic force is sensitive to the ionic strength determining the extent of the ionic atmosphere around the ion.

It follows from the Debye-Hückel theory that, at low concentrations, the activity coefficient γ_i of an ion i of charge number z_i is given by:

$$\log \gamma_i = -Az_i^2 I^{1/2} \quad (1.9.6)$$

where I is the ionic strength of the solution and parameter A depends on the solvent and temperature (it is $0.509 \text{ dm}^{-3/2} \text{ mol}^{1/2}$ for water at 298 K).

The ionic strength I is defined by:

$$I = \frac{1}{2} \sum_i c_i z_i^2$$

where c_i and z_i are the concentration and the charge number of each ionic species in the solution.

* PETER DEBYE, 1884–1966, a Dutch physicist and chemist, Nobel Prize for chemistry for 1936;

ERICH HÜCKEL, 1896–1980, a German physicist.

Thermodynamic equilibrium constant of activation (expressed in terms of the activities of reactants, A and B, and the transition state, $X^\ddagger$) is defined as:

$$K^{\ddagger 0} = \frac{a_{X^\ddagger}}{a_A a_B} = \frac{[X^\ddagger]c^0}{[A][B]} \frac{\gamma_{X^\ddagger}}{\gamma_A \gamma_B} \quad (1.9.7)$$

where $c^0 = 1 \text{ mol dm}^{-3}$ and the concentration of the activated complex is:

$$[X^\ddagger] = \frac{K^{\ddagger 0}[A][B]}{c^0} \frac{\gamma_A \gamma_B}{\gamma_{X^\ddagger}} \quad (1.9.8)$$

Now, we can combine the rate laws (a) and (b) (*cf.* eqs. 1.4.3 and 1.4.4):

$$(a) \quad \frac{d[P]}{dt} = k^\ddagger [X^\ddagger]$$

$$(b) \quad \frac{d[P]}{dt} = k[A][B]$$

with eq. (1.9.8) to obtain:

$$k[A][B] = k^\ddagger [X^\ddagger] = k^\ddagger K^{\ddagger 0} (c^0)^{-1} [A][B] \frac{\gamma_A \gamma_B}{\gamma_{X^\ddagger}}$$

and

$$k = k^\ddagger K^{\ddagger 0} (c^0)^{-1} \frac{\gamma_A \gamma_B}{\gamma_{X^\ddagger}}$$

As the ionic strength tends to zero, the activity coefficients tend to 1, so the limiting value of the rate constant k_0 is:

$$k_0 = k^\ddagger K^{\ddagger 0} (c^0)^{-1}$$

and further:

$$\frac{k}{k_0} = \frac{\gamma_A \gamma_B}{\gamma_{X^\ddagger}}$$

The charge of the activated complex is the sum of the charges of A and B; $z_{X^\ddagger} = z_A + z_B$. Thus, we can write:

$$\log \frac{k}{k_0} = -AI^{1/2}[z_A^2 + z_B^2 - (z_A + z_B)^2] = 2Az_A z_B I^{1/2}$$

and for aqueous solutions:

$$\log \frac{k}{k_0} = 1.02 z_A z_B (I/c^\circ)^{1/2}$$

To test the equation, we usually plot the logarithm of the rate constant against $I^{1/2}$. The result should be linear, with the slope of $2Az_A z_B$. If one of the reactants is neutral, there is no kinetic salt effect.

1.9.3. IUPAC recommendations for the representation of reaction mechanisms

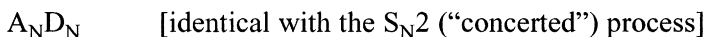
In more than 20 years, the IUPAC Commission on Physical Organic Chemistry has met several times trying to define recommendations for the nomenclature of reaction mechanisms.

A potential revision of the Ingold symbolism has been vigorously discussed. Description of both systems has been published in *Pure Appl. Chem.*^{53a} An extensive report by Guthrie and Jencks⁵⁴ is very informative.

The Ingold system of nomenclature was designed primarily for organic chemistry. Several alternatives were suggested. The proposal of Langford and Gray is nowadays extensively used by inorganic chemists.⁴⁴

Around 1980, the IUPAC Commission decided that the revision of the Ingold system was impractical. It was concluded that actually two systems would be required: a simple version for the description of the main characteristics of a mechanism, and a more detailed one that could eventually form the basis for a computerized information system.⁵⁴ Though it appears that these recommendations have not been especially well accepted, they nevertheless deserve attention. Guthrie and Jencks maintain that the new system will simplify the teaching of chemistry and help students to better understand how the chemical bonds are broken and formed.

The new system adopted the basic symbols from the nomenclature of inorganic reaction mechanisms already in use: A (for an associative mechanism) and D (for a dissociative mechanism). Thus, the new symbol for a S_N2 mechanism is:



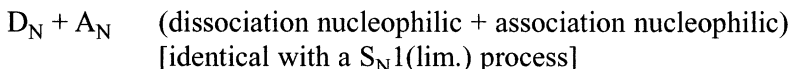
where N stands for a nucleophilic (or nucleofugic process), which tells us that

the entering and leaving groups carry a free electron pair. The symbol $A_N D_N$ has no punctuation because we deal with a concerted one-step mechanism.

By analogy, an electrophilic displacement has the symbol:

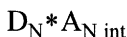


Substitution of the S_N1 type, in which a relatively stable intermediate is formed, stable enough to discriminate (distinguish) entering ligands, has the symbol:



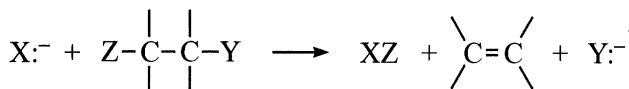
Separation of the symbols indicates two discrete processes: a dissociation in which the leaving group is a nucleophile (carries its free electron pair) and then the intermediate can diffuse through the solvent before it reacts with a nucleophilic reagent.

If in the first reaction step an unstable carbocation is formed, it will react with a neighboring nucleophilic molecule faster than it can diffuse away. Such a fast reaction can be a "preassociation" with a nucleophile, a fast formation of an "intimate" (or "contact") ion pair. The asterisk indicates a short-lived intermediate and the subscript "int" indicates an ion pair intermediate:



The detailed glossary of symbols (about 20) recommended by IUPAC was listed by Guthrie and Jencks.⁵⁴ The system appears complicated, at least at first glance. The application of the system provides the best demonstration of its use and usefulness.

The one-step E_2 elimination, *e.g.*, the reaction



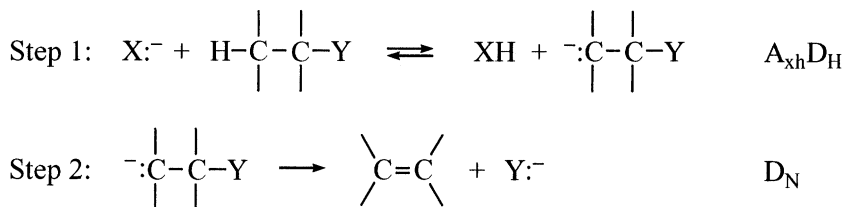
is characterized by the symbols:



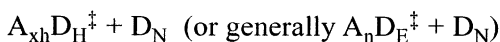
Here, $A_n D_E$ refers to removal of the electrofugic group Z and tells us that an association of Z with the nucleophile $X:^-$ has taken place. The symbol D_N refers to dissociation of the leaving group $Y:^-$ with its electron pair. The two C atoms are "core atoms". The use of subscripts indicates that the bond undergoing change is between non-"core atoms". This means that the bonding of

$X:^-$ to Z is a nucleophilic association, thus symbolized by A_n . This association does not involve the two carbon atoms which are “core-atoms” (the two C atoms will become double bonded). If $Z = H$, the symbol A_{xh} indicates that the hydron (proton, deuteron, or triton) dissociates from one of two carbon atoms (“core-atoms”). Absence of punctuation tells us that the one step (“concerted”) mechanism has taken place.

Following this principle, the $E1cB$ mechanism for β -elimination of the type:

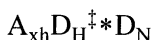


has the symbol:



The punctuation shows that the hydrogen removal yields a relatively stable intermediate, the carbocation. The following separate step is the dissociation of the leaving group, $Y:^-$. The symbol ‡ (unfortunately similar to the symbol for the activated complex) means that hydrogen removal is the rate-limiting step.

If the leaving group leaves very rapidly, *i.e.*, the second step is very fast, the protonated base, XH , cannot diffuse away and the reaction has the symbol:



Symbols: + (on the line) means: stepwise process

* (on the line) means: same as +, but the intermediate is short lived

‡ (superscript) means: preceding step is rate limiting

Some of the IUPAC recommendations presented apply primarily to physical organic chemistry, but the recommendations will certainly influence the development of naming inorganic reaction mechanisms, as well. The idea is to remove mechanistic ambiguities of the traditional system.

Resistance to this new system is expected to be strong. Guthrie and Jencks⁵⁴ stressed that the new system of naming mechanisms deserves attention. It appears that the present naming of mechanisms is incomplete and should be improved. For more detail see the references cited.

1.9.4. Nomenclature of coordination compounds

Recommendations of the IUPAC committee regarding nomenclature of coordination compounds are contained in their publications.^{53a,53b}

In writing the formula of a complex, the central atom is given first, for instance $[\text{Fe}(\text{CN})_6]^{4-}$, hexacyanoferrate(II). The complex is anionic and the characteristic ending is “ate”. The name of the central atom is not changed for neutral or cationic complexes; thus $[\text{Fe}(\text{H}_2\text{O})_6]^{2+}$, hexaaquairon(II) (not aquo). The acid $\text{H}_4[\text{Fe}(\text{CN})_6]$ is named tetrahydrogen hexacyanoferrate(II). The formal oxidation state of the central atom is indicated by a Roman numeral in parentheses after the name of the complex, but with no space between them. The name of the complex species is written as one word. Negatively charged ligands (Cl^- , SO_4^{2-} , PO_4^{3-} , chloro, sulfato, phosphato, *etc.*) all end in “o”. Ligands should be listed in alphabetical order (previously, the negatively charged ligand preceded uncharged ligands). Prefixes such as di-, tri-, bis-, *etc.* do not determine the alphabetic order. Such ligands were previously quoted in the order of increasing complexity.

In writing the formulas of compounds, the symbol of the central (metal) atom is written first, unlike writing the name of a compound when the metal name is written last, followed by the anionic ligands in alphabetical order, then the neutral ligands, also in alphabetical order. The previously used ligand aquo is now replaced by aqua. When an H atom is coordinated, it is regarded as H^- and therefore named hydrido, though its chemical behavior is nearer to H^+ than H^- . The ligand thiocyanato-*N* ($-\text{NCS}^-$) may now be written thiocyanato- κN , using the Greek letter *kappa* (κ). Similarly ($-\text{SCN}^-$) could be written thiocyanato-*S* or thiocyanato- κS .

A ligand may be bonded to a metal through several atoms. This is denoted by the prefix η (Greek letter *eta*), with a superscript indicating the number of atoms bonded. We talk of the “hapticity” (from Greek *hapto*, which means to fasten). See also Chapter 9. An example is the complex pentahaptocyclopentadienyl ligand, C_5H_5^- , or tricarbonyl(η^5 -cyclopentadienyl)manganese:

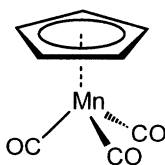


Figure 1.9.3. Tricarbonyl(η^5 -cyclopentadienyl)manganese: the pentahapto bonding (η^5) is depicted, showing the delocalized nature of the π electrons of the cyclopentadienyl group (C_5H_5^-).

The task of providing nomenclature of inorganic chemistry was, as already mentioned, assigned to the IUPAC, whose *Rules for Inorganic Nomenclature* were published and revised in 1958, 1970 and 1990. Since then, many new compounds have appeared, which were difficult to name using the 1990 rules. Therefore, the IUPAC Commission on the Nomenclature of Inorganic Chemistry thoroughly revised the last edition of the "Red Book", and the revised edition is in two parts. Whilst Part I is mainly concerned with general inorganic chemistry, Part II, which recently appeared,* deals with the specialized systems, based on the fundamental nomenclature described in Part I of "1990 Rules".

1.10. DIRECT OBSERVATION OF THE ACTIVATED COMPLEX

Spectroscopy of species in the transition state region was developed in the last fifteen years. In a typical experiment, a femtosecond pulse ($1 \text{ fs} = 10^{-15} \text{ s}$) is used to excite the reactant, producing a dissociative state that corresponds to the activated complex, also called the transition state. The frequency of the second pulse is set at the absorption frequency of one of the free fragmentation products, which can be traced by laser-induced fluorescence. In this way, it has been found that the activated complex survives a few hundred of femtoseconds only.

In a chemical reaction, old chemical bonds are broken and new bonds are formed. In the gas phase, a rough estimate of the time needed for this event is the time of a collision, which is about 10^{-12} s . In this time, a molecule of an average thermal speed of ≈ 100 to 1000 m s^{-1} passes a distance of 0.1 to 1 nm ($= 1$ to $10 \text{ \AA}$). Thus, the whole trip from reagents to products involves changes in the internuclear separation of $\approx 10 \text{ \AA}$, which takes 10^{-12} – 10^{-11} s . According to J. C Polanyi and A. H. Zewail,⁵⁵ we are used to look at the transition state of a reaction $A + BC \rightarrow AB + C$ as $(ABC)^{\ddagger}$. In reality, there is an agglomeration of transition states caused by collisions of reactants of different collision energies, under different angles and collision parameters. The time available for the observation of the transition state is a period of 1–10 ps (10^{-12} – 10^{-11} s). Therefore, the intervals at which the configuration and energy of the transition state should be recorded is about 1% of the time interval mentioned, viz. 10^{-14} – 10^{-13} s (10–100 fs).⁵⁵ The observation of the activated com-

* *Nomenclature of Inorganic Chemistry II*, Recommendations 2000, Edited by J. A. McCleverty and N. G. Connelly, University of Bristol; Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, CB4 0WF, UK. See also: S. F. A. Kettle, *Physical Inorganic Chemistry*, Oxford University Press, New York 1998, Chapter 3, pp. 24–50.

plex (or transition state) must therefore be performed in these femtosecond intervals.

1.10.1. Spectroscopy in the transition state region

In the last fifteen years several papers were published in this field.^{56–60} Lasers have been used in the preparation of some initial states or in determinations of various reaction products.^{61–63} Numerous observations have been reported on reactive transition species when light is absorbed and some when light is emitted.⁶⁰ Table 1.10.1 contains some of these observations.

Table 1.10.1. Observed reactive transition region species:
(a) when light is absorbed, and (b) when light is emitted

Reagents	Products	Measured (fluorescence)	Ref.
(a) $\text{K} + \text{HgBr}_2 + h\nu$	$\text{KBr} + \text{HgBr}^*$	of HgBr^*	64
$\text{Xe} + \text{Cl} + h\nu$	XeCl^*	of XeCl^*	65, 66
(b) $\text{O}_3 + h\nu$	$\text{O}_2 + \text{O}$	$\text{O}_2 \cdots \text{O}$	67
$\text{NO}_2 + h\nu$	$\text{NO} + \text{O}$	$\text{N} \cdots \text{O}$	68

The femtosecond laser pulse enables direct observation of the bond breakage process.

In 1985, Zewail and coworkers⁵⁹ studied the reaction:

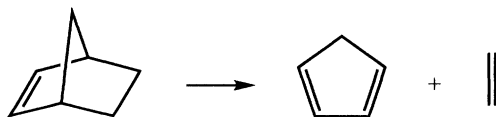


In their experiments, a femtosecond pulse (photolysis pulse) initiated the dissociation by exciting ICN with 306 nm light. The second pulse (probe pulse) monitored the recoiled CN at 388 nm. By observing the laser-induced fluorescence of the rotationally excited CN fragment as a function of the time delay between the photolysis and probe pulses, Zewail and coworkers measured the buildup time for the formation of the CN photoproduct. These measurements provided a direct view of the bond breakage process. It was found that the CN-signal is zero until the fragments separate by about 600 pm (= 6 Å). The time needed for this separation is about 205 fs (= 2.05×10^{-13} s). Zewail, Po-Yuan Cheng, and the graduate student D. Zhong (see A. M. Rouhi⁶⁹) followed the reaction between benzene and I_2 in real times from $t = 0$ to the product formation. Using a “molecular beam”, benzene and I_2 were brought to a distance of 0.3 nm (3 Å). The femtosecond laser initiated the reaction and

defined the time $t = 0$. A series of probe pulses followed, supplying information on the reaction progress. It was shown that the electron is expelled from benzene and transferred to I_2 . The result is the charge separation and the formation of I_2^- . Benzene attracts the I^- anion, while the neutral I atom dissociates, which results in the ionic bonding of $C_6H_5^+$ and I^- . The time needed for I^- dissociation from I_2^- is about 750 fs. Zewail and coworkers also found that the electron of I_2^- leaves I_2^- , being transferred back to $C_6H_6^+$. However, since the I-I bond is already stretched and weakened, it might get broken. A neutral $[C_6H_6-I]$ complex is thus formed and the iodine atom is released. All that can be detected on the time scale of 250 fs. On the other hand, the $[C_6H_6-I]$ complex is unstable and tends to disintegrate in benzene and another iodine atom. In this way, the femtosecond kinetics showed the complexity of the dynamics of the reaction of benzene and iodine (see also K. N. Houk *et al.*⁷⁰).

Zewail and coworkers⁷¹ also studied the mechanism of Diels-Alder reaction using the laser technique. This reaction was and still is the subject of many discussions.⁷² The dilemma is whether the addition of a double bond (or triple bond) to a diene, or the dissociation in the reverse reaction, follow a “concerted” (one step) mechanism or the additions proceed in two steps *via* an intermediate (diradical or a “zwitterion”). These two mechanisms correspond to different transition states.⁷² In the last 55 years it was thought that the Diels-Alder additions follow a one-step mechanism. The main argument in favor of a one-step mechanism was seen in the fact that the additions proceed with retention of configuration. It was thought that in a two-step mechanism the rotation about the carbon-carbon bond should lead to “stereochemical scrambling” of mixed structures. Zewail and coworkers found⁷² that both one-step and two-step mechanisms are possible. Their femtosecond kinetics showed that Diels-Alder additions are extremely fast and therefore there is not enough time for the rotation and scrambling of the stereochemical structures (see also K. N. Houk *et al.*⁷³).

Zewail and coworkers also studied the retro Diels-Alder reaction of norbornene,



the product of cycloaddition of cyclopentadiene with ethylene (and also of norbornadiene, the product of the cycloaddition of cyclopentadiene and acetylene).⁷¹ The reactions were studied in a molecular beam in order to isolate the elementary process, free of solvent perturbation. The time needed for the rotation of the C-C bond is about 1 to 10 ps. On the other hand, the reaction was

finished in about 160 fs, so there was not enough time for stereochemical scrambling of the structures involved.

Therefore, the intermediate that the authors observed is not in contradiction with the general observation that these additions proceed with a retention of configuration. Thus, the retention of configuration is not a valid criterion for solving the mechanism of Diels-Alder addition reactions. The reactions may follow either one- or two-step mechanisms, depending on several factors, such as energies, energy barriers, and the degree of asymmetry of structures.

Research done by Zewail and his coworkers is considered to be of great importance in the mechanistic sense. Thanks to the new laser technique, surprises and corrections of viewpoints are to be expected.⁷⁴

In typical Zewail's experiments, the laser system generates a pump pulse and a probe pulse. As shown in Figure 1.10.1, the pump pulse and the probe pulse leave the laser system at the same time. The probe pulse is diverted, so a time delay of a few femtoseconds is introduced between the two pulses. In fact, both pulses come from the the same source. The light of the probe pulse is forced to follow a longer route, as shown in Figure 1.10.1. Since the speed of light is $300\,000\text{ km s}^{-1} = 3 \times 10^{11}\text{ mm s}^{-1}$, the extension of the light path by 0.03 mm takes $0.03 / 3 \times 10^{11}\text{ s} = 100\text{ femtoseconds}$. In this way, the time delay between the pump pulse and the probe pulse is 100 fs.

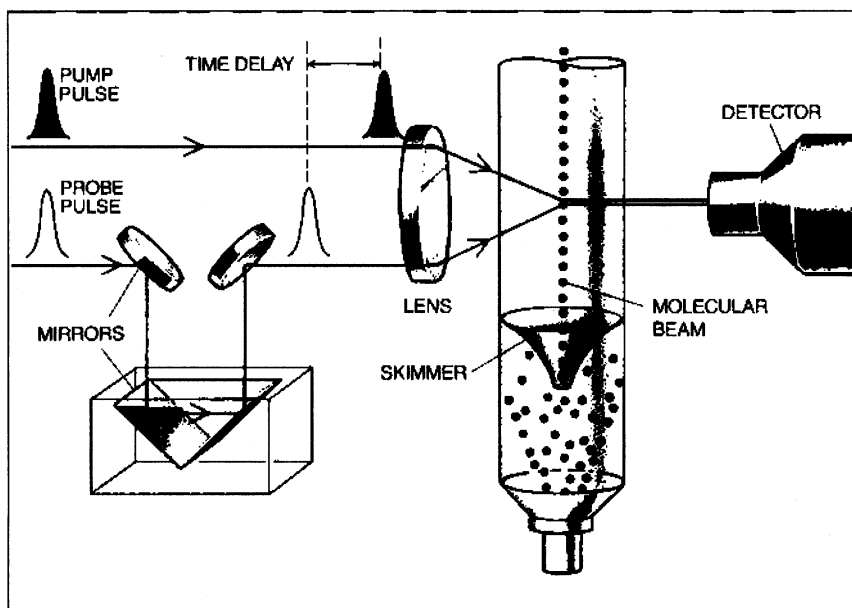


Figure 1.10.1. Zewail's femtosecond photography captures the dynamics of molecular reactions in real times⁷⁵ (reproduced by permission of the author and the *Scientific American*).

By 1984, the time resolution in molecular beam experiments was about three picoseconds (3000 fs). Zewail and coworkers achieved a critical femto-second time resolution as short as 6 femtoseconds. This corresponds to a “shutter speed” of about 10 femtoseconds. Because the speed of the typical molecular motion is about 1000 ms^{-1} , an adequate shutter resolution should be less than 100 femtoseconds.⁷⁵ Hence, the time delay between the pump pulse and the probe pulse is 100 fs.

Zewail’s basic idea is simple: when the probe pulse hits a molecule, a light quantum is emitted. Such interactions with numerous molecules result in a spectrum that is specific for the reactants A and B and for the transition state $(A\cdots B)^\ddagger$. In this way, Zewail and coworkers were able to determine the timing of these signals and follow the ultrafast motions of molecules, including direct observation of the transition state.

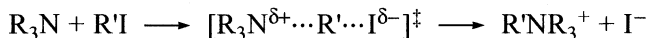
1.11. THE INFLUENCE OF THE SOLVENT ON THE REACTION RATES AND MECHANISMS

Solvents can influence the reaction rates and mechanisms. In some cases, the rates change, but not the mechanism of products formation. If solvents change the mechanism, they also change the rates at which the products are formed (equal rates are accidental). Solvents can entirely change the reaction path so that new products are formed. There are also cases when the reaction medium does not exhibit any considerable influence upon the reaction rate or its mechanism, so the rates are comparable in vacuum, in the melt, or in solvents of different ionization powers.

1.11.1. Influence of solvent polarity on the rates of chemical reactions

Reactions in which electrically charged species are formed proceed at increased rates in solvents of increased polarity. A typical example is the Menshutkin* reaction.

The Menshutkin reaction yields quarternary ammonium salts from amines:



For the reactants Et_3N and MeI , the relative rates in hexane, carbon tetra-

* NIKOLAI ALEKSANDROVICH MENSHTUTKIN, 1842–1907, Russian chemist, one of the founders of chemical kinetics.

chloride, chlorobenzene, acetonitrile and dimethylsulfoxide relate as 1 : 31 : 1200 : 12000 : 50000.⁷⁶ We see that, due to charge separation in the transition state, the rates are very sensitive to the solvent's nature. Polar solvents cause a decrease of the Gibbs energy of activation ($\Delta^\ddagger G^\circ$), and, which is very important, polar solvents suffer very small reorganization because they are already partly "frozen" (*e.g.*, water) due to hydrogen bonding. Thus, the ion solvation with polar solvents causes small entropy changes. On the other hand, apolar solvents are relatively free in the liquid phase and ion solvation with such a solvent significantly increases the order of the reaction system, leading to an entropy decrease.

As already pointed out, the influence of solvents on ionic equilibria and on the rates of chemical reactions cannot be exactly determined. Thus, we must be satisfied with some generalization, based on the simple model of separation of two opposite electric charges in different media. Let us assume a charge separation from an equilibrium distance (r_e) of 1 Å (10^{-10} m) to infinity in a medium of known relative permittivity $\epsilon_r = \epsilon/\epsilon_0$, where ϵ_0 is the permittivity in vacuum ($\epsilon_0 = 8.8542 \times 10^{-12} \text{ C}^2 \text{ J}^{-1} \text{ m}^{-1}$), and ϵ is the permittivity of the dielectric under study. Relative permittivity ϵ_r is broadly known as the dielectric constant (D); it is 1.0 for vacuum. The distance of 1 Å is the distance encountered in reality. A model for the charge separation often quoted is the ionization of HCl in the gas phase:⁷⁷



The separation of charges according to the above equation requires energy, which can be supplied by, *e.g.*, a thermostat. This energy must be equal to work W_{el} , needed for charge separation (to overcome the Coulomb forces):

$$W_{\text{el}} = \int_{r_e}^{\infty} F dr \quad (1.11.2)$$

where the Coulomb force F is:

$$F = \frac{z_A z_B e^2}{4\pi\epsilon_0\epsilon_r r^2} \quad (1.11.3)$$

and

$$W_{\text{el(vac)}} = \frac{z_A z_B e^2}{4\pi\epsilon_0\epsilon_r} \int_{r_e}^{\infty} \frac{dr}{r^2} = \frac{z_A z_B e^2}{4\pi\epsilon_0\epsilon_r r_e} \quad (1.11.4)$$

Finally,

$$\begin{aligned} W_{\text{el(vac)}} &= \frac{(1.6 \times 10^{-19} \text{ C})^2}{(1.1 \times 10^{-10} \text{ C}^2 \text{ J}^{-1} \text{ m}^{-1}) \times (10^{-10} \text{ m})} \\ &= 2.3 \times 10^{-18} \text{ J} \end{aligned}$$

equivalent to a molar work of

$$W_{\text{el(vac)}} N_A = 1400 \text{ kJ mol}^{-1}$$

Since W_{el} must be equal to the energy brought into the system to enable charge separation, the molar free energy of the system will increase by the same amount, *i.e.*, by 1400 kJ mol^{-1} . If the charge separation took place at constant temperature and standard pressure, one can write:

$$\Delta G_{\text{m}}^{\text{el}} = N_A W_{\text{el(vac)}} = 1400 \text{ kJ mol}^{-1}$$

Since the relative permittivity of water at 298.15 K is 78.5, the separation of charges in aqueous solution causes a decrease in the Gibbs energy of $1400/78.5 = 17.7 \text{ kJ mol}^{-1}$.

1.11.1.1. Entropy change in charge separation

Separation of charges according to eq. (1.11.1) causes an entropy change that can be theoretically predicted. Since entropy determines the variation of the Gibbs energy with temperature $[(\partial G/\partial T)_p = -S]$, and $[(\partial \Delta G/\partial T)_p = -\Delta S]$, it follows:

$$\Delta S_{\text{m}}^{\text{el}} = - \left(\frac{\partial N_A W_{\text{el}}}{\partial T} \right)_p \quad (1.11.5)$$

and further:

$$\Delta S_{\text{m}}^{\text{el}} = - N_A \frac{z_A z_B e^2}{4\pi \epsilon_0 \epsilon_r r_e} \left(\frac{\partial \ln \epsilon_r}{\partial T} \right)_p \quad (1.11.6)$$

Eq. (1.11.6) shows that we can calculate the entropy change of the charge separation if we know the temperature dependence of the relative permittivity of the dielectricum. The value of the differential quotient $(\partial \ln \epsilon_r / \partial T)_p$ is

approximately equal to $[(\ln \epsilon_{r(2)} - \ln \epsilon_{r(1)})/(T_2 - T_1)]_p$ for a narrow temperature interval. It can be shown that ΔS_m^{el} decreases with the increase of solvent polarity. Thus, at 293 K, the values of $\Delta S_m^{\text{el}}/\text{J mol}^{-1}\text{K}^{-1}$ are -518, -330, and -81, for hexane, ethanol and water, respectively.

A similar argument to that used in eqs. (1.11.4) and (1.11.5) was applied by Born⁷⁸ some 80 years ago. Born estimated the change in the Gibbs free energy when an ion of radius a and a charge number of z_i was transferred from a medium with relative permittivity ϵ_1 to a medium with a relative permittivity ϵ_2 . He found the corresponding free energy change to be:

$$\Delta G_m^{\text{el}} = -\frac{N_A(z_i e)^2}{8\pi\epsilon_0 a} \left(\frac{1}{\epsilon_{r,1}} - \frac{1}{\epsilon_{r,2}} \right) \quad (1.11.7)$$

With $\epsilon_{r,1} = 1$ for an ion in vacuum, eq. (1.11.7) gave the solvation free energy of the ion. The Born equation is not accurate, since the bulk dielectric constants (relative permittivities) are not valid in the immediate neighborhood of an ion. This is the reason why Born inserted $2a$ instead of a in (1.11.7), the value closer to the “effective” radius. Other investigators tried to improve eq. (1.11.7), for example, Latimer and co-workers,⁷⁹ but with a limited success.

1.11.1.2. The effect of solvents on reaction rates

This effect was successfully analyzed by Hughes and Ingold.⁸⁰ A concise review of the effect appeared in the first edition of Ingold's well known book, *Structure and Mechanism in Organic Chemistry* (1953),^{81a} and in its second edition (1969).^{81b} The effect primarily depends on the fact whether the substrate is positively or negatively charged, or electrically neutral. In an electrically neutral substrate, the ground state will be poorly solvated, but the transition state will be strongly solvated due to the charge separation. Thus, an increase in solvent polarity will increase the reaction rate. On the other hand, if the substrate is positively charged, then the charge of the transition state will be dispersed, leading to a small reaction rate decrease with increasing solvent polarity. This results from the reaction ground state being better solvated (better stabilized) than the transition state. In this way, the Gibbs energy of activation, $\Delta^\ddagger G$, increases, causing a reaction rate decrease.

In nucleophilic substitutions, we must first know whether the substitution is S_N2 or S_N1 . Table 1.11.1, according to Ingold *et al.*,^{81b} shows the possible reaction types and the relevant solvent effects.

We can see the importance of the charge of the transition state relative to

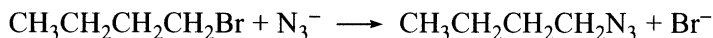
Table 1.11.1. Transition states of S_N1 and S_N2 reactions⁸¹

Reactants	Transition state (TS)	Charge of the TS relative to the ground state	Influence of solvent polarity increase on the reaction rate
<i>Monomolecular reactions (S_N1)</i>			
RX	$R^{\delta+}\cdots X^{\delta-}$	increased	large increase
RX^+	$R^{\delta+}\cdots X^{\delta+}$	dispersed	small decrease
<i>Bimolecular reactions (S_N2)</i>			
$RX + Y^-$	$Y^{\delta-}\cdots R\cdots X^{\delta-}$	dispersed	small decrease
$RX + Y$	$Y^{\delta+}\cdots R\cdots X^{\delta-}$	increased	large increase
$RX^+ + Y^-$	$Y^{\delta-}\cdots R\cdots X^{\delta+}$	dispersed	large decrease
$RX^+ + Y$	$Y^{\delta+}\cdots R\cdots X^{\delta+}$	dispersed	small decrease

the ground state. If the transition state is more charged than the ground state, it will be better solvated (increased order of the system) and the change in the entropy of activation between the transition state and the ground state, ($\Delta^\ddagger S$), will be negative. The reaction rate should decrease, as required by eq. (1.4.22) or (1.4.15). (As already mentioned, a decrease in the entropy of activation of $19.4 \text{ JK}^{-1} \text{ mol}^{-1}$ causes a decrease in the rate by a factor of 10.) We must also have in mind that the increased solvation of the transition state, relative to the ground state, reduces the Gibbs energy of activation, because the solvation stabilizes the transition state. This is commonly the dominant effect on the reaction rate. We recall that the decrease of the energy of activation of 5.85 kJ mol^{-1} causes a rate increase by a factor of 10.

The effect of polar aprotic solvents on reaction rates should be also commented. These are solvents without hydroxyl groups, but with a relatively high dipole moment and rather high relative permittivity (dielectric constant). Such solvents are, *e.g.*, acetone, acetonitrile, dimethylformamide (DMF), dimethyl sulfoxide, (DMSO), hexamethylphosphoric triamide (HMPT).

Many replacement reactions are often much faster in polar aprotic solvents than in hydroxylic solvents. Thus, the reaction of methyl bromide with iodide is about 500 times faster in acetone than in methyl alcohol. In addition, methyl iodide reacts with chloride about a million times faster in DMF than in methyl alcohol. This happens because the OH group of hydroxylic solvents solvates anions, forming the hydrogen bond ($ROH\cdots X^-\cdots HOR$). The solvated anions are therefore much less reactive. On the other hand, aprotic solvents having no hydrogen are unable to form hydrogen bonds. Anions in polar aprotic solvents are therefore more free, more reactive, and thus better nucleophiles. Another example of a strong solvent effect on a S_N2 reaction is the bimolecular replacement of bromide by azide in 1-bromobutane:



If the relative rate in methanol is taken as 1, then the rates in water, DMSO, DMF, and methyl cyanide (acetonitrile) are 7, 1300, 2800, and 5000, respectively.⁸² It is quite clear that the entering azide nucleophile is best solvated in methanol and least solvated in acetonitrile. Thus, the largest amount of energy is required to free azide from methanol in order to form the transition state, and the least energy is needed to remove the acetonitrile solvent.

1.11.1.3. The ionizing power of solvents

The ability of a solvent to dissolve a substance highly depends on its ability to solvate this substance. If a substance can ionize, both the anion and cation must be solvated. Cations are usually smaller than anions (*e.g.*, $\text{Ca}(\text{NO}_3)_2$), and the solvation of cations is of primary importance. Solvation of a simple cation is, in fact, formation of a complex in which the solvent molecules are entering ligands. The positive sides of a dipole solvent molecule will be oriented towards anions and its negative side towards cations.

Generally speaking, the dielectric constant (relative permittivity, ϵ_r) and the ability of a solvent to solvate ions are interrelated: the higher the solvent dielectric constant, the higher is its solvation ability. There is unfortunately no quantitative correlation because the relation is very complex and various factors are involved.⁸³ The following table illustrates this situation. Relative permittivity of 4 solvents and their dipole moments are compared and no correlation is observed.

Table 1.11.2. Relative permittivities (ϵ_r) and dipole moments of some solvents

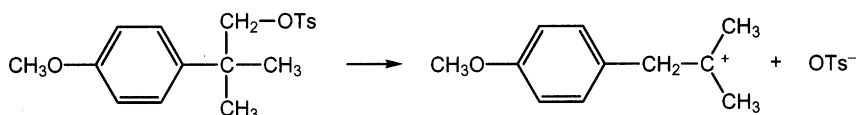
Solvent	ϵ_r	Dipole moment/D
HF	175	1.82
H ₂ O	78	1.85
DMSO	47	3.96
NH ₃	23	1.47

Water is often the best solvent because of its high relative permittivity and medium high dipole moment. Water has also an acidic hydrogen and a lone electron pair on oxygen, so it solvates well both acids and bases. On the other hand, NH₃ is probably a better electron-pair donor than water, but its hydrogens are less acidic. In general, NH₃, as solvent, ionizes the dissolved substance

less well than water because the relative permittivity of NH_3 is lower than that of water. In addition, the solvation with NH_3 through hydrogen bonding is weak. On the other hand, NH_3 can be an even better solvent than water in cases where solvent basicity is important. Hydrogen fluoride (HF) is clearly an acidic solvent and therefore it facilitates dissolution of molecules that are electron donors. Its high relative permittivity (175) supports ionization, but the fluorine atom is a very weak electron donor, which reduces the solvation of cations.

DMSO has a rather high relative permittivity, which supports ionization of both anions and cations; besides, DMSO is quite a good Lewis base and can solvate cations efficiently. Yet, DMSO has no acidic hydrogen atom.

The rate of a dissociative type reaction drastically depends on the solvent ionizing power, as shown by the classical kinetic studies of Winstein *et al.*⁸⁴ Table 1.11.3 contains a series of solvents ordered according to their decreasing ionizing power, as determined by measurements of the rate of ionization of *p*-methoxyneophyl *p*-toluenesulfonate:



Ratios of the highest and the smallest rates of ionization of the mentioned sulfonate in solvents of various ionizing power amount up to 7 orders of magnitude. Formic acid exhibits a very high ionizing power. Therefore, the last column of the table shows rates in different solvents relative to those in formic acid. This provides useful data of solvents' ionizing power for correlating the rates of certain reactions.

Trifluoroacetic acid has an even better ionizing power than formic acid,⁸⁵ but the mentioned authors did not study the former solvent. Besides, trifluoroacetic acid has very low nucleophilicity and is therefore a very appropriate solvent for studies of the dissociative type reactions. In this respect, $\text{CF}_3\text{CH}_2\text{OH}$ and $(\text{CF}_3)_2\text{CHOH}$ are very good solvents as well.⁸⁶

1.11.1.4. Ionic strength of the medium and the reaction rate

It has been shown how the polarity of solvents acts upon the rates of $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions. Increase of the ionic strength of the reacting solution has an effect similar to the increase of solvent polarity. The effect has not yet been quantitatively interpreted; different salts can exhibit different kinetic effects. The rate increase of $\text{S}_{\text{N}}1$ reactions upon addition of salts is called the kinetic

Table 1.11.3. Rates of ionization of *p*-methoxyneophyl *p*-toluenesulfonate in solvents of various ionizing power (relative to the rate in acetic acid)⁸⁴ (reproduced by permission of the American Chemical Society)

Solvent	ϵ_r (25 °C)	$\log k_1$	Relative rate
HCOOH	58 (20 °C)	-0.929	153
H ₂ O	78.54	-1.180	39
80% EtOH-H ₂ O	67.0	-2.505	1.85
AcOH	6.2	-2.772	1.00
MeOH	32.63	-2.796	0.947
50% AcOH-Ac ₂ O			0.540
EtOH	24.30	-3.204	0.370
Me ₂ SO	45	-3.738	0.103
MeNO ₂	36.7	-3.921	7.3×10^{-2}
n-C ₇ H ₁₅ COOH	2.4 (20 °C)	-4.139	4.30×10^{-2}
CH ₃ CN	36.7	-4.221	3.53×10^{-2}
HCONMe ₂	36.71	-4.298	2.94×10^{-2}
Ac ₂ O	20.7	-4.467	2.02×10^{-2}
C ₅ H ₅ N	12.3	-4.670	1.27×10^{-2}
Me ₂ CO	20.7	-5.067	5.07×10^{-3}
EtOAc	6.02	-5.947	6.69×10^{-4}
(CH ₂) ₄ O	7.39	-6.073	5.0×10^{-4}
Et ₂ O	4.23	-7.3	$\approx 3 \times 10^{-5}$

salt effect. The effect is discussed in section 1.9.2. We must also have in mind the so-called common ion rate depression effect, and the special salt effect, which will be discussed later.

1.11.1.5. Linear free energy relationships

The influence of solvents upon the rates and mechanism of S_N1 reactions was quantitatively studied by using the "linear free energy relationships". Grunwald and Winstein⁸⁷ have chosen the rate of solvolysis of *t*-butyl chloride in a solvent, (k_s), relative to the rate, (k_0), of the same substrate in the standard solvent, taken arbitrarily to be ethanol-water at 25 °C, $\phi_{\text{EtOH}} = 0.8 = 80\%$, as a measure of the solvent's ionizing power (Y):

$$Y = \log \frac{k_s}{k_0} \quad (1.11.8)$$

Table 1.11.4 shows the ionizing power Y of some mixed solvents for the substrate (CH₃)₃CCl at 25 °C. In standard solvent, at 25 °C, $Y = 0$ (by definition).

This standard solvent was chosen as the reference solvent because the solvolysis rates in this solvent are about halfway between solvents that exhibit the fastest and the slowest rates, respectively. Thus, the values of Y will be positive for solvents yielding solvolysis rates higher than in the standard solvent, and negative for solvents exhibiting rates lower than in the standard solvent. It is noteworthy that in this way we can characterize solvent mixtures to which an ionizing power factor is otherwise very difficult to ascribe.

Table 1.11.4. Ionizing power of $Y = \log(k_s/k_0)$ for some aqueous solvents at 25 °C⁸⁸

$100 \times \varphi$	Ethanol	Methanol	Dioxane	Acetone	Acetic acid	Formic acid
0 (water)	3.49	3.49	3.49	3.49	3.49	3.49
10	3.31	3.28	3.22	3.23		
20	3.05	3.03	2.88	2.91		
25	2.91			2.69	2.84	3.10
30	2.72	2.75	2.46	2.48		
40	2.20	2.39	1.95			
50	1.66	1.97	1.36	1.40	1.94	2.64
60	1.12	1.49	0.72	0.80	1.52	
70	0.60	0.96			2.31	
80	0.00	0.38	-0.83	-0.67		2.32
90	-0.75	-0.30	-2.03	-1.86		2.22
95	-1.29	-0.65		-2.76		2.16
100	-2.03	-1.09			-1.64	2.05

Recognizing Y as the measure of the ionizing power of a solvent, it appeared probable that Y should also depend on the nature of the substrate undergoing solvolysis. It was therefore necessary to introduce an additional parameter m and thus correct eq. (1.11.8) into eq. (1.11.9):

$$mY = \log \frac{k_s}{k_0} \quad (1.11.9a)$$

or

$$\log k_s = mY + \log k_0 \quad (1.11.9b)$$

Indeed, by plotting $\log k_s$ vs. Y , eq. (1.11.9b) yields a series of almost parallel lines with slope m being very near to 1. On the other hand, the straight line intercepts (k_0) vary appreciably for various substrates in the standard solvent. Although the Y values have limited significance, they nevertheless give

a reasonably good measure of the ionizing power of a solvent, though it can happen that quasi-good Y values fit fortuitously.

As previously shown, the transition state theory provided the expression for the dependence of the reaction rate constant on $\Delta^\ddagger G^\circ$ (cf. eq. 1.4.14):

$$k = \frac{k_B T}{c^\circ h} e^{-\Delta^\ddagger G^\circ / RT}$$

Taking a logarithm of k , a linear dependence of $\ln k$ and $\Delta^\ddagger G^\circ$ can be seen:

$$\begin{aligned} \ln k &= -\frac{\Delta^\ddagger G^\circ}{RT} + \ln \frac{k_B T}{h} \\ &= -\frac{\Delta^\ddagger G^\circ}{RT} + \text{constant} \end{aligned}$$

From the well known thermodynamic equation

$$-\Delta_r G^\circ = RT \ln K^\circ$$

we may expect that $-\Delta^\ddagger G^\circ$ would also be proportional to $\ln K^\circ$. This assumption is the basis of a class of the so-called linear free energy relationships.

The Grunwald-Winstein eq. (1.11.9) is valid when the substrate is kept constant (m is constant), and Y is the linear function of the free energy of activation (Gibbs energy of activation, $\Delta^\ddagger G^\circ$).

We have already discussed eq. (1.4.12):

$$\Delta^\ddagger G^\circ = \Delta^\ddagger H^\circ - T\Delta^\ddagger S^\circ$$

and since it has been shown that $\Delta^\ddagger H^\circ$ and $\Delta^\ddagger S^\circ$ in solvolyses of *tert*-butyl chloride in aqueous ethanol mixtures vary extensively,⁸⁸ it might be expected that $\Delta^\ddagger G^\circ$ and Y would not have a linear relationship. Fortunately, the sum of $\Delta^\ddagger H^\circ$ and $T\Delta^\ddagger S^\circ$ is a reasonably good linear function of Y . Thus, the Grunwald-Winstein equation proved to be very useful, because it gives a reasonably good information about the ionizing power of solvents.

There are also other scales for characterization of solvents' ionizing power. For instance, Kosower found that positions of certain absorption maxima ("charge transfer bands") in the UV spectrum of 1-methyl-4-carbomethoxy-pyridinium iodide depend very strongly on solvent polarity:⁸⁹ the better the ionizing power of a solvent, the better is the solvation of the ion pair ground state, which is, therefore, lower in energy relative to the ion pair in the gas phase. Thus, more energy is needed for formation of the excited state in solution

Table 1.11.5. Characterization of solvents with regard to ionizing power, nucleophilicity, and electron-donor ability

Solvent	Scale				$Z^{(a)}/\text{kJ mol}^{-1}$	$E_T^{(b)}/\text{kJ mol}^{-1}$	ϵ_r (20 °C)	$DN_{\text{SnCl}_4}^{(c)}$
	Y	N	Y_{OTS}	N_{OTS}				
CF_3COOH	1.84 ^(d)	-4.74	4.57	-5.56				
H_2O	3.49	-0.26			396	264	80.37	18.0
HCOOH	2.05	-2.05	3.04	-2.35			58.5 (16.5 °C)	
$\text{CF}_3\text{CH}_2\text{OH}$	1.045 ^(e)	-2.78	1.80	-3.0				
HCONH_2	0.6				349	237	113.5	
80% EtOH	0.00	0.00	0.00	0.00	355	225		
MeOH	-1.09	0.01	-0.92	-0.04	350	232	33.62	19.0
CH_3COOH	-1.64	-2.05	-0.61	-2.35	331	214	6.1	
90% Dioxane- H_2O	-2.03	-0.65			321	195		
EtOH	-2.03	0.09	-1.75	0.00	333	217	24.3 (25 °C)	31.5
<i>i</i> -PrOH	-2.7				319	203	18.3 (25 °C)	
<i>t</i> -BuOH	-3.3				298	184	10.9 (30 °C)	
MeCN					298	192	38.8	14.1
Me_2SO					297	188	48.9	29.8
HCONMe_2					287	183	36.7 (25 °C)	27.0
Acetone					275	177	20.7 (25 °C)	17.0
Pyridine					268	168	12.3 (25 °C)	33.1
CHCl_3					264	164	4.81	
THF						156		
Dioxane						151		
Et_2O						145	4.33	19.2
C_6H_6					226	144	2.28	0.1
CCl_4						136	2.24	0.0
Hexane						129	1.89	0.0

(a) Kosower *et al.*⁸⁹ (b) Reichard *et al.*⁹⁰⁻⁹³ (c) Donor number.⁹⁹ (d) The value is anomalous because of the effect of partition in ion pairs.⁹⁷ (e) V. J. Shiner *et al.*⁹⁸

than in the gas phase. Consequently, spectral changes of substrates can be observed in various solvents. Positions of absorption bands are expressed as transition state energies, Z , and are calculated from the frequencies of maximum absorptions. Table 1.11.5 contains Kosower's Z values for a series of solvents. The higher the Z value of a solvent, the greater is its ionizing power.

Very useful is the so-called E_T scale of Reichard *et al.*⁹⁰⁻⁹³ The scale is based on absorption maxima of the electronic spectra of pyridinium *N*-phenolbetaine in different solvents.⁹⁰⁻⁹² The energies of the transition states, for the compound denoted $E_T(30)$, depend on solvent nature, providing a very useful survey of the ionizing power of the majority of known solvents. Table 1.11.5 contains some of these E_T values.

One should bear in mind that both the Z values (Kosower *et al.*) and $E_T(30)$ values (Reichard *et al.*) are data obtained from the energies of excited states of two different compounds in various solvents, under the same conditions (25 °C, 1 bar), and can be therefore usefully compared, indicating the trend of solvents' ionizing power effect.

Lately, the 2-adamantyl tosylate scale (Y_{OTs} values) is much used for characterization of a solvent's ionizing power and nucleophilicity.^{94,95} The compound solvolyses with less than 1% rearrangement, does not undergo a S_N2 reaction with azide, yields a very large α -deuterium kinetic isotope effect, characteristic of a dissociation type mechanism (*vide infra*), and also satisfies other criteria for a limiting S_N1 mechanism.^{94,95}

Table 1.11.5 summarizes the mentioned solvent characteristics: Grunwald-Winstein Y values,⁹⁶ Y_{OTs} values,⁹⁴ Z and $E_T(30)$ values^{89, 91, 92} for some important solvents. Solvents with a large ionizing power are listed high in the column. According to Y_{OTs} values, CF_3COOH is the solvent with the highest ionizing power. On the other hand, the Grunwald-Winstein Y value of CF_3COOH is, contrary to expectation, relatively low (1.84). It was determined by measurements of the rate of solvolysis of *tert*-butyl chloride in CF_3COOH , upon addition of water and/or sodium trifluoroacetate; according to the authors,⁹⁷ this was necessary because of otherwise very low rates. Nevertheless, all experience suggests that CF_3COOH is probably the solvent with the highest ionizing power. It appears that *tert*-butyl chloride behaves abnormally in some fluorinated solvents because of the effect of solvent partition in ion pairs.⁹⁸

Table 1.11.5 contains only a few $E_T(30)$ values, but Reichard *et al.*⁹⁰⁻⁹³ published $E_T(30)$ values of 243 solvents, and ordered them according to their decreasing ionizing power, which is of great practical use.

Solvents with a low ionizing power usually have low relative permittivity as well. However, one should be careful here because the relative permittivity of a solvent does not always give adequate information on the ionizing power of that solvent. Thus, formamide has the highest relative permittivity (113.5), but its ionizing power is not among the highest.

1.11.1.6. Solvent nucleophilicity and definition of the nucleophilic constant N

Winstein, Fainberg and Grunwald, later expanded eqs. (1.11.8) and (1.11.9), taking into account the nucleophilicity of solvents, which obviously exerts influence upon reaction rates.¹⁰⁰ They derived eq. (1.11.10):

$$\log \frac{k}{k_0} = mY + lN \quad (1.11.10)$$

where N is the measure of solvent nucleophilicity, and l is the susceptibility of substrate to solvent nucleophilicity. Symbols m and Y were defined previously.

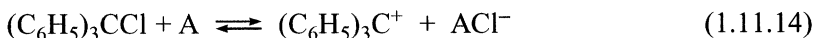
There are other expressions that correlate ionizing power and nucleophilicity, *e.g.*, that of Swain, Mosely and Brown,¹⁰¹ but it appears that eq. (1.11.10) is the most frequently used one.^{95,102,103}

1.11.1.7. Solvent coordinating property and electron-donor ability

According to chemical properties, solvents can be divided into electron donors and electron acceptors. An electron-donor solvent (D) will react with an electron-acceptor solvent (A), as shown in the following examples:



On the other hand, an electron-acceptor solvent (A) reacts with an electron-donor solvent (D). Since the anions are usually electron-pair donors, the reaction of solvent (A) and the anion will take place as follows:



The quantitative measure for the electron-donating ability of solvents is adequately given by reaction enthalpy; *e.g.*, for reaction (1.11.11) it is $-\Delta_r H^\circ$ $[\text{D} \cdot \text{SbCl}_5]$. Very diluted solutions are used in practice so that gas laws can be applied. Changes in the Gibbs energy (ΔG°) can be determined by spectroscopic and NMR measurements,¹⁰⁴ thus enabling determination of the equilibrium constants of reactions with certain solvents. A linear relationship has

been established between $\Delta_r H^\circ[\text{D} \cdot \text{SbCl}_5]$ and $\log K^\circ[\text{D} \cdot \text{SbCl}_5]$, suggesting that the contribution of entropy is approximately equal for all the studied solvents.¹⁰⁴ This conclusion follows from the comparison of the two well-known thermodynamic equations:

$$\Delta H^\circ = \Delta G^\circ + T\Delta S^\circ$$

and

$$\Delta G^\circ = -RT \ln K^\circ$$

$$\Delta_r H^\circ = -RT \ln K^\circ + T\Delta_r S^\circ$$

It is generally taken that $-\Delta H[\text{D} \cdot \text{SbCl}_5]$ values yield useful information on the degree of interaction between an electron-donor solvent (D) and the chosen substrate (SbCl_5). The number ascribed to a solvent to indicate its electron-donor ability bears the symbol DN_{SbCl_5} .

1.11.1.8. Drastic acceleration of the oxidation of hexacyanoferrate(II) in solvents, strong electron donors

The mechanism of ligand substitution in the pentacyano(ligand)ferrate(II) ion has been the subject of many investigations.^{105–108} Substitutions are of the dissociative type and one would expect that the rate of dissociation of an uncharged ligand would not depend, at least not very much, on solvent polarity, since there is no charge separation in the reaction transition state. Nevertheless, experiments show that the rates of dissociation of X in $[\text{Fe}(\text{CN})_5(\text{X})]^{3-}$, where X = H_2O , pyridine (py), 3CN-py, 4CN-py, piperidine, and nitrosobenzene (PhNO), depend strongly on the electron-donor ability of solvents.¹⁰⁸ the better electron donor the solvent, the faster is the dissociation of ligand X. It appears that the cyanide ligands of the pentacyanide, due to their triple bonds, enable good electron mobility. Thus, the cyanide electron density can be shifted towards the iron metal center, or towards solvent molecules solvating CN^- ligands. The better electron donor the solvent, the larger is the electron shift towards the metal center, and the higher are the rates of dissociation of X, which leaves the complex with its electron pair, as X^- .

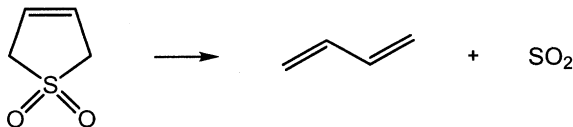
Analogously to the dissociation of X in $[\text{Fe}(\text{CN})_5(\text{X})]^{3-}$, the oxidation of $[\text{Fe}(\text{CN})_6]^{4-}$ to $[\text{Fe}(\text{CN})_6]^{3-}$ by O_2 in aqueous-organic solvent mixtures depends drastically on the electron-donating abilities of solvents, the reaction in dimethyl sulfoxide and dimethylformamide being about 10^4 times faster than

in water. The rate does not correlate with the solvent's relative permittivity. The reaction mechanism is also dissociative. The slowest process is the dissociation of a CN^- and the coordination position freed is filled with molecular oxygen; O_2 accepts an Fe^{II} electron, causing its oxidation to Fe^{III} . This is the so-called Weiss' mechanism.¹⁰⁹ The coordinated oxygen is bonded to iron as superoxide radical (O_2^-).¹¹⁰ Elimination of O_2^- from the complex requires¹¹⁰ 75 kJ mol^{-1} , which is rather high energy. This is the reason why the oxidation does not spontaneously follow Weiss' mechanism, but the presence of protons is required to enable formation of HO_2 radicals, and their slow elimination. The freed coordination place is then filled with CN^- , the final product being $[\text{Fe}(\text{CN})_6]^{3-}$. Therefore the oxidation of $[\text{Fe}(\text{CN})_6]^{4-}$ in mixed solvents requires at least some water as the source of protons.

Oxidation rates depend very strongly on the solvent electron-donor ability. Oxidation is the fastest in DMSO, which is the best electron donor among those investigated [the rate acceleration factor $\approx 2 \times 10^4$ (relative to the rate in water where $k_{\text{obs}} = 1.3 \times 10^{-5} \text{ s}^{-1}$, at 35°C , and at $\text{pH} = 6.0$), the electron-donor number, $DN_{\text{SbCl}_5} = 29.8$, relative permittivity, $\epsilon_r = 48.9$, at 20°C], see Table 1.11.5. The next largest rate acceleration is in DMF [acceleration factor $\approx 5 \times 10^3$, $DN_{\text{SbCl}_5} = 27$, $\epsilon_r = 36.7$ (25°C)]. The donor number of acetonitrile is 14.1, and the acceleration factor is only 160. The oxidation rates, as already mentioned, do not correlate with the relative permittivities of solvents. Thus, the relative permittivity of formamide is the highest of all solvents used (113.5 at 20°C), but the acceleration factor is only 100.

1.11.1.9. The dissociative type reaction may not depend on solvent polarity

An example of a dissociative type reaction the rate of which is practically independent of solvent nature is the thermal decomposition of 2,5-dihydrothiophene-1,1-dioxide (3-sulfolene). Its thermal decomposition follows the equation:



The rate of this thermal decomposition is practically equal in 1-butanol and in diethylene glycol diethyl ether and only 10% higher in the melt.¹¹¹ Independence of the reaction rate of the medium polarity is taken to be due

to the reaction transition state, whose polarity was not changed with respect to the ground state.¹¹²

The mechanism of the 3-sulfolene decomposition was studied by the α -deuterium secondary kinetic isotope effect (*vide supra*) and it was concluded that the reaction follows a “concerted” mechanism. Both S–C bonds are equally weakened in the transition state, as predicted by Woodward and Hoffmann (see section 7.2) on the basis of orbital symmetry arguments.

Since there is no charge development in the transition state relative to the ground state, the reaction rate is practically independent of solvent media. Earlier investigations^{113,114} also support the claim that the thermal decomposition of 3-sulfolene is a concerted disrotatory process.¹¹⁵ In general, the rates of other pericyclic reactions are commonly solvent independent as well. To use the terminology of organic chemistry, the Diels-Alder reaction is a pericyclic reaction, that is, a reaction that takes place in a single step, without intermediates, and involves a cyclic rearrangement of bonding electrons (for more information see elsewhere).

1.12. STEADY-STATE APPROXIMATION AND ITS APPLICATION TO REPLACEMENT REACTIONS

The replacement of a ligand in a metal complex does not usually stop after one replacement, but most probably several replacements will follow. In fact, we have to deal with a sequence of several consecutive reactions and the kinetic treatment becomes extremely complicated, practically insoluble. Simplification of the problem is known as the steady-state approximation.

An intermediate is said to be in its steady-state when its concentration does not change with time. The assumption is that during the largest part of the reaction the concentration of all intermediates (I) is practically constant and negligibly small:

$$\frac{d[I]}{dt} \approx 0$$

This means that the rate at which the intermediate, I, is formed and the rate of its disappearance are practically equal. Strictly speaking, the steady-state is reached almost immediately after initiation of the reaction. Figure 1.12.1 schematically depicts this situation: curve (a) shows how the concentration of the final reaction products changes with time, curve (b) shows the rate of reactant disappearance, and curve (c) represents the rate of formation of the reaction intermediate (I). We can see that during most of the reaction the concentration of I is practically constant and very low; point S is a small

maximum at which the slope is zero, *i.e.*, $d[I]/dt = 0$. At that point the steady-state is reached, which happens shortly after initiation of the reaction and is maintained almost to the end of the reaction. We can compare this situation with someone's very small bank account. The money in the account is not constant but because the sum is very small, we can conclude that the rates of earning and spending are (practically) equal.

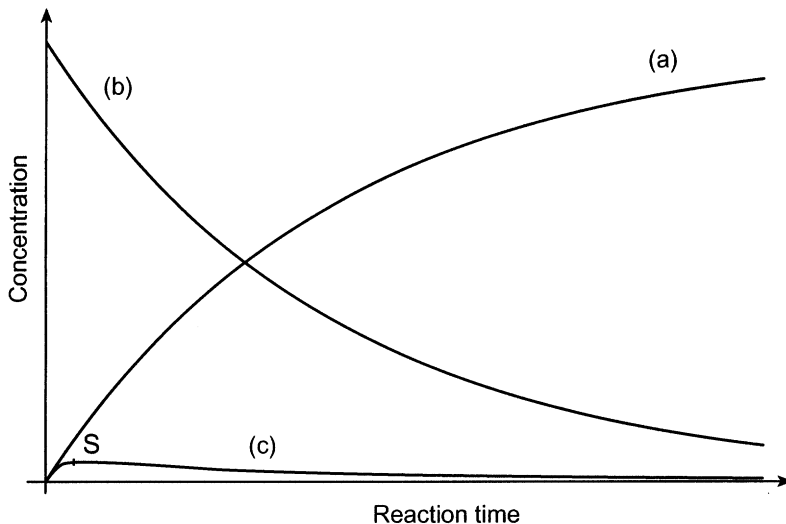


Figure 1.12.1. The concentration of the intermediate is low and practically constant; at S curve (c) has a small maximum where $d[I]/dt = 0$.

Let us consider a consecutive reaction:



If we apply the steady-state approximation, the rates of formation and of disappearance of I must be equal:

$$k_1[A] = k_{-1}[I] + k_2[I] \quad (1.12.2)$$

It follows that:

$$[I] = \frac{k_1[A]}{k_{-1} + k_2} \quad (1.12.3)$$

and the rate of product formation is:

$$\frac{d[P]}{dt} = k_2[I] = \frac{k_1 k_2 [A]}{k_{-1} + k_2} \quad (1.12.4)$$

Let us consider the border case (a):

$$k_{-1} \ll k_2$$

From (1.12.4) it follows:

$$\frac{d[P]}{dt} = k_1[A] \quad (1.12.5)$$

In this border case, the slowest and therefore the rate-determining step is the conversion of A to I. This means that almost all molecules of the intermediate (I) are converted into product P, only few revert to A.

Let us consider the border case (b):

$$k_{-1} \gg k_2$$

From (1.12.4) it follows:

$$\frac{d[P]}{dt} = \frac{k_1 k_2}{k_{-1}} [A] \quad (1.12.6)$$

In this case, almost every molecule of intermediate I reverts to A, only few yield the product (P). Thus, the conversion of I to P is the slowest and therefore the rate-determining step.

But, let us point to the reaction scheme that is most often encountered in ligand replacement reactions when a ligand X of a metal complex MX is replaced by a ligand Y:



If we apply the steady-state approximation to intermediate M, we get:

$$k_1[MX] \approx k_{-1}[M][X] + k_2[M][Y] \quad (1.12.9)$$

It follows that the concentration of the short-lived intermediate M is:

$$[M] \approx \frac{k_1[MX]}{k_{-1}[X] + k_2[Y]} \quad (1.12.10)$$

and the reaction rate is:

$$\frac{d[MY]}{dt} \approx \frac{k_1 k_2 [Y][MX]}{k_{-1}[X] + k_2[Y]} \quad (1.12.11)$$

and further:

$$k_{\text{obs}} \approx \frac{k_1 k_2 [Y]}{k_{-1}[X] + k_2[Y]} \quad (1.12.12)$$

For the case

$$k_{-1}[X] \ll k_2[Y]$$

it holds:

$$\frac{d[MY]}{dt} \approx k_1[MX] \quad (1.12.13)$$

which means that the first reaction step, the dissociation of MX, is the slowest and therefore the rate-determining step.

In case that

$$k_{-1}[X] \gg k_2[Y]$$

then:

$$\frac{d[MY]}{dt} \approx \frac{k_1 k_2 [Y][MX]}{k_{-1} [X]} \quad (1.12.14)$$

From (1.12.10) it follows that the concentration of the short-lived intermediate is:

$$[M] \approx \frac{k_1[MX]}{k_{-1}[X]} \quad (1.12.15)$$

i.e.,

$$\frac{[M][X]}{[MX]} = \frac{k_1}{k_{-1}} = K$$

Thus, the first reaction step is in fast equilibrium and the second step is the slowest and thus the rate limiting one.

We should keep in mind that X might be uncharged (*e.g.*, pyridine, imidazole) though it is often charged, like SCN^- , N_3^- , *etc.*

Coming back to the mentioned general scheme



let us assume that the reaction in A is of the first order. Applying the steady-state approximation, as we did in deriving eq. (1.12.11), we shall obtain eq. (1.12.17):

$$-\frac{d[\text{A}]}{dt} = \frac{d[\text{P}]}{dt} \approx \frac{k_1 k_2 [\text{A}]}{k_{-1} + k_2} \quad (1.12.17)$$

Assuming that A converts directly to P (not through an intermediate), we have the reaction:



This is again a first order reaction:

$$-\frac{d[\text{A}]}{dt} = \frac{d[\text{P}]}{dt} = k'[\text{A}] \quad (1.12.19)$$

In expressions (1.12.17) and (1.12.19) the reaction rate is proportional to [A] and both reactions are kinetically indistinguishable.

The reaction system might involve the following simultaneous reactions:



Assuming a rapid equilibrium between A and B, we have:

$$-\frac{d[\text{A}]}{dt} = \frac{d[\text{P}]}{dt} = k'[\text{A}]$$

The reaction is of the first order, like in the case when the reaction product is formed through intermediate B. Thus, B is part of the reaction system, but it

is not the reaction intermediate. This case was analyzed by Espenson.¹¹⁶ If there is a reagent X that reacts very fast with B, it prevents its reverse to A, possibly also a further reaction to P. In the case that B is an intermediate, $d[BX]/dt$ will be equal to $k_1[A]$, which may or may not be identical with k_{obs} . If it is identical, then that proves that B is the reaction intermediate on the way to product P.¹¹⁶

Eq. (1.12.11) shows that, if a D mechanism is operative and the entering ligand Y is in large excess, then $k_{\text{obs}} = k_1$; we say that the reaction exhibits “limiting” or “saturation rates”. This situation is schematically depicted in Figure 1.12.2.

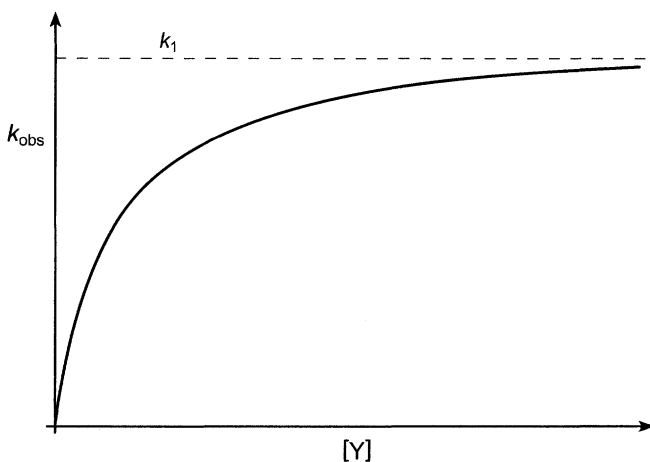


Figure 1.12.2. Schematic representation of the dependence of k_{obs} on the entering ligand (Y) concentration in a D-type reaction: $RX + Y \longrightarrow RY + X$; in large excess of Y, limiting rates are obtained that are equal to k_1 .

In the case of a bimolecular reaction, the rate will steadily increase with the entering ligand (Y) concentration, and the rate increase will be almost linear. A mild departure from linearity will be observed at very high concentrations of Y, due to mutual interactions between molecules.

Let us consider a D-type substitution reaction where the leaving ligand X is a solvent molecule that dissociates into the same solvent X. Under such circumstances, $k_{-1}[X] \gg k_2[Y]$, so that the expression (1.12.12)

$$k_{\text{obs}} \approx \frac{k_1 k_2 [Y]}{k_{-1}[X] + k_2[Y]}$$

is reduced to:

$$k_{\text{obs}} \approx \frac{k_1 k_2 [\text{Y}]}{[\text{solvent}]} = \text{const.} [\text{Y}] \quad (1.12.22)$$

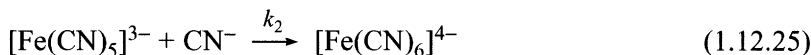
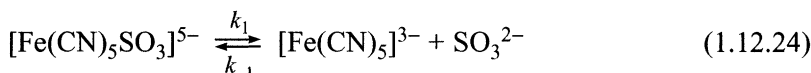
Indeed, in reactions of this type (when the entering ligand is an anion, such a reaction is called anation), a linear dependence of k_{obs} on $[\text{Y}]$ has been observed (k_{-1} and k_2 are usually of similar magnitude).

Expression (1.12.12) can be transformed into:

$$\frac{1}{k_{\text{obs}}} \approx \frac{k_{-1}[\text{X}]}{k_1 k_2 [\text{Y}]} + \frac{1}{k_1} \quad (1.12.23)$$

This expression enables determination of the competition ratio k_2/k_{-1} because by plotting $1/k_{\text{obs}}$ vs. $1/[\text{Y}]$, in excess of the known extra added X, a linear dependence is obtained with the slope $k_{-1}/k_1 k_2$ and the intercept $1/k_1$.

In this way, the competition ratio k_2/k_{-1} was determined in the D-type replacement of SO_3^{2-} by CN^- in pentacyanosulfiteferrate(II) in aqueous solution, the reaction that proceeds according to eqs. (1.12.24) and (1.12.25):¹¹⁷



Competition ratios can also be determined by plotting $1/k_{\text{obs}}$ vs. X, in excess of the known concentration of Y. Both plots are equally satisfactory.¹¹⁷ The average competition ratio k_2/k_{-1} amounted to 8.76 ± 0.53 , and $k_1 = (9.50 \pm 0.21) \times 10^{-4} \text{ s}^{-1}$.

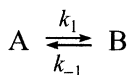
The procedure for determination of competition ratios was first applied by Haim and Wilmarth,¹¹⁸ and later by Halpern *et al.*,¹¹⁹ when intermediates $[\text{Co}(\text{CN})_5]^{2-}$ and $[\text{Co}(\text{NH}_3)_4\text{SO}_3]^+$ were involved.

Determination of competition ratios is of a special mechanistic importance, since in this way we can prove that a reaction intermediate really exists, and lives long enough as to discriminate (distinguish) entering ligands.

Mention should be also made of the application of the steady-state approximation to the reaction scheme (1.12.26), which is more complex than scheme (1.12.1). In (1.12.26), the conversion of intermediate I into the final product B is reversible:



Elementary kinetics teaches us that the rate of a reversible reaction of the type:



is given by the equation:

$$-\frac{d(a-x)}{dt} = \frac{dx}{dt} = k_1(a-x) - k_{-1}x \quad (1.12.27)$$

where a is the initial concentration of A, and x is the concentration of B, at any time t ; when $t = 0$, $x = 0$. When equilibrium is established, then $x = x_e$, and

$$k_1(a - x_e) = k_{-1}x_e \quad (1.12.28)$$

Now we can insert the value of

$$k_{-1} = \frac{k_1(a - x_e)}{x_e}$$

into (1.12.28), and we get:

$$\frac{dx}{dt} = \frac{k_1 a}{x_e} (x_e - x) \quad (1.12.29)$$

After integration {the procedure is analogous to that for an irreversible first-order reaction yielding the familiar equation: $k = (1/t)\ln[a/(a-x)]$ }, we get:

$$\frac{k_1 a}{x_e} = \frac{1}{t} \ln \frac{x_e}{x_e - x} = k_1 + k_{-1} \quad (1.12.30)$$

Assuming that in scheme (1.12.26) $k_{-2} = 0$, and by applying the steady-state approximation we get:

$$k_{\text{obs}}^{\rightarrow} = \frac{k_1 k_2}{k_{-1} + k_2} \quad (1.12.31)$$

By applying the same treatment to scheme (1.12.26) but in the reverse direction (from right to left), under assumption that $k_1 = 0$, we get:

$$k_{\text{obs}}^{\leftarrow} = \frac{k_{-2} k_{-1}}{k_2 + k_{-1}} \quad (1.12.32)$$

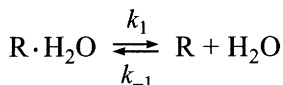
Since

$$k_{\text{obs}} = k_{\text{obs}}^{\rightarrow} + k_{\text{obs}}^{\leftarrow}$$

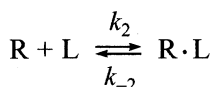
then:

$$k_{\text{obs}} = \frac{k_1 k_2 + k_{-1} k_{-2}}{k_{-1} + k_2} \quad (1.12.33)$$

By applying (1.12.33) to the reaction of the type:



and further,



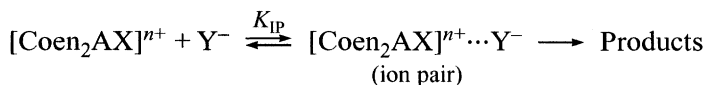
we finally get:

$$k_{\text{obs}} = \frac{k_1 k_2 [\text{L}] + k_{-1} k_{-2}}{k_{-1} + k_2 [\text{L}]}$$

1.13. REACTIONS OF ION PAIRS

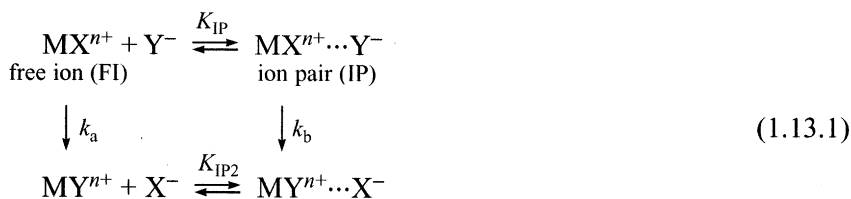
Electrostatic attraction causes formation of ion pairs. The lower is the solvent relative permittivity, ϵ_r , and the smaller are ion radii, the larger is the ion pair formation. The degree of ion association can be very significant even in solvents of high relative permittivity, *e.g.*, in aqueous solution. Bjerrum* calculated that univalent ions, having a diameter of 0.282 nm, are about 14% associated in aqueous solutions; if the diameter is 0.176 nm, the ion association is about 29%. It may be concluded that ion association is important even in aqueous solutions, and of very great importance in solvents of low permittivity.

Let us consider the substitution of a ligand X by a ligand Y⁻ in a metal complex in which a ligand A is very strongly bonded, thus not undergoing substitution (en = ethylenediamine):



* NILS JANNIKSEN BJERRUM, 1879–1958, professor at the University of Copenhagen, significantly contributed to the theory of strong electrolytes and to solution coordination chemistry.

or generally:



The equilibrium is quickly established. The rate of product formation is given by:

$$\frac{d[\text{P}]}{dt} = k_a[\text{FI}] + k_b[\text{P}] \quad (1.13.2)$$

From (1.13.1) it follows that the equilibrium constant for ion pair formation is:

$$K_{\text{IP}} = \frac{[\text{IP}]}{[\text{FI}][\text{Y}^-]}$$

and:

$$[\text{IP}] = K_{\text{IP}}[\text{FI}][\text{Y}^-] \quad (1.13.3)$$

If the total concentration of the reacting complex is denoted as $[\text{complex}]_{\text{T}}$, then:

$$[\text{complex}]_{\text{T}} = [\text{FI}] + [\text{IP}] = [\text{FI}] + K_{\text{IP}}[\text{FI}][\text{Y}^-] \quad (1.13.4)$$

It follows that

$$[\text{FI}] = \frac{[\text{complex}]_{\text{T}}}{1 + K_{\text{IP}}[\text{Y}^-]} \quad (1.13.5)$$

If reagent RY is in excess, then $[\text{Y}^-]$ is practically equal to the concentration of the added salt, *i.e.*, $[\text{Y}^-] \approx [\text{RY}]$. From eqs. (1.13.2), (1.13.3) and (1.13.5) it follows that:

$$\begin{aligned}
 \frac{d[\text{P}]}{dt} &= \frac{k_a[\text{complex}]_{\text{T}}}{1 + K_{\text{IP}}[\text{RY}]} + \frac{k_b K_{\text{IP}}[\text{complex}]_{\text{T}}[\text{RY}]}{1 + K_{\text{IP}}[\text{RY}]} \\
 &= \frac{[\text{complex}]_{\text{T}}(k_a + k_b K_{\text{IP}}[\text{RY}])}{1 + K_{\text{IP}}[\text{RY}]} \quad (1.13.6)
 \end{aligned}$$

Experiments show that

$$\frac{d[P]}{dt} = k_{\text{obs}}[\text{complex}]_T$$

and equating this expression with the one above we obtain:

$$k_{\text{obs}}[\text{complex}]_T = \frac{[\text{complex}]_T(k_a + k_b K_{\text{IP}}[\text{RY}])}{1 + K_{\text{IP}}[\text{RY}]}$$

and

$$k_{\text{obs}} = \frac{k_a + k_b K_{\text{IP}}[\text{RY}]}{1 + K_{\text{IP}}[\text{RY}]} \quad (1.13.7)$$

or

$$k_{\text{obs}} - k_a = k_b K_{\text{IP}}[\text{RY}] - k_{\text{obs}} K_{\text{IP}}[\text{RY}] \quad (1.13.8)$$

If we insert k_{obs} from (1.13.7) into the reciprocal of eq. (1.13.8), we get:

$$\frac{1}{k_{\text{obs}} - k_a} = \frac{1}{k_b K_{\text{IP}}[\text{RY}] - \frac{k_a + k_b K_{\text{IP}}[\text{RY}]}{1 + K_{\text{IP}}[\text{RY}]} K_{\text{IP}}[\text{RY}]}$$

and finally:

$$\frac{1}{k_{\text{obs}} - k_a} = \frac{1}{K_{\text{IP}}[\text{RY}](k_b - k_a)} + \frac{1}{k_b - k_a} \quad (1.13.9)$$

By plotting $1/(k_{\text{obs}} - k_a)$ vs. $1/[\text{RY}]$, or which is the same, vs. $1/[\text{Y}^-]$, a straight line is obtained. The intercept is $1/(k_b - k_a)$, and the slope enables the determination of K_{IP} . See also Figure 1.13.1.

As an example for determination of k_a , k_b , and K_{IP} , we quote the replacement of Cl^- by SCN^- in 0.0005 M *trans*- $[\text{Co}^{\text{III}}(\text{en})_2\text{Cl}_2]^+$ in methanol ($\text{en} = \text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$; 60 °C). The ion pair equilibrium constant (K_{IP}) amounted to $180 \text{ dm}^3 \text{ mol}^{-1}$, and k_a and k_b were 2.0×10^{-5} and $1.0 \times 10^{-4} \text{ s}^{-1}$, respectively.¹²⁰ Since the complex is symmetrical and the positive charge dispersed, the ion pairing is weak.

On the other hand, K_{IP} in the replacement of chloride by NO_2^- in 0.001 M *trans*- $[\text{Co}(\text{en})_2\text{NO}_2\text{Cl}]^+$ in methanol (30 °C) is much larger and amounts to $4300 \text{ dm}^3 \text{ mol}^{-1}$; $k_a = 0$ and $k_b = 2.5 \times 10^{-4} \text{ s}^{-1}$, which means that the reaction product is formed exclusively from the ion pair. Strong ion pairing is to be

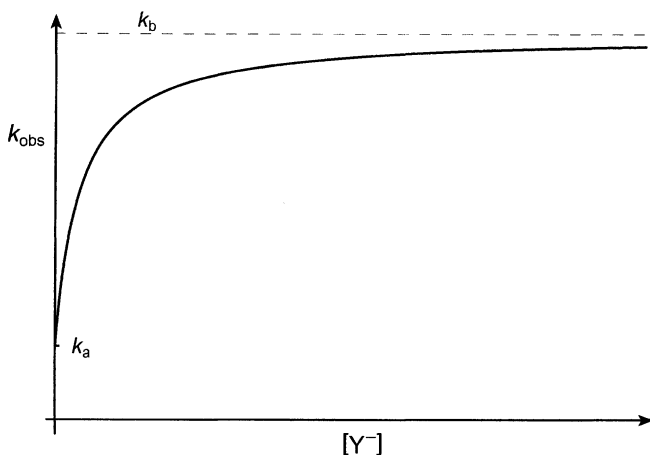


Figure 1.13.1. Schematic presentation of expression (1.13.7): when $[Y^-] = 0$, $k_{\text{obs}} = k_a$; when $[Y^-]$ is very large, $k_{\text{obs}} = k_b$.

expected because the “orienting” ligand, (NO_2), due to its negative electro-
meric effect, attracts electron density, thus increasing positive charge of the
central metal atom, which leads to increased ion pairing.¹²⁰

Table 1.13.1 contains values of equilibrium ion pair constants of some
positively charged cobalt(III) complex cations and univalent anions, includ-
ing also the divalent SO_4^{2-} anion, for comparison.

As expected, by far the largest is K_{IP} with the doubly negatively charged
 SO_4^{2-} . We can also notice that the smaller the anionic radii, the larger are the
 K_{IP} values. The ionic radii (in Å) increase in the sequence $\text{F}^-(1.36) < \text{Cl}^-$
(1.81) $< \text{Br}^-(1.95) < \text{I}^-(2.18)$.

Table 1.13.1. Equilibrium ion pair constants (K_{IP}) for some cobalt(III) complex
cations in aqueous solutions at 25 °C and practically zero ionic strength

Ion pair	K_{IP}	Reference
$\text{Co}(\text{NH}_3)_6^{3+} \cdots \text{I}^-$	17	121
$\text{Co}(\text{NH}_3)_6^{3+} \cdots \text{Br}^-$	46	121
$\text{Co}(\text{NH}_3)_6^{3+} \cdots \text{Cl}^-$	74	121
$\text{Co}(\text{NH}_3)_6^{3+} \cdots \text{SO}_4^{2-}$	2.2×10^3	122
$\text{Co}(\text{en})_3^{3+} \cdots \text{I}^-$	9	121
$\text{Co}(\text{en})_3^{3+} \cdots \text{N}_3^-$	11	121
$\text{Co}(\text{en})_3^{3+} \cdots \text{Cl}^-$	52	122
$\text{Co}(\text{NH}_3)_5\text{Cl}^{2+} \cdots \text{CH}_3\text{COO}^-$	5	123

1.14. PRIMARY AND SECONDARY KINETIC ISOTOPE EFFECTS

1.14.1. Primary kinetic isotope effects

The rate of certain chemical reactions can be significantly changed if one atom in a reactant molecule is replaced by an isotope of the same element. Changes in reaction rates which are brought about by isotopic substitution are called kinetic isotope effects. These effects are very important because they are used to elucidate the reaction mechanism.

The isotope effect is mainly due to the ground state vibrational energies, because these energies depend on atomic masses. Vibrational energies will change during a reaction on the way from the reaction ground state to its transition state, since some bonds will be weakened and broken and new bonds will be formed.

Considering eq. (1.4.15), we can conclude that the change in the reaction rate can be due to changes in $\Delta^\ddagger S^\circ$ or $\Delta^\ddagger H^\circ$, or both. The value of $\Delta^\ddagger S^\circ$ is normally insensitive to isotopic substitution. Thus, isotopic substitution must affect $\Delta^\ddagger H^\circ$. For reactions in solutions, we have shown (1.4.20) that:

$$\Delta^\ddagger H^\circ = E_a - RT$$

Let us now consider the kinetic effects due to different masses of atoms of the same element, *e.g.*, in a reaction involving C–H bond breaking as the slowest and therefore the rate-determining step. The reaction coordinate corresponds to the stretching of the C–H bond. If we replace hydrogen with deuterium, the replacement will take place on the bond being broken. The effects that follow are called primary kinetic isotope effects. On the other hand, if the heavy isotope is not on the bond being broken, but is only in the vicinity of the reaction center, still influencing the reaction rate, the effect is called the secondary kinetic isotope effect.

Replacement of hydrogen by deuterium leads to a lowering of the “zero-point energy” of the respective bond. However, the energy of the activated complex will change very little because the force constant (“spring constant”) of the activated complex is small; thus, the difference between the energies of the transition states for light and heavy isotopes becomes negligible. Replacement of hydrogen by deuterium will change the translation partition functions (*vide supra*). However, the mass of the molecule as the whole is usually so large that the total mass change can be neglected.

The energy of a molecule is the sum of electronic, vibrational, rotational, and translational energies. Isotopic replacement will not change the electronic

energy if the atomic nucleus contains, *e.g.*, one additional neutron. In addition, translational and rotational energies are not significantly changed by replacement of H by D either, as already mentioned. Thus, it is only the vibrational energy that does change significantly and should be considered. We can estimate these changes by supposing that a bond (*e.g.*, C–D bond) behaves like a harmonic oscillator.

As previously mentioned, the vibrational energy of a harmonic oscillator at absolute zero is given by the equation:

$$E_0 = \frac{1}{2} h \frac{1}{2\pi} \sqrt{\frac{f}{\mu}} \quad (1.14.1)$$

Since the reduced mass μ for a diatomic molecule is defined as

$$\mu = \frac{m_a m_b}{m_a + m_b} \quad (1.14.2)$$

$$\frac{1}{\mu} = \frac{1}{m_a} + \frac{1}{m_b} \quad (1.14.3)$$

E.g., if the relative reduced masses for oscillators C–H and C–D are denoted μ_1 and μ_2 , we have:

$$\mu_1 = \frac{12 \times 1}{12 + 1} = \frac{12}{13}$$

and

$$\mu_2 = \frac{12 \times 2}{12 + 2} = \frac{12}{7}$$

We see that $\mu_1 < \mu_2$, and from (1.14.1) and (1.14.3) it follows that the zero-point energy (E_0) for the heavy isotope is smaller than E_0 for the light isotope. The difference between the zero point energies of the ground state for the light and heavy isotopes is given by the following equation:

$$\Delta E_0 = \frac{1}{2} h \frac{1}{2\pi} \left[\sqrt{\frac{f}{\mu_1}} - \sqrt{\frac{f}{\mu_2}} \right] \quad (1.14.4)$$

The equation can be rearranged into

$$\Delta E_0 = \frac{h}{4\pi} \left[\frac{1}{\sqrt{\mu_1}} - \frac{1}{\sqrt{\mu_2}} \right] \sqrt{f} = \text{const.} \cdot \sqrt{f} \quad (1.14.5)$$

We can see that the difference between zero point energies, (ΔE_0), for light and heavy isotopes is proportional to $f^{1/2}$. The force constant f in the activated complex of the dissociative type reactions is very small, because the bond in the activated complex is almost broken, and thus the difference between ΔE_0 for light and heavy isotopes, in the activated complex, becomes negligible.

We can look upon the force constant as a spring constant, and a measure of the firmness of the spring of a two-atom harmonic oscillator. The stiffer the spring, the larger is the spring constant. For illustration, force constants of bonds C–C, C=C, C≡C amount to 450, 930 and 1590 N m⁻¹, respectively. The triple bond, being the strongest, has, of course, the largest f .

The described relations are depicted in Figure 1.14.1. We can see that the difference of zero point energies for the light and heavy isotopes ($= \Delta E_0^R$) is large in the reactants, but small in the reaction transition state ($= \Delta E_0^{TS}$). The difference between activation energies for the heavy and light isotopes ($E_a^D - E_a^H$) is approximately equal to the difference between the zero point energies of the reactants and the transition state, ($\Delta E_0^R - \Delta E_0^{TS}$). However, since ΔE_0^{TS} is very small, we can write:

$$E_a^D - E_a^H = \Delta E_a \approx \Delta E_0^R = N_A(E_0^H - E_0^D)^R \quad (1.14.6)$$

Thus, the difference between zero point energies for the light and heavy isotopes in the reaction ground state is practically equal to the difference of activation energies of the heavy and light isotopes. N_A is the Avogadro constant.

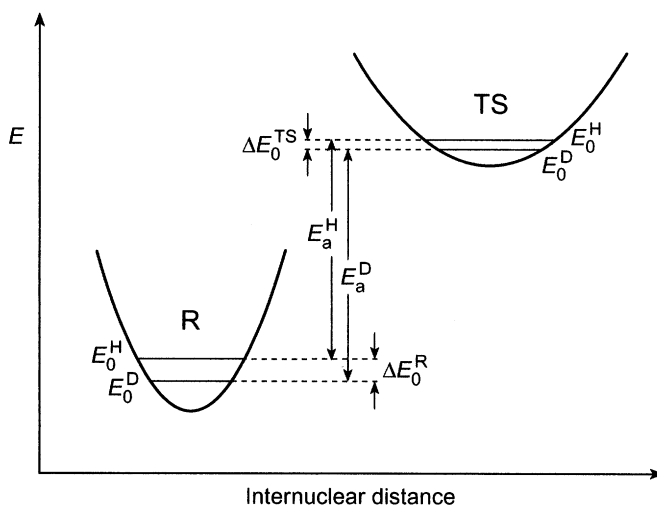


Figure 1.14.1. Potential energies for C–H and C–D oscillators in the reactants (R) and in the transition state (TS). The energy difference $\Delta E_0 = E_0^H - E_0^D$ is much larger in the reactants than in the transition state ($\Delta E_0^R \gg \Delta E_0^{TS}$).

In the following reactions, X is the light and X' is the heavy isotope.



The primary kinetic isotope effect is given by the ratio k_1/k_2 .

It is easy to show that the primary kinetic isotope effect, $k_{\text{H}}/k_{\text{D}}$, for breakage of C–H and C–D bonds, amounts to ≈ 7 (if in the reaction transition state, the proton or deuteron are “half transferred” to the base, causing a maximum energy change; on the other hand, if the proton or deuteron are more or less than half transferred to the base, the energy change is smaller than its maximum change, so $k_{\text{H}}/k_{\text{D}} < 7$ is to be expected).

In proton elimination reactions where hydrogen (or deuterium) are half transferred to the base in the activated complex, the IR spectra show that the wave numbers of C–H and C–D bonds are about 2950 and 2100 cm^{-1} , respectively. Since $E_0 = h\nu/2 = hc/2\lambda$, it follows that $\Delta E_0^{\text{R}} = (1/2)hc(1/\lambda_{\text{H}} - 1/\lambda_{\text{D}}) = (1/2) \times 6.63 \times 10^{-34} \text{ J s} \times 3 \times 10^8 \text{ m s}^{-1} \times 850 \times 10^2 \text{ m}^{-1} = 8.427 \times 10^{-26} \text{ kJ per molecule, i.e., } 5075 \text{ kJ mol}^{-1}$.

The ratio of Arrhenius equations for the rate constants of elimination of the light isotope (H) and of the heavy isotope (D) enables determination of $k_{\text{H}}/k_{\text{D}} = \exp(\Delta E_{\text{a}}/RT) = \exp[5075 \text{ J mol}^{-1} / (8.314 \text{ J K}^{-1} \text{ mol}^{-1} \times 300 \text{ K})] = 7.6$.

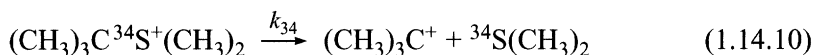
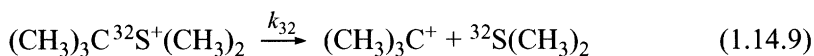
Indeed, in bromination of deuterated acetone, $k_{\text{H}}/k_{\text{D}}$ amounts to about 7.¹²⁴ This value is considered “normal”, and, as already pointed out, it is due to symmetrical bonding between the atoms involved in the H(D) transfer from the substrate to the base.¹²⁵ Calculations also show that the isotope effect is maximal when all three atoms involved in the H(D) transfer lie on a line in the transition state. In nonlinear configurations, $k_{\text{H}}/k_{\text{D}}$ is reduced to values of 1–2.^{126,127} Nonlinearity appears in several intermolecular mechanisms.^{126,127}

There are cases where the deuterium isotope effect is much higher than 7 (e.g., 24.2).¹²⁸ Such high isotope effects are ascribed to proton tunneling (a particle might be found on the outside of a container even though, according to classical mechanics, it does not possess sufficient energy to escape. Such passage through the classically forbidden zones is called tunneling, see section 1.15.). The H atom is small and, in principle, it can pass through the energy barrier and appear on the other side of the barrier, without ever reaching the top of the barrier. Thus, the hydrogen atom has not acquired the energy of activation, normally needed for passing over the barrier.

1.14.1.1. Primary kinetic isotope effect of sulfur-34

The lighter the element, the larger is the ratio of the heavy and the light isotope masses. Thus, the ratio of deuterium and hydrogen masses is 2/1, and that of sulfur-34 and sulfur-32 is $34/32 = 1.0625$. This is why the primary kinetic isotope effect of deuterium is relatively high compared to that of sulfur-34. Consequently, the lowering of the zero-point energies $E_0^H - E_0^D$ is much larger than that of the $^{32}\text{S}-^{34}\text{S}$ combination. As mentioned, the “normal” k_H/k_D ratio is about 7, or $[(k_H/k_D) - 1] \times 100 = 600\%$, while k_{32}/k_{34} ratio is only 1.015, *i.e.*, the isotope effect is about 1.5%.

Although the sulfur isotope effect is small, its determination might be very useful in studies of reaction mechanisms. This can be shown on the following example: the hydrolysis of *tert*-butyldimethylsulfonium iodide proceeds according to the scheme:



Reactions (1.14.9) and (1.14.10) have to be taken into consideration, since there is about 95.1% of ^{32}S and 4.2% of ^{34}S in nature. Isotopes ^{33}S (0.74%) and ^{36}S (0.016%) are not taken into account because of their small concentrations.

Relatively slow reactions (1.14.9) and (1.14.10) are followed by the fast reaction:



The reaction products are *tert*-butyl alcohol, H^+ and I^- . The reaction rate can be conveniently followed at 60 °C by titration of cooled aliquots with sodium hydroxide.¹²⁹ It should be assumed that slow reaction steps (1.14.9) and (1.14.10) involve breakage of the C–S bonds, that these steps are rate determining and that the C–S bonds are almost broken in the reaction transition state. If so, the rates of formation of reaction products with light and heavy isotopes are given by the first order rate equations:

$$x_{32} = a_{32}(1 - e^{-k_{32}t}) \quad \text{and} \quad x_{34} = a_{34}(1 - e^{-k_{34}t})$$

The ratio of products containing ^{32}S and ^{34}S is given by the expression:

$$\frac{x_{32}}{x_{34}} = \frac{a_{32}}{a_{34}} \frac{1 - e^{-k_{32}t}}{1 - e^{-k_{34}t}}$$

where a_{32} and a_{34} are initial concentrations of reactants with ^{32}S and ^{34}S , respectively, and x_{32} and x_{34} are concentrations of reaction products at reaction times t . Applying the above equation to our substrate, we can write:

$$[^{32}\text{S}(\text{CH}_3)_2]_t = [(\text{CH}_3)_3\text{C}^{32}\text{S}^+(\text{CH}_3)_2]_0(1 - e^{-k_{32}t}) \quad (1.14.12)$$

$$[^{34}\text{S}(\text{CH}_3)_2]_t = [(\text{CH}_3)_3\text{C}^{34}\text{S}^+(\text{CH}_3)_2]_0(1 - e^{-k_{34}t}) \quad (1.14.13)$$

In these equations, subscript zero denotes the initial concentrations of sulfonium salts, while subscript t refers to the concentration of dimethyl sulfide at time t . If we denote the reaction products $^{32}\text{S}(\text{CH}_3)_2$ and $^{34}\text{S}(\text{CH}_3)_2$ as ^{32}S and ^{34}S , respectively, and taking that the ratio $^{32}\text{S}/^{34}\text{S}$ in the sulfonium salt at $t = 0$ is exactly equal to the ratio $^{32}\text{S}/^{34}\text{S}$ in the reaction product, when the reaction is carried out to 100% completion, we can write (considering only the first two terms of expansion of exponential functions):

$$\left(\frac{^{32}\text{S}}{^{34}\text{S}}\right)_t \approx \left(\frac{^{32}\text{S}}{^{34}\text{S}}\right)_{t=\infty} \frac{1 - e^{-k_{32}t}}{1 - e^{-k_{34}t}} \quad (1.14.14)$$

and

$$\frac{k_{32}}{k_{34}} \approx \frac{\left(\frac{^{32}\text{S}}{^{34}\text{S}}\right)_{t=\text{small}}}{\left(\frac{^{32}\text{S}}{^{34}\text{S}}\right)_{t=\infty}} \quad (1.14.15)$$

In eq. (1.14.15), the subscript ($t=\text{small}$) denotes the initial reaction stage (about 2% completion of the reaction, while ($t=\infty$) denotes 100% completion of the reaction. This method gave the sulfur-34 kinetic isotope effect of 1.77%, *i.e.*, $^{32}k/^{34}k = 1.0177$. The meaning of this result can be evaluated if we know the maximum kinetic isotope effect for breaking the C–S bond. Assuming that the C–S bond is entirely broken in the reaction transition state, the maximum isotope effect can be approximately determined by applying the theory of Jacob Bigeleisen and Maria Goeppert-Mayer*.¹³⁰

* MARIA GOEPPERT-MAYER, 1906–1972, Polish-American physicist, shared the Nobel Prize for physics in 1963 with Eugene P. Wigner (1902–1995) and J. Hans D. Jensen (1907–1973).

In calculating the isotope effect, Bigeleisen considers all partition functions of translation and rotation, vibrational excitation, and vibrational zero-point energies. Complete analysis of a kinetic isotope effect may be carried out if the frequencies of all $(3N-6)$ modes of the reagents and $(3N-7)$ modes of the transition state are known (in the transition state, the stretching of the bond being broken is not a true vibration, but an anomalous one, with an imaginary frequency $\nu^\ddagger$).

At first, calculations of the kinetic isotope effect were possible only for molecules with a few atoms. Nowadays, there are computer programs for calculating vibrational frequencies for molecules with hundreds of atoms.

Calculation of the maximum isotope effect for C-S bond breakage is simple. Some of the C-S bond stretching frequencies of the relevant sulfonium salts can be found in literature, but some can not. In general, the stretching frequencies of C-S bonds of various sulfur-containing compounds lie between 700 and 800 cm^{-1} . The Bigeleisen equation for calculation of the kinetic isotope effect appears complicated:^{130b}

$$\frac{k_1}{k_2} = \sqrt{\frac{\mu_1}{\mu_2}} \left[1 + \sum_{i=1}^{3N-6} G(u_i) \Delta u_i - \sum_{j=1}^{3N-7} G(u_j^\ddagger) \Delta u_j^\ddagger \right] \quad (1.14.16)$$

In this equation, μ_1 i μ_2 are reduced masses of C-³²S and C-³⁴S “harmonic oscillators”, N is the number of atoms in the molecule under study, $3N-6$ is the number of modes of vibration for a non-linear molecule, and $3N-5$ for a linear molecule. The expression will be simplified owing to the fact that we wish to calculate the maximum isotope effect when, in the reaction transition state, the C-S bond is practically broken. For this reason, the right term in the bracketed expression of eq. (1.14.16) can be neglected, since we take the C-S bond, isolated from other atoms, as if it were a diatomic molecule, having $3N-5$ modes of vibration in the ground state (*i.e.*, one mode of stretching vibration), and $3N-6$ modes of vibration in the reaction transition state, *i.e.*, none.

Eq. (1.14.17) is the $G(u)$ free energy function of Bigeleisen and Goeppert-Mayer:¹³⁰

$$G(u) = \frac{1}{2} - \frac{1}{u} + \frac{1}{e^u - 1} \quad (1.14.17)$$

where u and Δu are defined by expressions:

$$u = \frac{hc}{k_B T} \omega \quad \text{and} \quad \Delta u = \frac{hc}{k_B T} \Delta \omega \quad (1.14.18)$$

where ω is the average wave number of the C-³²S (=750 cm⁻¹) and C-³⁴S (=744 cm⁻¹) vibrating combinations; their difference, $\Delta\omega$, is 6 cm⁻¹.

Simplified eq. (1.14.16) acquires the form:

$$\frac{k_1}{k_2} = \sqrt{\frac{\mu_1}{\mu_2}} [1 + G(u)\Delta u] \quad (1.14.19)$$

It follows:

$$\frac{1}{\mu_1} = \frac{1}{12.0000} + \frac{1}{31.9721}; \quad \mu_1 = 8.7252$$

$$\frac{1}{\mu_2} = \frac{1}{12.0000} + \frac{1}{33.9679}; \quad \mu_1 = 8.8674$$

By inserting in (1.14.18): $T = 298$ K; $h = 6.63 \times 10^{-34}$ Js; $c = 3 \times 10^{10}$ cm s⁻¹; $k_B = 1.380 \times 10^{-23}$ JK⁻¹, we get $hc/k_B T = 4.836 \times 10^{-3}$ cm. Since C-³²S vibrations occur between wave numbers 700 cm⁻¹ to 800 cm⁻¹, using eq. (1.2.3), we can calculate the corresponding limiting wave numbers for C-³⁴S as 694 to 794 cm⁻¹.

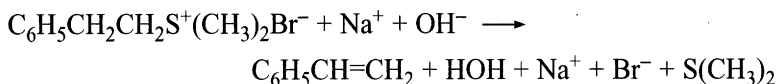
Thus, the values of the mentioned functions are:

$$\Delta u = 2.9016 \times 10^{-2} \quad u = 3.3707 \quad G(u) = 0.2389$$

Finally, $^{32}k/^{34}k = 1.0151$, or 1.51% (lower limit); $^{32}k/^{34}k = 1.0157$, or 1.57% (upper limit), the average calculated value being 1.54%.

We can see that the calculated ³⁴S kinetic isotope effect for the C-S bond breakage (1.54%) is smaller than the measured isotope effect (1.77%). It should be pointed out that such calculations are approximate, and that they are based on C-S vibrations, where vibrations of lighter carbon atom predominate. In addition, the sulfur atom is bonded to the rather large effective mass of *tert*-butyl group, causing an increase of the isotope effect.

Regardless of all these approximations, a valuable mechanistic conclusion can be drawn: hydrolysis of *tert*-butyl iodide is a dissociative process. Since most reactions that produce carbonium ion appear to have transition states closely resembling carbonium ion, it seems reasonable to assume that the isotope effect for the hydrolysis of *tert*-butyldimethylsulfonium iodide in water is a good approximation of the maximum isotope effect for the C-S bond cleavage. In sharp contrast to this is the very small isotope effect in the E₂ reaction of 2-phenylethyldimethylsulfonium bromide with hydroxide ion in water:



which amounts to only 0.15%. It can be concluded that in this reaction the C–S bond is stretched very little in the transition state, and therefore the transition state must have a considerable carbanion character.

One should remember that in molecules with a number of atoms, substitution might also influence the remaining vibrational frequencies, not only stretching frequencies.

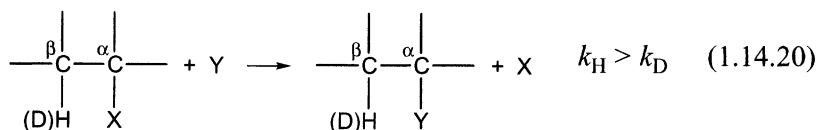
Isotope effects can explain many processes in nature. For instance, natural isotopic abundance of sulfur varies in different deposits. Thus, there is more sulfur-34 in sulfates than in elementary sulfur. Different chemical reactions with sulfur occur in nature, and in many cases sulfur circulates as hydrogen sulfide, various sulfides, sulfates, and so on. Sulfur-34 is enriched in sulfates, following the principle that the heaviest isotope forms the strongest bond. This fact offers the possibility of getting an insight into early geologic periods. *E.g.*, ocean water evaporating in the equatorial region yields water vapor poorer in deuterium but richer in protium. Thus, deuterium accumulates in the liquid phase. Winds transport hydrogen-enriched water vapor into polar regions, where ice contains deuterium in somewhat reduced concentrations. In this way, we can obtain some information about the temperatures of past geologic periods.

1.14.1.2. Isotope effects and the mechanism of enzymatic catalysis

It is generally accepted that enzymes act so as to stabilize reaction transition states. If the energy of a transition state is lowered, the reacting system will reach it with more ease and the reaction rate will increase. On the other hand, there are substances that can bind enzymes very strongly, yielding similar transition state, which may serve as enzyme inhibitors, a procedure of great importance in pharmaceutical sciences.¹³¹

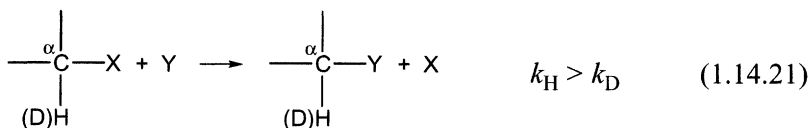
1.14.2. Secondary kinetic isotope effects

Until 1950, isotope effects were noticed only in reactions involving bond breaking (or bond making) between an atom (often carbon) and the isotope under study. Independently, Lewis and Boozer,¹³² and Shiner¹³³ observed that solvolyses, in which hydrogen, bonded to β -carbon, is replaced by deuterium, are significantly slowed down:



We notice that in (1.14.20) deuterium is bonded to β -carbon and that the bond between βC and $\text{H}(\text{D})$ is not broken during the reaction.

In 1957, three research groups, *viz.* Streitwieser and Fahey,¹³⁴ Saunders, Ašperger, and Edison,¹³⁵ and Mislow, Borčić, and Prelog*,¹³⁶ observed isotope effects in solvolyses of compounds deuterated on the reaction center, *i.e.*, on α -carbon, as in (1.14.21):



The bond between α -carbon and deuterium is not broken in the solvolysis transition state, but the presence of deuterium, bonded to the reaction center, causes the reaction rate decrease. Isotope effects such as in (1.14.20) and (1.14.21) are called secondary kinetic isotope effects, to be clearly distinguished from primary isotope effects. Secondary isotope effects were defined as rate effects caused by isotope substitution on the bond not broken in the rate-determining step.

The only condition for a kinetic isotope effect to occur is the change of the force constant on the way from the ground state of reactants to the transition state, as shown by eq. (1.14.5). This condition can be fulfilled though

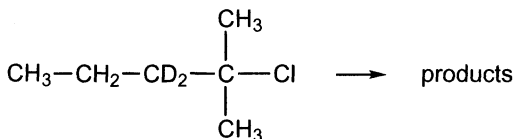
* VLADIMIR PRELOG, 1906–98, Croatian born Swiss chemist, shared the 1975 Nobel Prize for chemistry with J. W. Cornforth for studies in the stereochemistry of organic molecules and reactions. Prelog attended secondary school in Osijek and Zagreb, Croatia, studied chemistry at the University of Prague, receiving his PhD in 1929. He began teaching at the University of Zagreb in 1935, first as a lecturer and later as professor of organic chemistry. In 1941, on the invitation of Lavoslav (Leopold) Ružička [Croatian born Swiss chemist, 1887–1976, the recipient, with A. Butenandt, of the 1939 Nobel Prize for chemistry for his work on the terpenes, best known for his work on male sex hormones], Prelog joined the faculty of the Federal Institute of Technology (ETH) in Zürich, where in 1957 he succeeded Ružička as head of the laboratory of organic chemistry. Prelog was an excellent lecturer. Ružička attended some of his first lectures, delivered at ETH in somewhat broken German, and commented: "Prelog knows organic chemistry better than I do, but I am better in German". Ružička was born in Vukovar, Croatia; he attended secondary school in Osijek. By sheer coincidence the author of this book (S.A.) graduated from the same high school in Osijek, as Ružička and Prelog did. During his study at the University of Zagreb, S.A. was so enthusiastic about Prelog's stimulating lectures that he abandoned the studies of electrical engineering and switched to chemistry.

the bond to the isotope does not get broken but only weakened in the rate-determining step.

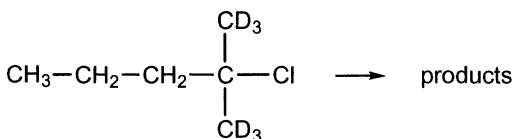
1.14.2.1. Secondary β -deuterium kinetic isotope effect

Secondary β -deuterium kinetic isotope effect is caused by hyperconjugation, *i.e.*, by the interaction of C–H or C–D bond electrons with the emptied p orbital of α -carbon after the formation of carbonium ion.* This interaction stabilizes the carbonium ion. The electron shift from $^{\beta}\text{C}$ –H bond into the emptied p orbital of $^{\alpha}\text{C}$ is larger than the analogous shift from $^{\beta}\text{C}$ –D bond, which means that the former electron shift stabilizes the carbonium ion better than the latter. The better-stabilized carbonium ion has a lower Gibbs energy of activation, which means a faster reaction with protium and slower with deuterium.

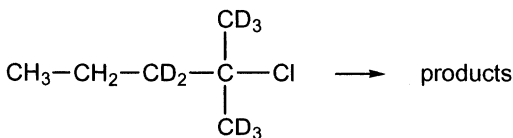
The secondary β -deuterium kinetic isotope effect is cumulative, as it has been shown by Shiner.¹³⁷ Thus, the rates of the *tert*-amyl chloride solvolysis depend on the degree of deuteration:



$$k_{\text{H}}/k_{\text{D}} = 1.40, \text{ or } 40\%/2\text{D} = 20\%/ \text{D}$$



$$k_{\text{H}}/k_{\text{D}} = 1.77, \text{ or } 77\%/6\text{D} = 13\%/ \text{D}$$



$$k_{\text{H}}/k_{\text{D}} = 2.35, \text{ or } 135\%/8\text{D} = 17\%/ \text{D}$$

* The term carbonium ion has been challenged because comparable oxonium ions (*e.g.*, H_3O^+) and ammonium ions (NH_4^+) have electron octets. The terms carbocation or carbenium ion have been suggested, and are often used.

1.14.2.2. Secondary α -deuterium kinetic isotope effect

Secondary α -deuterium kinetic isotope effect proved to be very useful in distinguishing between the organic reaction mechanisms of dissociative (S_N1) and associative (S_N2) types. A. Streitwieser, Jr. *et al.*¹³⁴ and K. C. Westaway¹³⁸ (see also the review article by D. E. Sunko¹⁴¹) explained the secondary α -deuterium kinetic isotope effect as being due to changes of the out-of-plane bending frequencies of the C–H(D) bonds. These frequency changes are due to the change of carbon hybridization from sp^3 in the ground state to sp^2 in the reaction transition state. Considerations on models suggest that out-of-plane bending frequencies are substantially lower in the carbonium ion-like transition state than in the tetrahedral ground state. On the other hand, the transition state of S_N2 substitutions has a geometry similar to the trigonal bipyramid, because the outgoing substituent has not yet left the molecule while the entering substituent is already weakly bonded. In such a geometric structure of the transition state, the out-of-plane bending vibrations are subdued, as compared to freer vibrations of the planar sp^2 hybrid. This simplified model explains why the α -deuterium kinetic isotope effect disappears in S_N2 reactions, while in S_N1 reactions the α -effect is substantial (up to 25% per one D atom). However, this simplified model does not enable calculations of the rates and isotope effects in S_N2 reactions.¹³⁹ A different explanation of the α -deuterium kinetic isotope effect was put forward by Wolfe and Kim.¹⁴⁰ They suggest that the decrease of the α -effect in S_N2 reactions is due to a looser rather than stiffer transition state. For a better insight, specific literature should be consulted.¹⁴¹ Nevertheless, experiments show that the α -deuterium kinetic isotope effect of S_N2 reactions is equal to one, or slightly larger than one, while in S_N1 reactions it is at its maximum, or very near to it.

1.15. INFLUENCE OF TUNNELING ON THE PRIMARY AND SECONDARY KINETIC ISOTOPE EFFECTS

There are cases where the primary deuterium kinetic isotope effect is much larger than 7, for instance 24.2, as found by Lewis and Funderburk.¹⁴² Such a high isotope effect is ascribed to proton tunneling. The hydrogen atom is small and, in principle, it can pass through the thin potential energy barrier and find itself on the other side of the barrier, though its energy is smaller than the energy of activation needed for passing over the barrier. The phenomenon of tunneling is due to the Heisenberg “uncertainty principle.” There are reactions where k_H/k_T (T refers to tritium) amounts to 79.¹⁴³ Unfortunately, the interpretation of kinetic isotope effects is often blurred by short-lived

intermediates. Thus, reaction branching can, under certain conditions, lead to anomalous temperature effects and extremely high kinetic isotope effects, which can imitate effects normally ascribed to tunneling.

The force that holds two similar atoms together, for instance two hydrogen atoms in a diatomic (H_2) molecule, is due to the fact that one electron, which only in the classical sense belongs to one or the other hydrogen nucleus, can exchange nuclei by quantum tunneling, and thus it belongs to both atoms.^{144,145} We are talking about a double harmonic oscillator. In this case, there are two masses, m_1 and m_2 , bonded by a spring, and therefore forced to move in a straight line, having the force constant f , and the equilibrium distance a . If x_1 and x_2 are coordinates of the point-masses involved, p_1 and p_2 are their moments, and the forces between these two bodies are equal but of opposite direction, then, in the classical sense, relative movement can be replaced by equivalent movement of one body of reduced mass.¹⁴⁶

Let us observe the movement of a particle towards a potential barrier of the final heights U_0 and thickness d . Let us assume that the particle energy is smaller than U_0 . In the classical sense, it is not possible for the particle to find itself on the other side of the barrier, but it is always reflected from the barrier. However, quantum mechanics shows that reflection and transmission of the particle (the wave packet) must be always considered, regardless of the particle energy, but with different probability. Figure 1.15.1 shows schematically the typical results for $|\psi(x,t)|^2$ (ψ = wave function), obtained by numerical solution of the problem of "dispersion" on the barrier.¹⁴⁵

Schrödinger equation (1.15.1) for one-dimensional motion

$$\frac{d^2\psi}{dx^2} + \frac{8\pi^2m}{h^2}(E - U) = 0 \quad (1.15.1)$$

can be used to calculate the tunneling probability of a particle of mass m , which penetrates the barrier from the left side (Figure 1.15.1). In case the wave packet energy is larger than the barrier ($E > U$) and the barrier is of constant height, the solution is obtained by integration:¹⁴⁷

$$\psi = Ae^{ikx}$$

where:

$$k = \frac{2\pi}{h}\sqrt{2m(E - U)}$$

and constant A is given by the expression:

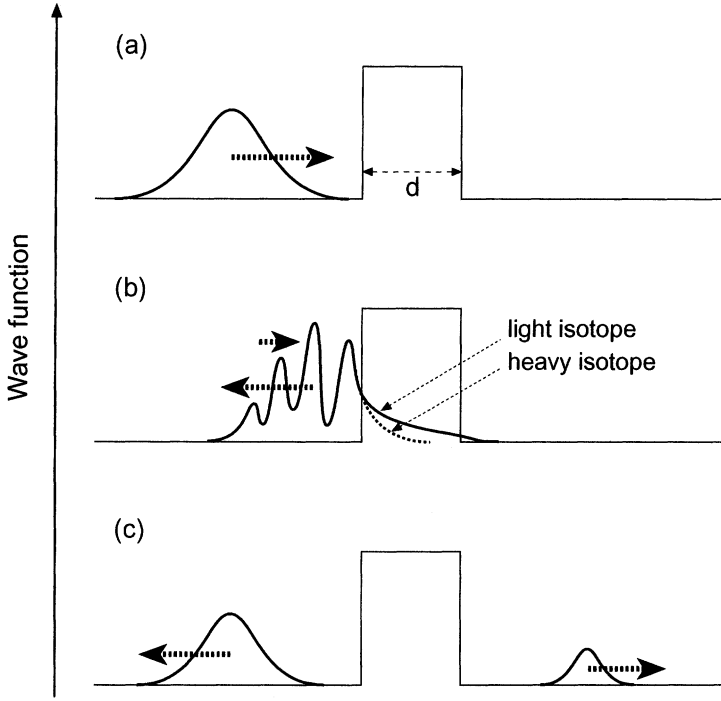


Figure 1.15.1. (a) Initial wave packet moves toward the barrier; (b) strong interference effects appear when part of the wave packet enters the barrier, and therefore the wave function oscillates (for $E < U$), but it decays exponentially inside the barrier. The wave function of the heavy particle decays inside the barrier, while the light particle has a significant probability of tunneling (c) the small wave packet has passed the barrier and the reflected wave package leaves the barrier in the opposite direction (adapted from ref. 145).

$$A^2 = \frac{1}{a\sqrt{\pi}} \quad |x| < a$$

which follows from the Gaussian function:

$$\psi(x, 0) = Ae^{-x^2/(2a^2)}$$

If $E < U$,

$$\psi = Ae^{-lx}$$

where:

$$l = \frac{2\pi}{h} \sqrt{2m(E - U)}$$

Thus, the wave function in front of the potential barrier is:¹⁴⁹

$$\psi_1 = A_1 e^{ikx} + A_2 e^{-ikx} \quad x < 0$$

The reflected wave appears in front of the potential barrier, part of the wave function corresponding to $A_2 \exp(-ikx)$. Behind the potential barrier, the wave continues in the positive direction of axis x :

$$\psi = ce^{i(kx-\alpha)}$$

where α is the phase shift.

The wave should be represented by a continuous function. As already mentioned, this function is very complicated because of the interfering effects. If the energy barrier is very broad (d is large), then the probability of passing through the barrier by tunneling is small, so that the total wave packet is practically reflected. If the barrier is thin (d is very small), the wave packet has a good chance to pass the barrier. If $d > 1$ (the barrier is rather broad), the coefficient of passage through the barrier (P) is approximately given by expression (1.15.2):¹⁴⁷

$$P = \frac{16E(U_0 - E)}{U_0^2} e^{-\frac{2d}{h}\sqrt{2m(U_0 - E)}} \quad (1.15.2)$$

We can see that P decreases exponentially with the barrier thickness (d), with the particle mass $m^{1/2}$, and with the energy difference $(U_0 - E)^{1/2}$. This is the reason why there is a probability of hydrogen tunneling, but for deuterium and tritium the probability of tunneling is negligible indeed. Hydrogen tunneling contributes to the size of the deuterium and tritium isotope effects. The ratio of probabilities for H and D tunneling (P_H/P_D) is approximately 300.

The rapidly established equilibrium in proton transfer reactions shows the proton's ability of tunneling.

Of special interest to chemists is the tunneling of H in NH_3 , which yields the characteristic inversion spectra. The appearance of these spectra can be only explained by tunneling. This is regarded as a great achievement of quantum mechanics.¹⁴⁶

1.15.1. Extremely high kinetic isotope effects and tunneling

It has been found that the measured kinetic isotope effects (primary and secondary) are sometimes significantly higher than the expected values. Maximum isotope effects will be observed when there is practically no difference between the zero-point energies of isotopically labeled substrates in the reaction transition state (eq. 1.14.6). Then, as already pointed out, the difference between the energies of activation $E_a^D - E_a^H \approx E_0^H - E_0^D$.

We should bear in mind that Arrhenius' pre-exponential factors ($A = PZ$, where P is the steric factor and Z is collision number) are almost equal for all isotopically labeled compounds. Namely, the change of the number of neutrons in nuclei does not significantly influence the value of PZ , because the charge of the species does not change. Investigating different reaction models it was found that A_H/A_D was always between 0.7 and 1.2 (for the temperature range 20–2000 K); the absolute minimum was 0.5.¹⁴⁸ Thus, we can write:

$$\frac{k_H}{k_D} \approx e^{-\Delta E_a/RT} \quad (1.15.3)$$

Smaller isotope effects than calculated from (1.15.3) are ascribed to reactions passing through an asymmetric transition state,^{149,150} as already discussed. If it is found that A_H/A_D is about 1, and ΔE_a is smaller than expected [smaller than $(E_0^H - E_0^D)$], while k_H/k_D follows eq. (1.15.3), we can conclude that the temperature dependence of the reaction under study is "normal". Larger effects than those foreseen are explained as being due to tunneling. Tunneling effects are always connected with abnormal temperature dependence of the reaction rate, compared to that foreseen by the Arrhenius equation.¹⁵² If $A_H/A_D < 0.6$, a correction for tunneling is considered necessary.¹⁵¹

Figure 1.15.2 explains schematically why tunneling leads to abnormal temperature dependence of the reaction rate and to the ratio of pre-exponential factors $A_H/A_D < 1$. As already mentioned, deuteration will not significantly change the values of $A = PZ$. Besides, steric configuration and the collision number will not be changed significantly by isotope substitution, because the increased number of neutrons does not affect the electric charge, on which the steric factor strongly depends. Figure 1.15.2 refers to the rates measured at temperatures close to room temperature; we can see that, as expected, the deuterated compound reacts more slowly than the protium compound. If tunneling is present, it involves hydrogen only, not deuterium. Tunneling will increase the reaction rate constant, k_H , but this kinetic effect will be lost at higher temperatures, since at higher temperatures the passage over the energy barrier becomes easier for all molecules, whether deuterated or not.

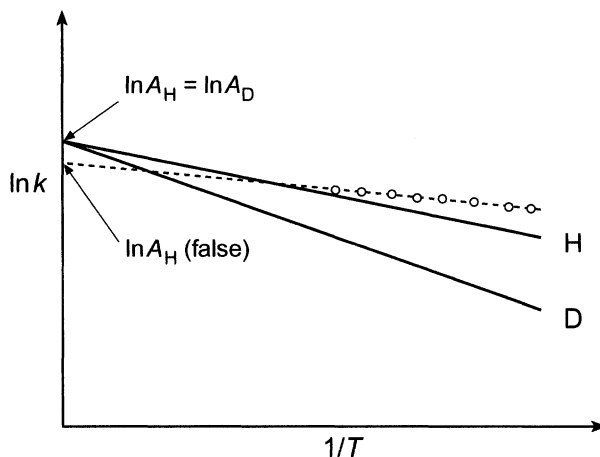


Figure 1.15.2. Arrhenius' plot yields $A_H/A_D < 1$, suggesting the presence of tunneling in the reaction system.

Experimentally obtained $\ln A_H$ and $\ln A_D$ values can differ because they are invariably determined by extrapolation of straight lines to $1/T = 0$ in Arrhenius plots. However, it is expected that at high temperatures, when tunneling becomes unimportant, the data for H will deviate from the straight line in the high temperature region, and the $\ln A_H$ and $\ln A_D$ values will coincide. Since $\ln A_H$ and $\ln A_D$ are determined by extrapolation of the rates measured around room temperature, extrapolation yields a false value of $\ln A_H$, causing $A_H/A_D < 1$; this points to the possible presence of tunneling in the reaction system.

1.15.2. Secondary α -deuterium kinetic isotope effect and tunneling

In reactions where the secondary α -deuterium kinetic isotope effect (α -D KIE) was substantial (20% per one D, or more) the mechanism was found to be dissociative (S_N1), with the transition state similar to the carbonium ion. Small α -KIE were found in nucleophilic substitutions of the associative type (S_N2).¹⁵³ In these substitutions $k_H/k_{\alpha-D}$ amounted to about 1.00 (no isotope effect). The size of the α -D KIE is characteristic of the leaving group. It is about 1.15 for the leaving chloride, and about 1.23 for sulfonates.^{154,155}

Lately, it was observed that the measured α -D KIE considerably exceeds the maximum value of the expected isotope effect. Thus, the α -D KIE for proton dissociation in some elimination reactions was found to be much higher than the expected maximum. Such results are ascribed to tunneling.¹⁵⁶ That tunneling can contribute not only to primary but also to secondary KIE is sup-

ported by model calculations, which predict appreciable tunnel corrections when the bending motions of the non-transferred proton are coupled with the stretching motion of the transferred proton.¹⁵⁷ Calculations also indicate that tunneling can lead to the same kind of abnormal temperature dependence as that observed for primary isotope effects; the ratio of Arrhenius' pre-exponential factors A_H/A_D (or A_H/A_T) is significantly less than unity. An example of this behavior is the reaction of $\text{PhCHTCH}_2\text{NMe}_3^+$ with EtO^- , which gives $A_H/A_T = 0.705 \pm 0.024$.¹⁵³ Tunneling is expected to be diminished when an atom heavier than the proton is transferred, and $(k_D/k_T)_{\text{sec}}$ is in fact lower when deuterium is transferred than when protium is transferred.¹⁵⁸ The assumption, which can be *a priori* accepted, is that α -D KIE reflects changes on the bond of the electron-donor atom in the reaction transition state, which is, in most cases, related to hybridization changes. If so, α -D KIE should vary monotonously from a small value for a transition state similar to the reactant to an equilibrium value for a transition state similar to the product.¹⁵⁷ However, experiments show that α -D KIE of the hydride ion transfer are significantly higher than equilibrium effects.^{159,160} Of special interest is the calculation of the transfer of the hydride ion.^{161,162} In any case, studies of α -D KIE often offer new important mechanistic information.

Despite the fact that the possibility of hydrogen tunneling in chemical reactions had been foreseen almost at the beginning of the quantum theory development, its acceptance took a long time because it was difficult to supply unambiguous experimental proofs.¹⁶³ Most evidence involved primary KIE. Thus, it has been shown that correction for tunneling, Q_t , decreases with an increase of isotopic masses: $Q_{t(H)} > Q_{t(D)} > Q_{t(T)}$. It is generally accepted that primary KIE: $k_H/k_D > 12$ and $k_H/k_T > 36$ (at 25 °C) provide reasonable evidence of the presence of tunneling.¹⁶⁴ But smaller effects than those mentioned can be also due to tunneling. Additional criteria for tunneling include an unusually steep temperature dependence of the reaction rate, and ratios of Arrhenius' pre-exponential factors A_H/A_D , and A_H/A_T smaller than 1, as already discussed.

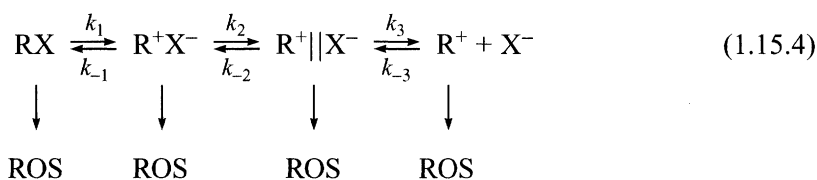
1.15.2.1. Reaction branching and extreme kinetic isotope effects

We have just mentioned that extreme KIEs are often accompanied by anomalous temperature effects, but these effects can be also due to reaction "branching", which can fully mimic the effects caused by tunneling.

Appearance of reaction branching, accompanied by extreme KIEs, often serves as evidence of the existence of short-lived intermediates. Thus, efforts were made to procure evidence for the existence of carbanions in proton

transfer reactions, and also to support the existence of carbocations and ion pairs in solvolyses. It has been shown in a series of papers¹⁶⁴ that competition between two processes with different KIEs, but with a common rate-determining step, leads to an increase of KIE in the process with a larger KIE.

Early literature explains extremely high isotope effects as being due solely to tunneling.¹⁶⁵ Today, however, it is known that unusually high primary KIEs, as well as ratios of Arrhenius' pre-exponential factors much less than 1, may be due to reaction branching if the rate of the reaction studied increases with temperature much more than the rate of the parallel reaction. Let us consider the composite reaction:



Scheme (1.15.4), the so-called Winstein's* scheme of ion pairs, includes the tight (intimate) ion pair (R^+X^-), the solvent separated ion pair ($\text{R}^+||\text{X}^-$), and the free ions. The scheme also includes reverse reactions at specific rates k_{-3} , k_{-2} and k_{-1} . It is just such a mechanism that can yield activation parameters mimicking those caused by tunneling.¹⁶⁶ Thus, acetolysis and formolysis of dideuterioferrocenylmethyl benzoate yield a very high α -D KIE, and exhibit an abnormal temperature dependence. In the presence of LiClO_4 ($\approx 0.1 \text{ mol dm}^{-3}$), which prevents the reverse of the solvent separated ion pair into the tight ion pair, $k_{\text{H}}/k_{\text{D}}$, at 25 °C, amounts to 1.53 ± 0.02 (acetolysis), and to 1.48 ± 0.03 (formolysis).¹⁶⁷ In the presence of LiClO_4 , the ratios of Arrhenius' pre-exponential factors, $A_{\text{H}}/A_{\text{D}}$, amount to 0.49 ± 0.01 (acetolysis), and to 0.38 ± 0.04 (formolysis).

* SAUL WINSTEIN, 1912–1969, professor of chemistry at the UCLA, was a leading figure in the development of the ion-pair chemistry. He showed that the carbocation could often be associated with some negatively charged ions to give contact-ion pairs and/or solvent-separated ion pairs. The carbocations, however, were so short-lived that, at that time, they could not be directly observed with spectroscopy. Investigations of the nucleophilic substitutions and rearrangements of 2-norbornyl derivatives led S. Winstein to suggest, in the early 1950s, that the intermediate carbocation was nonclassical and contained a pentacoordinated carbon. As the structures of carbonium ions were of great theoretical interest, the ensuing scientific controversy lasted for decades before finally solved.

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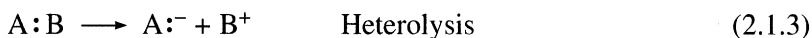
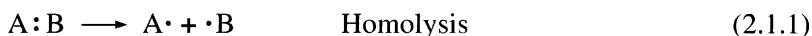
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Chapter 2

SUBSTITUTION REACTIONS ON METAL COMPLEXES

2.1. INTRODUCTION

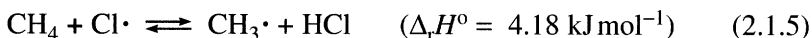
A chemical bond, represented in terms of shared pairs of electrons, can be broken homolytically or heterolytically, as shown by the following equations:



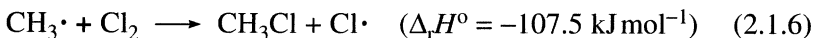
In homolysis, both fragments hold one electron each. If neither A nor B are transition metals, homolysis will lead to formation of free radicals. For instance, molecular chlorine, Cl_2 , whose dissociation energy is relatively low ($\Delta_r H^\circ = 242.67 \text{ kJ mol}^{-1} = 58 \text{ kcal mol}^{-1}$) will yield free radicals under the influence of light, or at elevated temperatures:



Radicals formed in this way can, even in small quantities, initiate chain reactions:



Methyl radical reacts further with chlorine:



Chlorine atom proceeds to react in the chain reaction. In practice, the chain reaction stops after some 10 000 cycles. The reason why the chain reaction discontinues is destruction of the chain carrier, as in eq. (2.1.7), when two radicals collide:



or



or



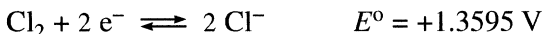
In reaction (2.1.8), two colliding chlorine atoms form a molecule, the released bond energy remains in the molecule as vibrational energy and exceeds the dissociation energy. Thus, the molecule just formed will dissociate unless a third body or wall happens to be present to take up the excess energy.

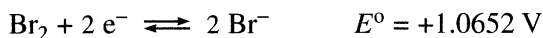
In homolyses of complexes, as in (2.1.1), the electron left on the metal, “metal radical”, is relatively stable so that homolysis leads to a reduction of the metal center [*e.g.*, cobalt(III) is reduced to cobalt(II)]; in other words, a redox process takes place.

Heterolytic reactions (2.1.2) and (2.1.3) are basically different. Reaction (2.1.2) requires an entering ligand that is a nucleophile, *i.e.*, a Lewis base. Such substitutions are called nucleophilic and carry the well-known symbol S_N . They can be unimolecular (S_N1) or bimolecular (S_N2), as already discussed in section 1.7. On the other hand, heterolysis as in (2.1.3) leaves the metal center with an electron pair. Such substitutions are called electrophilic and carry the symbol S_E . Analogously to nucleophilic substitutions (S_N1 and S_N2), electrophilic substitutions can be unimolecular or bimolecular, and carry symbols S_E1 or S_E2 .

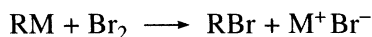
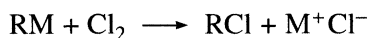
2.2. REACTIONS OF ORGANOMETALLIC COMPLEXES WITH HALOGENES (S_E2 MECHANISM)

Many organometallic complexes react strongly with chlorine and bromine. Their standard reduction potentials are as follows:





Reactions:



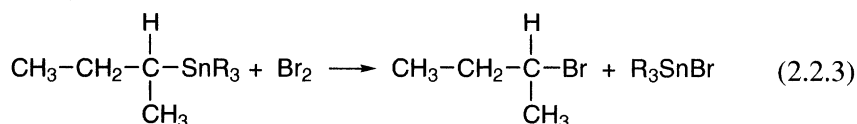
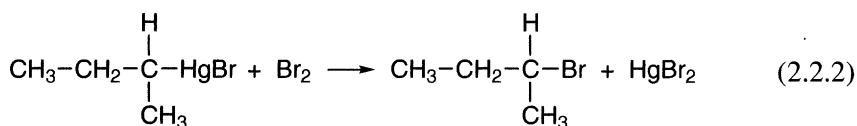
are considered electrophilic and can be written:



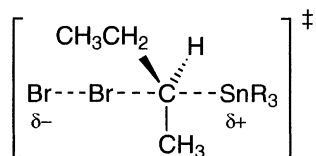
where Br^+ symbolizes the reaction with Br_2 , and reminds us that Br_2 reacts as an electrophile ($\text{Br}^+ \text{Br}^-$).

Substitutions of the $\text{S}_{\text{E}}1$ type are encountered in reactions of organometallic compounds in which carbon-metal bond ($\text{C}-\text{M}$) is clearly ionic in character.

Bimolecular electrophilic substitutions ($\text{S}_{\text{E}}2$) are very frequent. They proceed with retention or with inversion of configuration at the alkyl group. Examples are $\text{S}_{\text{E}}2$ reactions (2.2.2) and (2.2.3):



The transition state for reaction (2.2.3) is similar to that in reactions of the $\text{S}_{\text{N}}2$ type; steric factors are similar as well. The transition state has the structure:

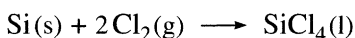


2.3. LABILE AND INERT COMPLEXES

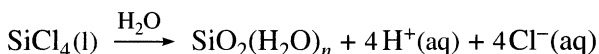
Labile complexes are complexes that react within a few minutes at room temperature. Inert complexes are complexes that react so slowly that their rates can be followed by conventional techniques.

The concepts lability and inertness are related to the reaction rate. They should not to be confused with (in)stability, which is a thermodynamic concept. Thermodynamics is concerned with the initial and final stages of a reaction only, *i.e.*, the reaction equilibrium, which depends on the Gibbs free energy: $-\Delta_r G^\circ = RT \ln K^\circ$. On the other hand, the rate at which equilibrium is reached is a kinetic problem, connected with the reaction mechanism.

A kinetically inert complex can be stable at the same time, but these concepts are not necessarily connected. Thus, a stable complex can be kinetically labile. For instance, $[\text{Hg}(\text{CN})_4]^{2-}$ has a high stability constant ($\beta_4 = 10^{42}$). Nevertheless, its cyanides are exchanged very rapidly in solutions, as shown by labeled CN^- . In addition, SiCl_4 is a very reactive compound. However, the equilibrium of its formation from elements is shifted entirely to the SiCl_4 side, according to the scheme:



which points to the conclusion that SiCl_4 is thermodynamically stable. On the other hand, the following fast reaction takes place in aqueous medium:



As can be seen, SiCl_4 has become thermodynamically unstable and at the same time kinetically labile.

Transition metal complexes were intensively studied at the beginning of the 20th century. As Alfred Werner anticipated, complexes with the coordination number six are octahedral. (Coordination number is the number of ligands bonded to the central metal atom). Just as the tetrahedral configuration is most common in organic chemistry, so is the octahedral configuration the dominant structure of inorganic complexes. This is the reason why most attention is paid to the octahedral structure.

Henry Taube* offered a theoretical explanation of the reactivity of octahedral complexes, in the qualitative sense. He assumed that a labile metal complex

* HENRY TAUBE is a Canadian-born American chemist. He was educated at the University of Saskatchewan at Saskatoon (Canada) and the University of California at Berkeley. He taught at Cornell University in Ithaca, N.Y., and at the University of Chicago before joining the faculty of Stanford University (California.) in 1961. His most important contribution relates

ion must have an empty t_{2g} orbital of low energy, or at least one electron in e_g orbital of high energy. Under such conditions, the t_{2g} orbital can accept electrons of an entering ligand in the transition state of either an associative (A) or an interchange associative (I_a) process. On the other hand, if electrons in the transition state occupy an e_g metal orbital of high energy, the interchange mechanism (I), or interchange dissociative mechanism (I_d), will be favored, because the bond will be weak in the ground state.

An inert metal ion must have at least one electron in the t_{2g} orbital, and none in the e_g orbital. Such ideas about labile and inert complexes can explain many experimental data of the rates of octahedral substitutions. Thus, the low spin complexes of chromium(III) (t_{2g}^3), cobalt(III) (t_{2g}^3), iron(II) (t_{2g}^6), and iron(III) (t_{2g}^5) are inert. This approach explains why vanadium(III) (t_{2g}^2) is more labile than vanadium(II) (t_{2g}^3).

This rationalization helps us understand why chromium(III) (t_{2g}^3) is inert whereas chromium(II) ($t_{2g}^3e_g^1$) is labile. Nevertheless, some experimental data remain unexplained, *e.g.*, why the exchange of water in hydrated nickel(II) ($3d^8$) is 10^2 times slower than in cobalt(II) ($3d^7$), and more than 10^4 times slower than in copper(II) ($3d^9$).

2.4. CRYSTAL-FIELD THEORY

The crystal-field theory was first put forward by Bethe¹ in 1929. Several review articles were published in the following forty years.² The essence of the theory is the fact that all five d orbitals are degenerated (equal in energy), in a gaseous metal ion, but not in an electrostatic field of lower symmetry, formed by ligands (crystal field).

Orgel³ and Jørgenson⁴ were the first to note the importance of the stabilizing effect of the crystal field and its influence on the rate of ligand substitutions in metal complexes. Earlier contributions in the field were described in a review article by H. Taube.⁵ Orgel pointed out that the reactivity of d^0 , d^1 and d^2 complexes, as compared with d^3 complexes, can be explained assuming that the first two complexes react by the S_N2 mechanism, the entering ligand occupying the empty d orbital of low energy. Thus, if the d_{xy} orbital is

to the oxidation or reduction of one metal ion by another involving exchange of electrons. Many such reactions occur rapidly in aqueous solutions though the water shells or other ligands prevent the two ions from approaching close enough for a direct electron exchange. However, if there were an atom, or group of atoms, firmly bonded both to the oxidant and the reductant, this would provide a path along which the electrons might travel. Taube demonstrated that such a mechanism involving a firm ligand bridge may be present at the time of electron transfer. Taube obtained the Nobel Prize for chemistry in 1983, "for his work on the mechanisms of electron transfer reactions, especially in metal complexes".

empty, the entering ligand will occupy this orbital. This will not be possible in d^3 and higher systems, because the electrons must pair, and pairing of electrons requires energy and increases the energy of these orbitals. Thus, all octahedral systems, regardless of whether they pass through the transition state of coordination number five (dissociative mechanism) or through the transition state of coordination number seven (associative mechanism), will react slowly. This is so because the crystal field stabilization energy lowers the energy of the ground state, thus increasing the energy needed for formation of the transition state. In other words, the energy of activation will be increased, which will cause a decrease of the reaction rate, in accordance with the Arrhenius equation. These ideas were elaborated in a semiquantitative manner by Basolo* and Pearson** in their first book,^{6a} and further elaborated in its second edition.^{6b}

2.4.1. Splitting of d orbitals in the octahedral crystal field

Let us consider the behavior of a metal ion in the center of an octahedron, surrounded by six ligands placed in the corners of the octahedron. Six electron pairs of ligands repel each other. These repulsions are the smallest if the six electron pairs are placed in six corners of the octahedron. There is no more favorable geometry, with less repulsions than the octahedral configuration. Let us consider titanium Ti^{3+} ion ($3d^1$). When ligands are still free, *i.e.*, not bonded to the metal, the lone d electron finds all five d orbitals equivalent for its accommodation. However, after the ligands are bonded, their six electron pairs mutually repel and the “crystal field” raises the energy of d orbitals. A metal-ion electron, in a d orbital that has lobes directed toward ligands, has a higher energy (because of electrostatic repulsion) than an electron in an orbital with lobes between the ligands. In octahedral complexes, therefore, orbitals of the e_g group have higher orbital energies than those of the t_{2g} group. We may conclude that in an octahedral complex the degeneracy of the metal d orbital may be considered to be split into a threefold degenerate set t_{2g} , and a higher energy twofold degenerate set, which is labeled e_g . The difference

* FRED BASOLO was born in Coello, Illinois. He made his University career at the Northwestern University, Evanston, Illinois. In 1983, Basolo served as president of the American Chemical Society. He is a member of the US National Academy of Sciences. Basolo is Willard Gibbs Medalist (1996). See also: F. Basolo, *From Coello to Inorganic Chemistry: A Lifetime of Reactions*, Kluwer Academic Publishers, New York, NY, 2002.

** RALPH G. PEARSON received his Ph.D. in 1943 from the Northwestern University, Evanston, Illinois. He was on the Northwestern University until he came to the University of California, Santa Barbara, California, in 1976. Pearson is a member of the US National Academy of Sciences.

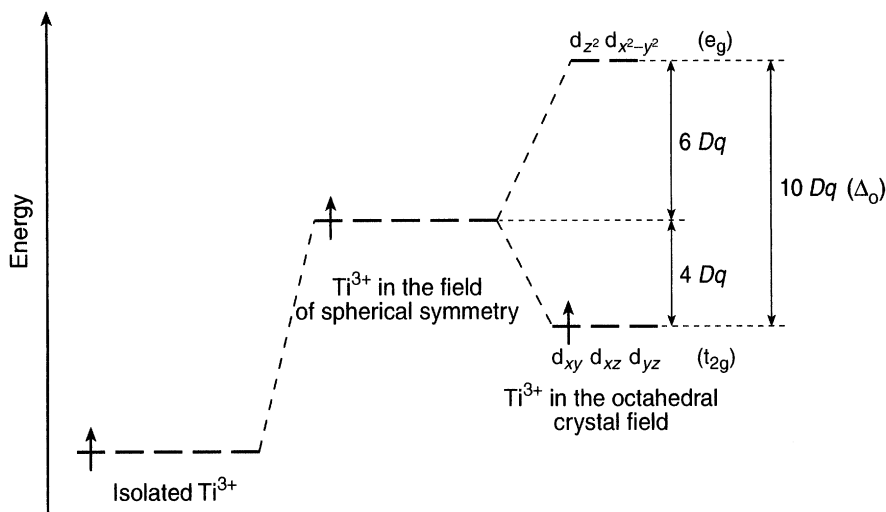


Figure 2.4.1. Splitting of Ti^{3+} d orbitals in the octahedral crystal field.

between orbital energies of the t_{2g} and e_g orbitals in an octahedral complex is given the symbol Δ_o (or the earlier symbol $10 Dq$).

The strength of the crystal field determines the magnitude of the d orbital splitting. The stronger the field, the larger the splitting, and the higher are the values Δ_o , Figure 2.4.1.

The value Δ_o is approximately given by the equation:^{7,8}

$$\Delta_o \approx 5(-e)q \frac{\bar{a}^4}{3r^5} = 5(-e)\mu \frac{\bar{a}^4}{3r^6} \quad (2.4.1)$$

where $-e$ is the electron charge, q is the charge of the six ligands, r is the distance between the central metal atom and the central ligand atom, $\bar{a}^4$ is the mean value of the distance between the central metal atom and the d electron raised to the fourth power, and $\mu = qr$.

Titanium oxide, Ti_2O_3 , has absorption at 500 nm, but the isolated Ti^{3+} has no absorption at that wavelength. The absorption corresponds to the titanium electron transfer from the t_{2g} into e_g level, so it is easy to calculate the value of Δ_o for $\lambda = 500$ nm; it amounts to 238 kJ mol^{-1} (57 kcal mol^{-1}), or ≈ 2.5 eV per one electron. Consequently, the stabilization energy of the octahedral crystal field of $4 Dq$ is approximately 1 eV per one electron.

In square planar complexes, the d orbitals exhibit four different relationships. The lobes of the $d_{x^2-y^2}$ orbital point towards ligands and have the highest orbital energy. The lobes of the d_{xy} orbital lie between orbitals but are coplanar with them, so this orbital is the next highest in energy. The lobes of

the d_{z^2} orbital point out of the complex plane. The electron density belt, containing about one third of the electron density, lies in the complex plane. The d_{z^2} orbital is therefore the next highest in energy. The degenerate d_{xz} and d_{yz} orbitals are least affected by the crystal field, since their lobes point out of the plane of the complex, and are, therefore, of the lowest energy.

The order of splitting of the d orbitals in a tetrahedral complex may be derived using the relation of tetrahedrally arranged ligands to a set of Cartesian coordinates and a hypothetical cube. In such an arrangement the lobes of the d_{xy} , d_{xz} , and d_{yz} orbitals point toward cube edges, and the lobes of the d_{z^2} and $d_{x^2-y^2}$ orbitals point toward the centers of cube faces. We can conclude that the threefold degenerate t_{2g} orbitals are of higher energy than the twofold degenerate e_g orbitals. The difference in energy bears the symbol Δ_t .

The $3d_{z^2}$ and $3d_{x^2-y^2}$ orbitals of an octahedral complex, along with the 4s and three 4p orbitals are assumed to overlap six ligand orbitals, forming six bonding molecular orbitals and six antibonding molecular orbitals.

One should bear in mind that the crystal field theory foresees the electron transition from the t_{2g} orbital into the e_g level, but these transitions are symmetry forbidden. The t_{2g} orbitals which do not overlap the σ orbitals of the ligands are actually nonbonding, but the t_{2g} orbitals can form bonds through π bonding.

The crystal field effects are of the order of $\approx 40\text{--}200\text{ kJ mol}^{-1}$ ($\approx 10\text{--}50\text{ kcal mol}^{-1}$).⁹ This is, in fact, a small fraction of the total bonding energy of a complex; the energy of attraction of a positive metal ion and negative ligands is somewhere between 2000 to 6000 kJ mol^{-1} (500–1500 kcal mol^{-1}). Thus, the geometry of a complex and the reaction rates cannot be determined by crystal field stabilization energies only, but these effects can tip the balance in favor of, *e.g.*, a reaction intermediate which has a square pyramidal structure, or, alternatively, a reaction intermediate which has a trigonal bipyramidal geometry.¹⁰

2.4.2. Crystal-field stabilization energies of d orbitals for various geometric configurations, and substitution rates

Differences of d orbital energies in a crystal field have been calculated for various geometries of the possible transition states of some replacement reactions.¹⁰ The calculations assume a pure crystal field (without covalent bonds), equal bond lengths in the ground and transition states, and some additional simplifications. In this way, crystal field stabilization energies were calculated for the ground state and the transition state, and the difference between

these energies was taken to be the crystal field activation energy. Table 2.4.1 is the result of these calculations.¹⁰ It shows the splitting of d orbitals of the central metal ion of different geometric structures. We should bear in mind that in bonding of a ligand with a metal ion the total energy of the reacting system decreases. However, since ligands are negatively charged and suffer mutual repulsion, the energy of all orbitals is increased (crystal field). But, the energy of some orbitals rises more than that of the others. We are, thus, concerned with the relative d orbital energies in a crystal field, which makes Table 2.4.1 very useful.

Table 2.4.1. Energies of d orbitals (in Dq units) in crystal fields of different symmetries (according to F. Basolo and R. Pearson¹⁰)

Structure	$d_{x^2-y^2}$	d_{z^2}	d_{xy}	d_{xz}	d_{yz}
Octahedron	6.00	6.00	-4.00	-4.00	-4.00
Trigonal bipyramid	-0.82	7.07	-0.82	-2.72	-2.72
Square pyramid	9.14	0.86	-0.86	-4.57	-4.57
Pentagonal bipyramid	2.82	4.93	2.82	-5.28	-5.28
Octahedral wedge (Fig. 2.4.2)	8.79	1.39	-1.51	-2.60	-6.08
Tetrahedral	-2.67	-2.67	1.78	1.78	1.78
Square planar	12.28	-4.28	2.28	-5.14	-5.14
Linear (bonds lie along z axis)	-6.28	10.28	-6.28	1.14	1.14

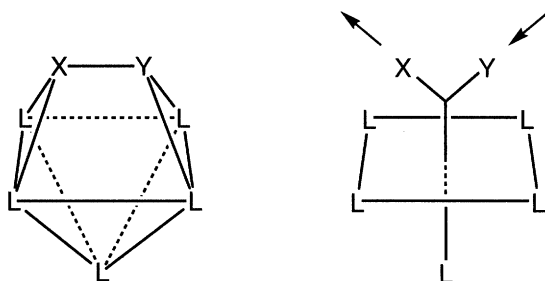


Figure 2.4.2. Structure of the heptacoordinated “octahedral wedge”. X is the leaving ligand and Y is the entering ligand.

Table 2.4.2 provides data on crystal field stabilization energies for the octahedral d^n complexes in strong and weak fields.¹⁰ We can see that in a strong crystal field (low spin) the cobalt(III) complex (d^6) has the stabilization energy of $24 Dq$. This energy should be reduced by the electron pairing energy. It follows from spectral data that, for H_2O ligand, $10 Dq \approx 234 \text{ kJ mol}^{-1}$. The crystal field is stronger for NH_3 ligand and $10 Dq$ has $\approx 25\%$ higher value.

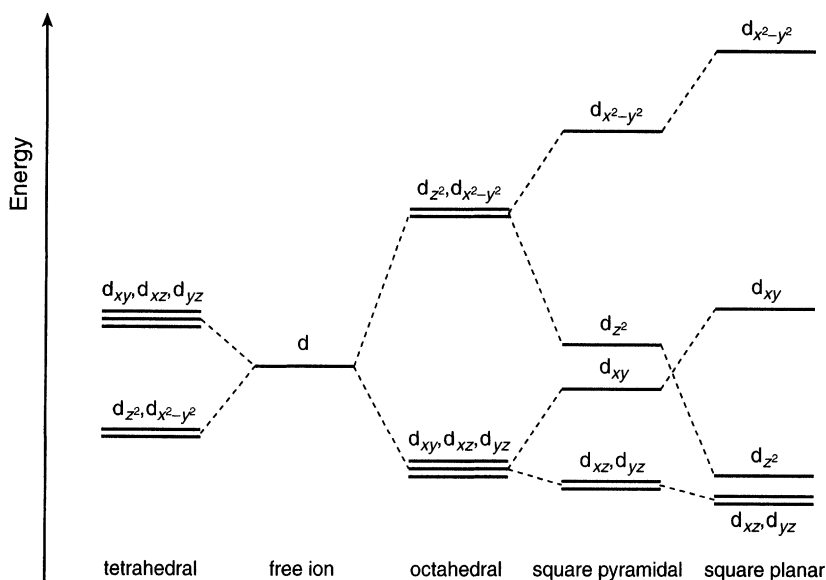


Figure 2.4.3. Splitting of d orbitals of the central metal atom in crystal fields of various geometries^{6b} (reproduced by permission from F. Basolo and R. G. Pearson, and the John Wiley and Sons, Inc.).

Table 2.4.2. Crystal field stabilization energies (in Dq units) for octahedral metal complexes in weak and strong fields (according to F. Basolo and R. G. Pearson¹⁰)

Example		Octahedral configuration						Gain in orbital energy
		Weak field			Strong field			
		t_{2g}	e_g	ΔE	t_{2g}	e_g	ΔE	
d^0	$\text{Ca}^{2+}, \text{Sc}^{2+}$	0	0	0	0	0	0	0
d^1	$\text{Ti}^{3+}, \text{V}^{4+}, \text{U}^{4+}$	1	0	4	1	0	4	0
d^2	$\text{Ti}^{2+}, \text{V}^{3+}$	2	0	8	2	0	8	0
d^3	$\text{V}^{2+}, \text{Cr}^{3+}$	3	0	12	3	0	12	0
d^4	$\text{Cr}^{2+}, \text{Mn}^{3+}$	3	1	6	4	0	$16(1)^{(a)}$	10
d^5	$\text{Mn}^{2+}, \text{Fe}^{3+}, \text{Os}^{3+}$	3	2	0	5	0	$20(2)^{(a)}$	20
d^6	$\text{Fe}^{2+}, \text{Co}^{3+}, \text{Ir}^{3+}$	4	2	4	6	0	$24(2)^{(a)}$	20
d^7	$\text{Co}^{2+}, \text{Ni}^{3+}, \text{Rh}^{2+}$	5	2	8	6	1	$18(1)^{(a)}$	10
d^8	$\text{Ni}^{2+}, \text{Pd}^{2+}, \text{Pt}^{2+}, \text{Au}^{3+}$	6	2	12	6	2	12	0
d^9	$\text{Cu}^{2+}, \text{Ag}^{2+}$	6	3	6	6	3	6	0
d^{10}	$\text{Cu}^+, \text{Zn}^{2+}, \text{Cd}^{2+}, \text{Ag}^+, \text{Hg}^{2+}, \text{Ga}^{3+}$	6	4	0	6	4	0	0

^(a) Numbers in parentheses denote the number of electrons that must be paired when the field changes from a weak to a strong one.

Thus, the crystal field stabilization energy of $24 Dq$ depends on the nature of the ligand involved and amounts to $565\text{--}710 \text{ kJ mol}^{-1}$ ($135\text{--}170 \text{ kcal mol}^{-1}$). Electron pairing energy is estimated at $355\text{--}420 \text{ kJ mol}^{-1}$ ($85\text{--}100 \text{ kcal mol}^{-1}$) for two electrons;⁹ thus, for $\text{Co}(\text{H}_2\text{O})_6^{3+}$, the net gain in stabilization energy is at least 40 kcal mol^{-1} . For $\text{Cr}(\text{H}_2\text{O})_6^{3+}$, crystal field stabilization energies, in strong and weak field, are $12 Dq$ (see Table 2.4.2). Since there is no electron pairing (d^3 system), and $10 Dq$ corresponds to the wave number of 17400 cm^{-1} ($208.5 \text{ kJ mol}^{-1}$, or $49.88 \text{ kcal mol}^{-1}$), the stabilization energy of $12 Dq$ corresponds to $249.78 \text{ kJ mol}^{-1}$ ($59.76 \text{ kcal mol}^{-1}$).

2.4.3. Influence of crystal field stabilization energies on the rates and mechanism of octahedral substitutions

Crystal field stabilization energies are obtained as a result of the preferential entry of electrons into orbitals that are oriented as far as possible from the ligands, in order to reduce their electron repulsions. The better the stabilization of the transition state, with regard to its geometry, the lower is the energy of activation, and the faster is the substitution reaction. On the other hand, a transition state that is better stabilized is also more probable. Thus, an octahedral complex reacting by a D-type mechanism [$\equiv S_N1(\text{lim})$] may react through an activated complex of a square pyramidal structure or over a trigonal bipyramid. It appears that the square pyramidal transition state is better stabilized by the crystal field than the trigonal bipyramid and therefore the square pyramidal structure of the activated complex appears to be more likely.

Table 2.4.3 contains crystal field stabilization energies for reactions of octahedral complexes d^0 to d^{10} , proceeding over the square pyramidal activated complex, while Table 2.4.4 pertains to the trigonal pyramidal activated complex.

We can see that reactions proceeding over a square pyramidal activated complex are faster than those reacting over a trigonal bipyramidal activated complex. Thus, the Co^{3+} complex ($3d^6$) reacts in a strong field with an increased E_a of $4.00 Dq$; should the activated complex be trigonal bipyramidal, the energy of activation in the strong field would be raised by $11.48 Dq$. Thus, the trigonal bipyramid is not a very probable geometry of the activated complex; in a weak field, the reaction path over the square pyramidal transition state has a lower energy of activation (by $-0.57 Dq$), while the reaction path over trigonal bipyramid has a higher energy of activation (by $1.27 Dq$).

Table 2.4.5 shows the crystal field effects on energies of activation in an associative type reaction (S_N2). The reaction intermediate is pentagonal bipyramid with coordination number 7.

Table 2.4.3. Calculated crystal field stabilization energies (in Dq units) of octahedral complexes, reacting by the D mechanism through a square pyramidal transition state (according to F. Basolo and R. G. Pearson¹⁰)

Octahedron $\longrightarrow$ Square pyramid						
	Strong field			Weak field		
	Octahedron	Square pyramid	ΔE_a	Octahedron	Square pyramid	ΔE_a
d^0	0	0	0	0	0	0
d^1	4	4.57	-0.57	4	4.57	-0.57
d^2	8	9.14	-1.14	8	9.14	-1.14
d^3	12	10.0	2.0	12	10.00	2.00
d^4	16	14.57	1.43	6	9.14	-3.14
d^5	20	19.14	0.86	0	0	0
d^6	24	20.00	4.00 ^(a)	4	4.57	-0.57 ^(b)
d^7	18	19.14	-1.14	8	9.14	-1.14
d^8	12	10.00	2.00	12	10.00	2.00
d^9	6	9.14	-3.14	6	9.14	-3.14
d^{10}	0	0	0	0	0	0

^(a) E_a increased by 4 Dq and substitution is slowed down.

^(b) E_a decreased by 0.57 Dq and substitution is accelerated.

Table 2.4.4. Crystal field stabilization energies (in Dq units) for substitution reactions of an octahedral complex reacting by the D mechanism over an activated complex of a trigonal bipyramid geometry (calcd. from data in Table 2.4.1)

Octahedron $\longrightarrow$ Trigonal bipyramid						
	Strong field			Weak field		
	Octahedron	Trigonal bipyramid	ΔE_a	Octahedron	Trigonal bipyramid	ΔE_a
d^0	0	0	0	0	0	0
d^1	4	2.72	1.28	4	2.72	1.28
d^2	8	5.44	2.56	8	5.44	2.56
d^3	12	6.26	5.74	12	6.26	5.74
d^4	16	8.98	7.02	6	7.08	-1.08
d^5	20	11.70	8.30	0	0.01	-0.01
d^6	24	12.52	11.48 ^(a)	4	2.73	1.27 ^(a)
d^7	18	13.34	4.66	8	5.45	2.55
d^8	12	5.27	6.73	12	5.27	6.73
d^9	6	7.09	-1.09	6	7.09	-1.09
d^{10}	0	0	0	0	0	0

^(a) Slow reaction.

Table 2.4.5. Influence of the crystal field on activation energies (in Dq units) in reactions of the associative type octahedral complexes (calcd. from data in Table 2.4.1)

	Octahedron $\rightarrow$ Pentagonal bipyramid					
	Strong field			Weak field		
	Octahedron	Pentagonal bipyramid	ΔE_a	Octahedron	Pentagonal bipyramid	ΔE_a
d^0	0	0	0	0	0	0
d^1	4	5.28	-1.28	4	5.28	-1.28
d^2	8	10.56	-2.56	8	10.56	-2.56
d^3	12	7.74	4.26	12	7.74	4.26
d^4	16	13.02	2.98	6	4.93	2.07
d^5	20	18.30	1.70	0	0	0
d^6	24	15.48	8.52	4	5.28	-1.28
d^7	18	12.66	5.34	8	10.56	-2.56
d^8	12	7.74	4.26	12	7.74	4.26
d^9	6	4.93	1.07	6	4.93	1.07
d^{10}	0	0	0	0	0	0

Tables 2.4.3 and 2.4.5 show that, for d^0 , d^1 and d^2 complexes, crystal field stabilization energies (ΔE_a) are negative or zero, which means that their reactions are fast regardless of the mechanism. In fact, these complexes are labile. On the other hand, d^3 octahedral complexes as well as d^4 , d^5 and d^6 complexes have positive ΔE_a , which indicates slow reactions. Indeed, complexes of this type are inert. In addition, d^5 and d^6 and d^7 complexes ("outer-orbital" complexes, *i.e.*, complexes of a weak crystal field) are labile, as expected. Their ΔE_a are negative or zero (E_a is lowered) and therefore the reactions are fast regardless of the mechanism).

The crystal field theory has significantly contributed to the understanding of the reactivity of metal complexes, but many kinetic data have remained unexplained. It can be concluded that the Basolo and Pearson approach to the reactivity of metal complexes, based on the crystal field theory, is very useful and, which is important, simple, but it is not complete because of several approximations. Nevertheless, it is most successful when applied to relative reactivities for a particular reaction of a series of complexes that differ only in the nature of the central atom.

More recently, alternatives to the crystal field approach of Basolo and Pearson were proposed which lead to more accurate results but are theoretically and computationally very demanding and not easy to perform.

Nowadays, it is a common practice to carry out *ab initio* calculations on small to medium-sized organic molecules. *Ab initio* methods produce a wave

function using no experimental data other than the masses and charges of the elementary particles. Such calculations are expected to yield bond lengths and bond angles in good agreement with experiments. Difficulties, however, arise with molecules containing transition metals. The problem is in determining electron repulsions. The central difficulty in applying the Schrödinger equation are the electron-electron interactions.

The potential energy of the electrons consists of two terms, the first being the total attractive interaction between the electrons and the nuclei whilst the second term is the total repulsive interaction between electrons. Analytical solution of the Schrödinger equation with such complicated potential energy terms (based on the Coulomb law) is impossible. One of simpler approximate solutions, *viz.* the Hartree-Fock procedure, offers a solution to the problem. All electrons except one are placed in the lowest orbitals, but one of these orbitals will have a “hole” since one electron is temporarily ignored. For instance, if we consider the sodium atom (Na), the expected configuration is $1s^2 2s^2 2p^6 3s^1$. The Schrödinger equation can be written for the 3s electron because the repulsive field generated by all of the involved electrons is averaged and taken as that acting upon the selected electron, modifying its orbitals. The selected 3s electron is then placed into this modified orbital. This procedure is repeated for all remaining electrons, each time using the improved orbitals from the previous stage, and so over and over again until the input and output are practically the same. In this way, a self-consistent field (SCF) is obtained, and accepted as the solution to the problem.

The weakness of this method is that it smears the density of the selected electrons over the whole molecule. The consequence is that the electrons will tend to avoid the surroundings of the selected electron, but not so much the surroundings of other electrons. Calculations can take into account this situation. Further difficulties arise because the d electrons cover a relatively small volume, while the ligands' electron densities are much more diffuse and cover large volumes.

It is obvious that such calculations are far from being simple. Thus, the Fe–C bond in ferrocene was found to be 0.07 Å longer than experimentally determined, after calculations which included configuration interactions with over a million excited state configurations. However, these results have been found useful because they suggest that the iron-carbon bond in ferrocene is more covalent than indicated by calculations. This observation is in agreement with the very high secondary α -deuterium kinetic isotope effect (about 25% per one D) observed in acetolysis and formolysis of dideuterioferrocenyl-methyl benzoate, suggesting a carbonium ion-like transition state, stabilized mainly by conjugation with the π system of the pentadienyl ring (see Chapter 1, ref. 167).

2.5. LIGAND FIELD AND ELECTRON TRANSITIONS

The crystal field theory assumes electron transitions from t_{2g} into e_g orbitals, but these transitions are symmetry-forbidden, which gives this absorption a relatively low probability. Quantum mechanics shows that a photon has an intrinsic spin angular momentum corresponding to $I = 1$. If a photon is generated by an electronic transition, then the angular momentum of the electron must change to compensate for the angular momentum carried away by the spinning photon. It follows that a d electron ($l = 2$) cannot make a transition into an s orbital ($l = 0$) because the photon cannot leave the molecule with enough angular momentum. Quantum mechanics quotes the following rules:

A. Electron transitions where the number of unpaired electrons changes on the way from the ground state to the transition state are “forbidden” (spin forbidden), in other words, not probable. [This is not the case with $Ti(H_2O)_6^{3+}$, because this ion has one unpaired electron in the t_{2g} orbital, and in the excited state this electron only passes into the empty e_g orbital.]

B. Transitions from a centrosymmetric orbital (such an orbital is called “gerade”, it comes from German, and means “even”) into another centrosymmetric orbital is said to be Laporte forbidden.¹¹ Transitions between “gerade” and “ungerade” (odd) orbitals are allowed. Since d orbitals (t_{2g} and e_g) are centrosymmetric, electron transitions between these orbitals are forbidden. In other words, the probability of such transitions is zero. However, this rule holds if the d orbitals are “pure”, which means that they are not mixed with ligand orbitals, or with orbitals of some other metal. A disadvantage of the crystal field theory is the fact that the theory does not take into account interactions between metal and ligand orbitals. The ligand field theory does just that. If the metal orbitals are impure, due to mixing with ligand orbitals, they lose their symmetrical purity (for instance, d orbitals) and the transitions between them becomes possible. The molar absorption coefficient is not zero any more, but remains small. Thus, the molar absorption coefficients for $d \rightarrow d$ transitions amount to about 50 to $100 \text{ dm}^3\text{cm}^{-1}\text{mol}^{-1}$, while in $d \rightarrow p$ transitions, which are allowed (because p orbitals are *ungerade*), they amount to about 1000 units.

The molecular orbital theory adequately explains light absorption. Namely, while nonbonding t_{2g} orbitals are, let us say, pure *gerade* orbitals, the e_g bonding and e_g^* antibonding orbitals are definitely not “pure” orbitals, because they are, according to the theory, formed by mixing of orbitals. Under such conditions the electron transfer from t_{2g} into the impure antibonding (e_g^*) orbital becomes possible.

On the other hand, not even the t_{2g} nonbonding orbitals can be considered symmetrically pure; they cannot form a σ bond, but can form a π bond. This means that the t_{2g} orbitals become impure by π bonding and electronic transitions may include these orbitals. Such π bonding lowers the t_{2g} orbital energy, as depicted in Figure 2.5.1. The energy difference $E(e_g) - E(t_{2g}) = \Delta E$ increases, and the complex starts to absorb shorter wavelength radiation, which is often called a blue shift.

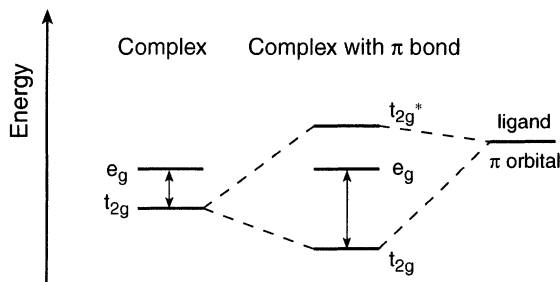


Figure 2.5.1. Effect of ligand π bonding with the metal t_{2g} orbital. Specific case: the metal orbital is occupied while the ligand orbital is empty (metal $\rightarrow$ ligand π bonding).

The question may now arise whether it is possible to use the crystal field theory for mechanistic predictions. It is taken that the answer is positive, assuming that the degree of orbital overlap is not too large. Experience shows that the orbital overlap is often small, which leads to the modified (adjusted) crystal field theory. However, if the orbital overlap is large, then the molecular orbital approach is the only solution. On the other hand, molecular orbital overlap calculations are not easy to perform.¹²

The ligand field theory is a complex concept. It offers different approaches, from the simple crystal field approach to the molecular orbital calculations of various accuracy.¹³ Attempts have been made to supplement the crystal field theory by taking into account that the effective charge on metal changes with ligand numbers,¹⁴ causing variations in Dq up to 40% for equatorial ligands of pentagonal bipyramid, as compared with axial ligands.

There have also been attempts to improve the crystal field theory by including new parameters, e.g., the change of the intermediate spin state relative to the ground state, but nothing important has been achieved.¹⁴

Other theoretical approaches to reactivity of metal complexes have been developed with time, including Hückel's molecular orbital model.^{15,16}

A very complicated quantum mechanical model for computation of the energies of metal ion hydration has been used which, in addition to the coordination sphere, included two hydration shells, with limited success.¹⁷ There were attempts to apply molecular modeling for a better understanding of the ligand exchange processes.¹⁸ Success has been achieved in applying the *ab ini*-

tio SCF (“self-consistent field”) method to computing the energies of dissociation of H_2O from $\text{M}(\text{H}_2\text{O})_6^{2+}$, where $\text{M} = \text{V}, \text{Cr}, \text{Mn}, \text{Fe}, \text{Co}, \text{Ni}$ and Cu .¹⁹

2.6. SUBSTITUTION REACTIONS ON OCTAHEDRAL COMPLEXES

The largest number of complexes of transition metals have octahedral configuration and it is no wonder that special attention has been paid to substitution mechanisms of these complexes. Nowadays, we know with certainty that substitutions of octahedral complexes follow a dissociative mechanism, but this mechanism varies in details. In some cases, the mechanism is D , which is identical to the $[\text{S}_{\text{N}}1(\text{lim})]$ mechanism, as previously discussed. In the D mechanism, the pentacoordinate intermediate lives long enough to discriminate (distinguish) between the entering ligands and to preferentially react with one of them. In some other case, substitution can follow an I_{d} mechanism, involving dissociative activation, but with no evidence for an intermediate. Both of these mechanisms are essentially different from the associative mechanisms (A and I_{a}) discussed in section 1.9.

If an octahedral substitution follows a D or an I_{d} mechanism, we should expect:

- (a) a weak dependence of the substitution rate on the nature of the entering ligand;
- (b) an increase of the central metal atom charge should cause a decrease of the reaction rate because the leaving ligand dissociates more slowly. On the other hand, an increase of the metal charge will increase the rate of an associative type process, because the electron pair of the entering ligand will be accepted with more ease;
- (c) steric accumulation should increase the rate of a dissociative type process while the rate of an associative type process is decreased. There are also other effects, which will be discussed when considering replacements of coordinated water in aqua complexes.

2.6.1. Rates of water exchange in octahedral aqua complexes

Rates of water exchange in octahedral aqua complexes can vary up to 20 orders of magnitude. Modern techniques enable determination of rate constants in the mentioned rate span. There are several reasons for these rate differences. Thus, the replacement rates for univalent cations increase in the order $\text{Li}^+ < \text{Na}^+ < \text{K}^+ < \text{Rb}^+ < \text{Cs}^+$. Figure 2.6.1 shows that the ionic radii increase in the same manner.

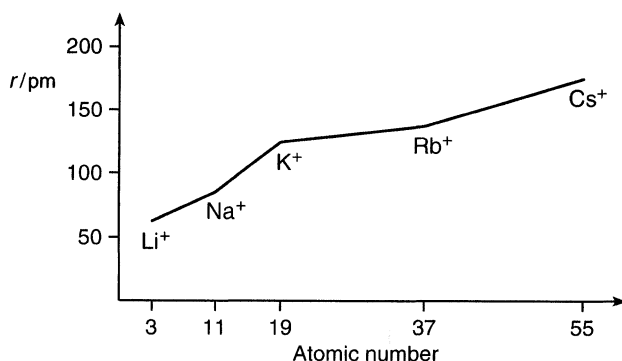


Figure 2.6.1. Ionic radii (r) of the group 1 (IA) elements of the periodic table.²⁰

The smaller the ions, the lower are the rates of water replacements. This suggests that the rates are controlled by the electric charge of the ion, *i.e.*, by $z_i e / r_i$. The same holds for group 2 (IIA). An exception is Be^{2+} , which is probably caused by the complexity of the mechanism of water replacement. There is a large difference in replacement rates of water coordinated to Mg^{2+} and Ca^{2+} , a fact important in enzymatic reactions.

A further observation is that for M^+ and M^{2+} ions of similar size the ions with smaller charge exchange water faster. Since the bond strength $\text{M}-\text{OH}_2$

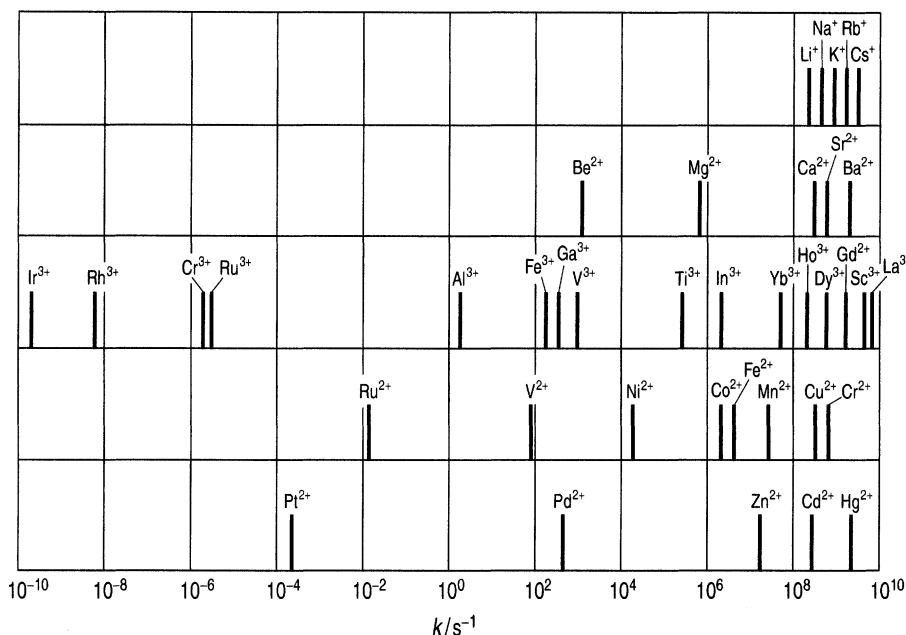


Figure 2.6.2. Rate constants of the exchange of inner sphere water molecules coordinated to various metal ions in aqueous solutions.²¹

increases with increasing electric charge, and decreases with increased size of the metal ion, it could be inferred that water replacement is due to M–OH₂ bond breaking to a larger degree than the new bond making. This indicates that D or I_d mechanisms predominate in water exchange, the associative mechanism being much less likely.

Regarding transition metals, the situation is less clear. Thus, Cr²⁺, Ni²⁺ and Cu²⁺ have almost equal radii but Ni²⁺ reacts 10⁵ times slower than Cu²⁺ and Cr²⁺ (see Figure 2.6.2.)

Fortunately, there is a convincing explanation: Cu²⁺(d⁹) and Cr²⁺(d⁴) are structurally distorted, with bonds longer (therefore weaker), towards axial ligands relative to equatorially positioned ligands (see Jahn-Teller effect in inorganic chemistry textbooks). This is the reason why the ground state structures for Cr²⁺ and Cu²⁺ are very similar to their transition state structures causing a faster water exchange in axial positions where water is more weakly bonded. Figure 2.6.2. depicts the rates of the inner sphere water exchange for various metal ions.

2.6.2. Pressure dependence of the reaction rate constant; volume of activation

By recalling a well known thermodynamic relations, *viz.* $(\partial G/\partial p)_T = V$, and the equation $\Delta_r G^\circ = -RT \ln K^\circ$, it is possible to derive the expression describing the pressure dependence of the activation equilibrium constant*:

$$\left(\frac{\partial \ln K_a^\ddagger}{\partial p} \right)_T = - \frac{\Delta^\ddagger V}{RT}$$

where $\Delta^\ddagger V$ denotes the difference between partial molar volumes of the activated complex and the reactants. Since the rate constant for the formation of the activated complex, 2k , is proportional to $K_c^\ddagger$ (eq. 1.4.5), the formula for the pressure dependence of k is readily obtained:

$$\left(\frac{\partial \ln k}{\partial p} \right)_T = - \frac{\Delta^\ddagger V}{RT} \quad (2.6.1)$$

If we assume that $\Delta^\ddagger V$ does not appreciably depend on pressure, by integrating we get:

* Unlike the standard thermodynamic constant, *e.g.*, K° , the so-called “activity constant” $K_a^\ddagger$ does not refer to standard pressure (100 kPa) but is a function of pressure: $K_a^\ddagger(p)$ (see M. L. McGlashan, *Physico-Chemical Quantities and Units*, The Royal Institute of Chemistry, London 1971).

$$\ln k = -\frac{\Delta^\ddagger V}{RT}p + \ln k_0 \quad (2.6.2)$$

where $\ln k_0$ is the integration constant. By plotting $\ln k$ against pressure, a straight line is obtained with a slope of $-\Delta^\ddagger V/RT$. The equation enables determination of $\Delta^\ddagger V$ from the slope, and the values obtained are about $\pm 25 \text{ cm}^3 \text{ mol}^{-1}$, and can be determined with a precision of $\pm 1 \text{ cm}^3 \text{ mol}^{-1}$.

Equation (2.6.1) shows that the reaction rate constant will increase with increasing pressure if $\Delta^\ddagger V$ is negative ($\Delta^\ddagger V < 0$), which means that the volume of the activated complex is smaller than the sum of molar volumes of reactants. This will happen in an associative mechanism. On the other hand, the transition state of a dissociative mechanism will have weakened (longer) bonds, and consequently $\Delta^\ddagger V > 0$.

The reason for measuring activation volumes is understandable. Unfortunately, the volume of activation is made up of two effects. The first effect is due to the change in bond lengths on the way from the ground state to the transition state and is a consequence of the intimate reaction mechanism. The second effect is a consequence of solvation of differently charged transition states relative to the ground state, which is difficult to determine. Fortunately, the contribution of solvation is of minor importance when the charges of the reactants in the transition state and the ground state are the same. This is the case of the exchange of water coordinated to transition metal ions, which is the reason why such exchanges have been studied very thoroughly.

The exchanges of water coordinated to Fe^{2+} , Co^{2+} and Ni^{2+} ions have $\Delta^\ddagger V > 0$, which speaks in favor of D or I_d mechanisms. On the other hand, the $\Delta^\ddagger V$ for Ti^{2+} , V^{2+} and Mn^{2+} values are negative ($\Delta^\ddagger V < 0$), which speaks in favor of I or I_a mechanisms. However, because of the complexity of the problem, one should be very careful in making mechanistic conclusions.

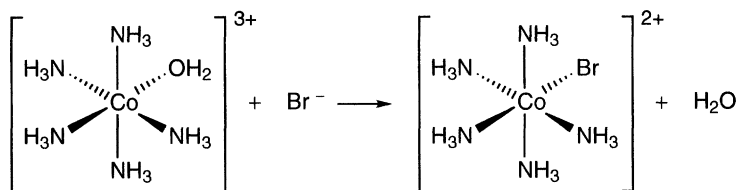
Table 2.6.1 provides data on activation volumes for the exchange of water coordinated to some transition metal ions.

Table 2.6.1. Volumes of activation for the exchange of water in some $\text{M}(\text{H}_2\text{O})_6^{2+}$ complexes²²

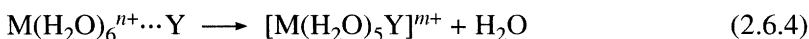
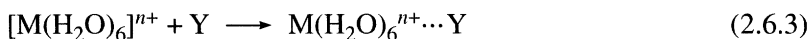
Complex	$\Delta^\ddagger V/(\text{cm}^3 \text{ mol}^{-1})$	Probable mechanism
$\text{Fe}(\text{H}_2\text{O})_6^{2+}$	3.8	I_a or I_d
$\text{Co}(\text{H}_2\text{O})_6^{2+}$	6.1	I_d
$\text{Ni}(\text{H}_2\text{O})_6^{2+}$	7.2	I_d
$\text{Ti}(\text{H}_2\text{O})_6^{2+}$	-12.4	A
$\text{V}(\text{H}_2\text{O})_6^{2+}$	-4.1	I_a
$\text{Mn}(\text{H}_2\text{O})_6^{2+}$	-5.4	I_a

2.6.3. Substitution of coordinated water of octahedral complexes with anions (“anations”)

Substitution of water in pentaammineaquacobalt(III) ions with anions in aqueous media has been the subject of many investigations.^{23,24} The term “anation” has been generally accepted. An example is the reaction:

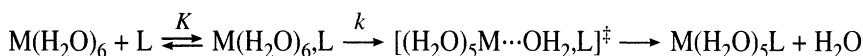


Manfred Eigen* found that substitution of water with the entering ligand Y most probably proceeds through the ion pair. The first step would, therefore, involve formation of the ion pair. The entering ligand Y is held in the solvation shell around the metal ion, which is usually called an outer-sphere complex, or a cage complex:



Further possibilities are as follows:

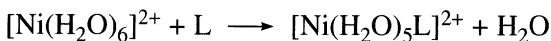
- A heptacoordinated intermediate is formed from the ion pair in a slow, rate-determining step. Should experiments indicate the presence of an associative intermediate, the mechanism would be associative (A mechanism);
- If experiments show that the intermediate cannot be determined, since it lives too short to be detected, then I_a mechanism is very probable;
- If, on the other hand, experiments suggest that in the transition state bond breaking is more important than bond making, then I_d mechanism is operative:



Complex $\text{M}(\text{H}_2\text{O})_6\text{L}$ is an outer-sphere complex or, if ML_6 is a cation and L an anion, we speak of an ion pair.

* MANFRED EIGEN, a German chemist, shared the Nobel Prize for chemistry in 1967 with English chemists R. G. W. Norrish and L. G. Porter for their studies of extremely fast reactions, effected by disturbing the equilibrium by means of very short energy pulses.

Data collected for reaction:



speak in favor of an I_d mechanism. In fact, rate constants of water replacement in $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ by various entering ligands show significant variations (even up to two orders of magnitude), but it may be shown that the variations are due to different charges of the entering ligands. Namely, the more negative is the charge of the entering ligands, the larger are the rate constants of coordinated water replacements. Thus, $\text{C}_2\text{O}_4^{2-}$ replaces water 10 times faster than SCN^- , and Hedta^{3-} 100 times faster than $\text{H}_2\text{edta}^{2-}$ (edta^{4-} = ethylenediaminetetraacetate).

Analogous substitution of water in $[\text{Co}(\text{NH}_3)_5(\text{H}_2\text{O})]^{3+}$ by Br^- and Cl^- proceeds by an I_d mechanism over ion pairs,²³ as already mentioned.

It is difficult to distinguish a D from an I_d mechanism in replacements of coordinated solvent with the entering ligand, L. For instance, in replacement of water of an aqua complex by L, both mechanisms, D and I_d , will yield a linear dependence of the reaction rate on the concentration of L. Thus, if replacement of water by L in the reaction $\text{M}\cdot\text{H}_2\text{O} + \text{L}$ proceeds by a D mechanism, then the following equation must hold:

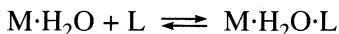
$$k_{\text{obs}} = \frac{k_1 k_2 [\text{L}]}{k_{-1} [\text{H}_2\text{O}] + k_2 [\text{L}]}$$

Since the solvent is water (its concentration being 55.5 mol dm^{-3}), $k_{-1} [\text{H}_2\text{O}]$ has a much higher value than $k_2 [\text{L}]$, so that $k_2 [\text{L}]$ can be neglected, and we get:

$$k_{\text{obs}} = \frac{k_1 k_2 [\text{L}]}{k_{-1} [\text{H}_2\text{O}]} \quad (2.6.5)$$

Thus, k_{obs} is a linear function of $[\text{L}]$ (under first order conditions, when the concentration of L is much higher than that of the complex – usually 20 times higher or more).

If the mechanism is I_d , involving a fast preequilibrium:



in which an outer orbital complex, $[\text{M}\cdot\text{H}_2\text{O}\cdot\text{L}]$ or an ion pair is formed, we talk of “accidental bimolecularity”, the rate law being

$$\text{rate} = K k_1 [\text{L}] [\text{M}\cdot\text{H}_2\text{O}] \quad (2.6.6)$$

where k_1 is the rate constant of formation of $M \cdot L$ from $M \cdot H_2O \cdot L$, and K is the pre-equilibrium constant of $M \cdot H_2O \cdot L$ (ion pair) formation. The higher the concentration of L in the outer sphere, the higher is the probability of its entry into the coordination sphere, compared to the probability of water molecules returning from the second into the first coordination sphere.

We can see that in both mechanisms, D and I_d , reaction rates depend linearly on the concentration of L , which is the reason why these mechanisms cannot be kinetically distinguished.

Replacements of water by L in $[Fe(CN)_5(OH_2)]^{3-}$ have been much investigated in an attempt to determine whether the replacement mechanism is D or I_d . It has been stressed that these replacements are especially convenient for this purpose because both the complex and the entering ligands are negatively charged, which excludes ion pair formation, but no final conclusion has been made, so the problem is still a topic of discussions.²⁴⁻²⁶ For many years it was thought that the replacement of X by L in $[Co^{III}(CN)_5X]^{n-}$ is of the D type, but I_d mechanism has also been proposed.²⁶

The mechanism of water replacement by N_3^- in $[Co^{III}(CN)_5(OH_2)]^{2-}$ in aqueous solution was studied by Haim and Wilmarth,²⁷ who took advantage of the fact that both the complex and the reagent are anions, which excludes ion pair formation. They found that the plot of the dependence of k_{obs} on azide concentration shows a tendency to limiting rates (or saturation rates), which can be ascribed only to a D mechanism. As already explained, I_d mechanism is characterized as accidental bimolecularity and cannot yield limiting rates. Later on, the results were reinvestigated and a linear dependence of k_{obs} on azide concentration was finally established.²⁸ Since linear dependence, when the solvent is the leaving ligand, can be caused by both mechanisms, the problem remained unsolved. Later on, D mechanism was established with certainty in the substitution of MeOH by amine ligands (4CN-py, py, 4Me-py; py = pyridine) in $[Co^{III}(PP)(MeO)(MeOH)]$ in methanol solvent (PP = proto-porphyrin IX dimethyl ester). All three pyridine derivatives gave limiting rates, as shown in Table 2.6.2.

The methoxo group in the mentioned complex is relatively strongly bonded, while coordinated methanol is weakly bonded and is easily replaced by amine ligands.

The following reactions are taking place:

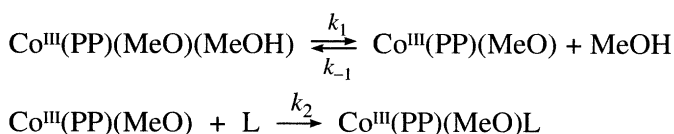


Table 2.6.2. Rates of substitution of CH_3OH in $5 \times 10^{-6} \text{ mol dm}^{-3}$ $[\text{Co}^{\text{III}}(\text{PP})(\text{CH}_3\text{O})(\text{CH}_3\text{OH})]$ with py, 4CN-py and 4Me-py in methanol (25 °C)^(a) (ref. 29)

$10^4[\text{L}]/\text{mol dm}^{-3}$	$k_{\text{obs}}/\text{s}^{-1}$		
	Entering ligands (L)		
	4CN-py	py	4Me-py
1	3.47 ± 0.15	2.89 ± 0.15	1.0 ± 0.05
5	6.93 ± 0.35	3.85 ± 0.2	3.85 ± 0.2
10	17.3 ± 0.8	8.6 ± 0.4	6.93 ± 0.3
20	34.7 ± 1.6	18.2 ± 0.7	10.7 ± 0.6
30		30.0 ± 1.5	
40	53 ± 3	38 ± 2	
50		46 ± 3	27 ± 1.8
60	58 ± 4		
80	58 ± 3	58 ± 3	
100		58 ± 3	49 ± 3
500			58 ± 4
1000			58 ± 4

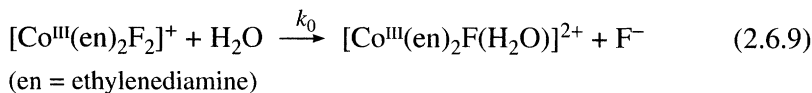
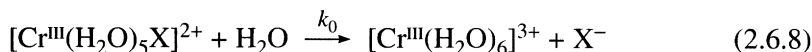
^(a) "Stopped flow" technique is used; bold figures are limiting rates.

L is in large excess relative to complex concentration and therefore k_2 is the pseudo first order rate constant. The ratio k_2/k_{-1} is called the competition ratio. It amounts to 6800, 3700 and 2800 for the entering ligands 4CN-py, py and 4Me-py, respectively.²⁹ It can be concluded that the intermediate $[\text{Co}^{\text{III}}(\text{PP})(\text{MeO})]$ lives long enough to be able to discriminate (distinguish) between the entering amine ligands, which proves the existence of the D mechanism. A favorable circumstance is the fact that the starting complex and the intermediate have no charge, which excludes ion pair formation. The situation is similar to that in the reaction of $[\text{Co}^{\text{III}}(\text{CN})_5(\text{OH}_2)]^{2-}$ and N_3^- where there was no ion pairing either, but this reaction did not exhibit limiting rates.

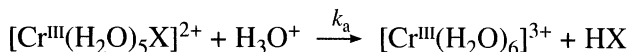
The question may arise why the replacement of coordinated water by N_3^- in $[\text{Co}^{\text{III}}(\text{CN})_5\text{OH}_2]^{2-}$, in water solvent, does not give a limiting rate, while analogous substitution of coordinated methanol by three amine ligands, in methanol solvent, yields limiting rates. The probable answer is that the "orienting" methoxide ligand, a very strong electron donor, stabilizes the reaction intermediate, $[\text{Co}^{\text{III}}(\text{PP})(\text{MeO})]$, which therefore lives long enough to discriminate between the entering ligands (H_2O and the mentioned pyridines). This is not the case of the CN^- "orienting" ligand of the pentacyano-complex, which is an electron acceptor, not an electron donor.

2.6.4. Aquation and acid catalysis

Substitution of a ligand by water molecule is called aquation. Here are some examples:



Aquations are usually acid catalyzed. Thus, aquation (2.6.8) is much faster in the presence of an acid:



The acid catalyzed reaction of $[\text{Co}(\text{NH}_3)_5\text{F}]^{2+}$ proceeds as follows:

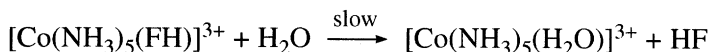
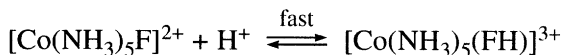


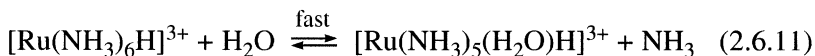
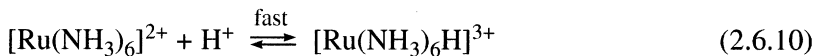
Table 2.6.3 contains the rate constants of some uncatalyzed and acid catalyzed aquations.

Table 2.6.3. Rates of aquation of $[\text{Cr}^{\text{III}}(\text{H}_2\text{O})_5\text{X}]^{2+}$ in neutral (k_0) and acidic aqueous media (k_a), at room temperature³⁰

X^-	k_0/s^{-1}	k_a/s^{-1}	k_a/k_0
N_3^-	2.6×10^{-8}	93×10^{-8}	≈ 36
F^-	6.2×10^{-10}	140×10^{-10}	≈ 23
CN^-	1.1×10^{-5}	59×10^{-5}	≈ 54
NH_3	no acceleration		

The reaction mechanism obviously involves protonation of the leaving ligand. Protonated ligand leaves the positive metal ion with increased ease. If the leaving ligand is NH_3 , acid addition has no effect on the rate because NH_3 is not charged.

There are exceptions. Thus, an acid aquation of $[\text{Ru}(\text{NH}_3)_6]^{2+}$ is very likely to proceed according to the following mechanism:³¹



The rate constant of an acid catalyzed reaction is a composite value:

$$k_{\text{obs}} = k_{\text{aq}} + k_{\text{H}^+}[\text{H}^+] \quad (2.6.13)$$

where k_{aq} is the rate constant of the uncatalyzed reaction and k_{H^+} that of the acid catalyzed reaction. Consequently, the reaction rate is given by the equation:

$$\text{rate} = k_{\text{aq}}[\text{complex}] + k_{\text{H}^+}[\text{complex}][\text{H}^+] \quad (2.6.14)$$

Figure 2.6.3 depicts the usual pattern of an acid catalyzed aquation.

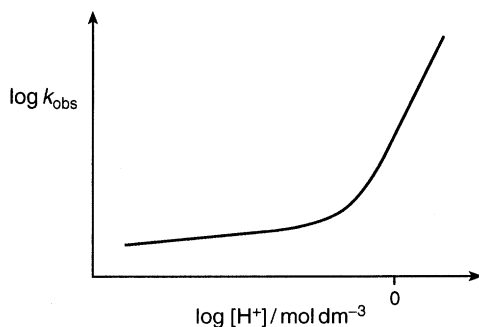
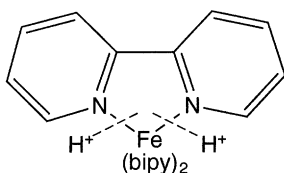


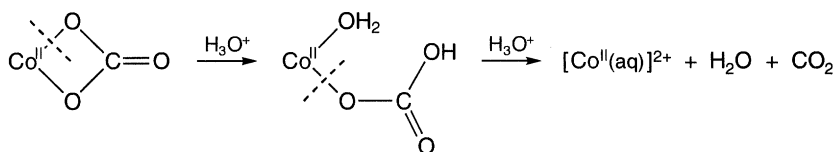
Figure 2.6.3. Pattern of an acid catalyzed aquation.

An acid can catalyze removal of a chelate (dechelation), *e.g.*, the removal of a bipyridyl from $[\text{Fe}(\text{bipy})_3]^{2+}$:



The first step involves the removal of one nitrogen atom from the iron atom; this nitrogen is quickly protonated, which prevents a reverse reaction. The following step is the removal of the other nitrogen.

A similar situation is that of carbonate complexes:



The chelate ligand first leaves at one end by breaking the $\text{Co}^{\text{II}}\text{--O}$ bond. Due to fast protonation, the probability of a reverse reaction is appreciably reduced. Removal of the remaining chelate follows in the second step, also assisted by protonation and inhibiting the reaction reverse. According to the principle of microscopic reversibility, the reverse reaction must also proceed in two steps, with exactly the same reaction mechanism, and over the same transition states.

2.6.5. Base catalysis

All research carried out on the mechanisms of octahedral substitutions speaks in favor of the dissociative mechanism: limiting rates at high concentrations of entering ligands, independence of the reaction rates of the nature of entering ligands, increase of reaction rates with steric crowding of constituents. However, it has been established that the reaction:



follows the kinetic expression:

$$\text{rate} = k[\text{Co}(\text{NH}_3)_5\text{X}^{2+}][\text{OH}^-] \quad (2.6.16)$$

namely, the reaction rate depends on the concentration of the entering OH^- ligand, which suggests that the reaction is bimolecular, and of the associative type. These results prompted earlier discussions, introduced by Ingold and coworkers,³² who claimed that the reaction mechanism of nucleophilic substitutions on saturated carbon can be changed from $\text{S}_{\text{N}}2$ to $\text{S}_{\text{N}}1$ if the nucleophilicity of the entering groups is systematically increased.

The larger is the electron release ability of an alkyl group, the higher is the probability of a dissociative ($\text{S}_{\text{N}}1$) mechanism, until a point is reached at

which it becomes the main route through which the reaction proceeds. In the transition state of a bimolecular reaction the bond with the leaving group must be weakened, which is helped by alkyl electron donation, but simultaneously a bond must be established with the entering group, which is obstructed by alkyl electron donation. The mentioned authors claimed that if there was no change of the mechanism, the rate of an S_N2 reaction would continuously decrease with increasing alkyl electron donation. The opposite effects of alkyl electron donation lead to a rate minimum, as shown in Figure 2.6.4.

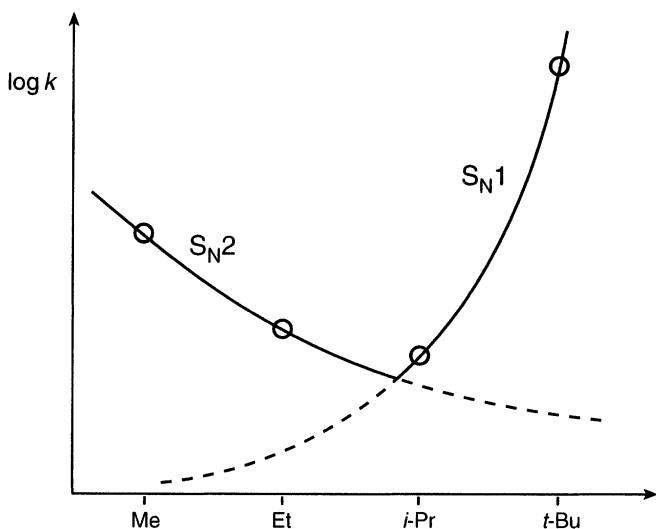
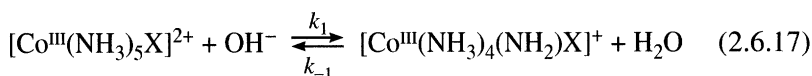


Figure 2.6.4. Schematic representation of the changes of the mechanism, kinetic order and rate in a nucleophilic substitution $Y + \text{AlkX} \rightarrow \text{AlkY} + X$, by variable Alk groups, ordered according to their increasing ability to supply electrons.³³

Ingold and Ašperger³⁴ tried to apply the theory of the reaction mechanism duality, observed in tetrahedral substitution reactions, to octahedral substitutions. The underlying idea was that an orienting ligand L, if it is an electron donor, *e.g.*, $L = \text{OH}^-$, will lead an aquation, *e.g.*, of $[\text{Co}^{\text{III}}(\text{en})_2\text{LCI}]^{n+}$ or of $[\text{Co}^{\text{III}}(\text{NH}_3)_4\text{LCI}]^{n+}$, by a dissociative (S_N1) mechanism, while, when $L = \text{NO}_2^-$ (a well known electron acceptor), it will promote a bimolecular (S_N2) substitution. However, it can be shown that octahedral substitutions are substantially different from tetrahedral substitutions, because the octahedral bimolecular substitutions require a heptacoordinated transition state, *i.e.*, the entry of electrons into antibonding orbitals. This is not impossible, but it is not very likely. As a result of many investigations, it can be shown that the base hydrolysis proceeds over the complex conjugate base, involving NH_2^- (amido) group:

If $X = \text{Cl}^-$, amine complex will react as follows:



Since the equilibrium (2.6.17) is quickly established, and the amido complex reacts with water almost instantaneously yielding the hydroxo complex, the slowest and rate determining step is (2.6.18). Thus the rate is given by the equation:

$$\text{rate} = k_2[\text{Co}^{\text{III}}(\text{NH}_3)_4(\text{NH}_2)\text{X}^+] = Kk_2[\text{OH}^-][\text{Co}^{\text{III}}(\text{NH}_3)_5\text{X}^{2+}] \quad (2.6.20)$$

where $K = k_1/k_{-1}$. We can see that the substitution rate is proportional to the concentration of the starting complex and to the concentration of the base. Nevertheless, the substitution is not bimolecular, but the reaction product is formed by a dissociative mechanism (2.6.18) from the conjugate base. This mechanism is known as $\text{S}_{\text{N}}1\text{cb}$ (Substitution Nucleophilic monomolecular from the conjugate base), or a Dcb mechanism, (according to Langford and Gray). Basolo and Pearson were the main protagonists of this mechanism.³⁵ It should be mentioned that the $\text{S}_{\text{N}}1\text{cb}$ mechanism was predicted by Garrick in 1937, and is known as Garrick's mechanism.³⁶ The $\text{S}_{\text{N}}1\text{cb}$ mechanism requires that the reacting complex should have at least one protonic hydrogen on the ligand that remained bonded to the metal. If the rates of base hydrolysis are compared with proton exchange rates, it can be seen that proton exchange is about 10^5 times faster than base hydrolysis. This holds for $[\text{Co}(\text{NH}_3)_5\text{Cl}]^{2+}$ and for $[\text{Co}(\text{en})_2\text{NH}_3\text{Cl}]^{2+}$, in accordance with the $\text{S}_{\text{N}}1\text{cb}$ mechanism. Experiments support the claim that the conjugate base reacts in a dissociative manner, yielding a very reactive pentacoordinate intermediate, which lives long enough to be able to discriminate between the entering ligands.³⁵

2.6.6. Stereochemistry of octahedral substitutions

An object which is not superimposable upon its mirror image is chiral (like our right and left hands; *cheir* = hand in Greek). We can say that the general property of "handedness" is chirality. Two components that differ in handedness are called enantiomers (from Greek, meaning opposite forms). Stereo-

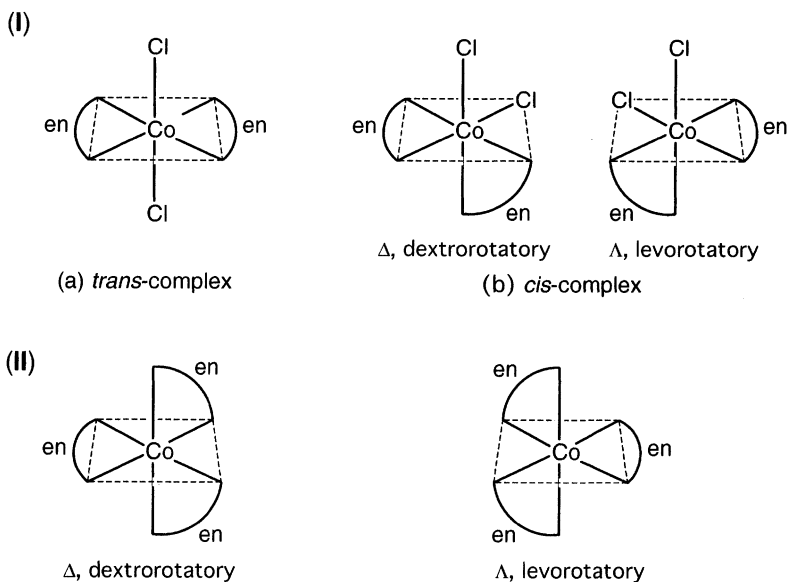
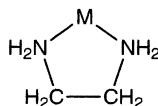


Figure 2.6.5. (I): isomers of dichlorobis(ethylenediamine)cobalt(III) ion, (II): isomers of tris(ethylenediamine)cobalt(III) ion.

isomers are compounds that contain the same ligands in their coordination spheres but these ligands are differently arranged in space. One type of stereo-isomers are *cis*- and *trans*-isomers. Figure 2.6.5 shows a *trans*-isomer of dichlorobis(ethylenediamine)cobalt(III) ion (I), and two optical *cis*-isomers (II), which are mirror images (enantiomers). Enantiomers have identical physical properties except for their effects on plane-polarized light. One enantiomer is *dextro* form, (Δ), (will rotate the plane of the plane-polarized light to the right), while the other is *levo* form, (Λ), (will rotate the plane of the plane-polarized light with equal intensity to the left). We speak of optical isomers. An equimolar mixture of enantiomers is called a racemic mixture and has no net effect on plane-polarized light. Figure 2.6.5 gives some examples of stereoisomers.

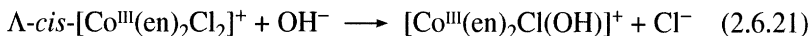
When ethylenediamine chelates to a metal atom, a five-membered ring is formed:



In this ring, the M–N bonds are longer than the C–C and C–N bonds, which causes a strain in the ring. The strain can be relieved by ring puckering. There are two different puckered forms, δ and λ , which are enantiomers.

Since there are three ethylenediamine ligands, it may be shown that there is a set of eight possible configurations. In the crystals of $[\text{Co}(\text{en})_3]^{3+}$ only one of the eight possible forms is usually present. Why this is so is a question that has not been fully answered yet. Additional information can be found in special literature.³⁷

Of special interest is the fact that base hydrolysis leads to substantial stereo changes:



63% *trans*

21% $\Lambda\text{-cis}$ (retention)

16% $\Delta\text{-cis}$ (inversion)

These results can be explained by assuming that the reacting intermediate has a trigonal bipyramidal structure so that water attack can take place from several sides, as shown in Figure 2.6.6.

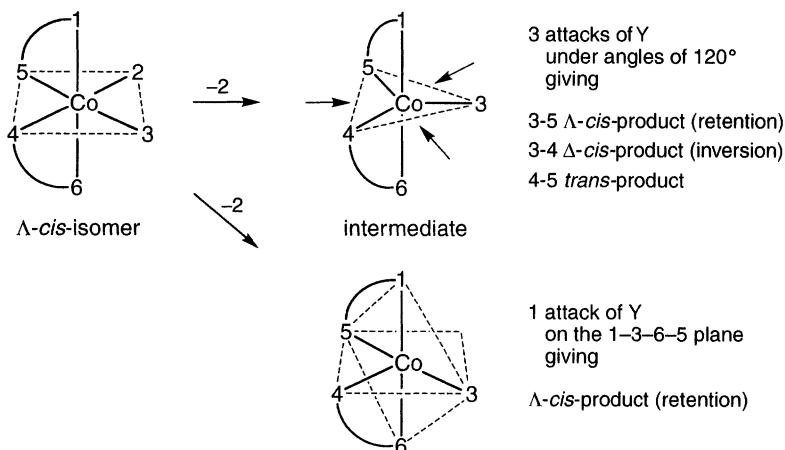
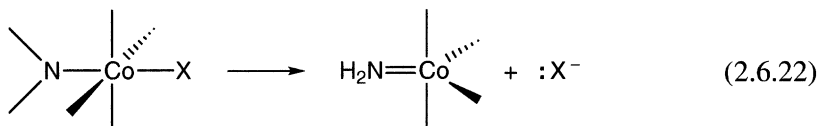


Figure 2.6.6. Base hydrolysis causes stereo changes because the intermediate is a trigonal bipyramidal rather than a square pyramid. If the intermediate were a square pyramid with apex 4 and base 1-3-6-5 (freely open to attack), this would lead to full retention of the configuration, yielding $\Lambda\text{-cis}$ -product only, which is not what happens.

The question remains why the conjugate base, $[\text{Co}^{\text{III}}(\text{NH}_3)_4(\text{NH}_2)\text{Cl}]^+$, dissociates Cl^- (as well as other leaving ligands X) so fast. Since coordinated amines are very weakly acidic, the concentration of the conjugate base must be very low compared to the complex concentration. On the other hand, the reactivity of the conjugate base should be very high, probably 10^6 times, or more, higher than that of the $[\text{Co}^{\text{III}}(\text{NH}_3)_5\text{Cl}]^{2+}$. The first thought is that this

might be a charge effect of the amido group, because the Cl^- dissociates from the conjugate base, which is by one unit less positively charged than the starting amine complex. It is, however, believed that this charge effect could not cause such a large kinetic effect ($>10^6$). It is much more likely that the effect is a combination of the NH_2^- electron repulsion toward the Cl^- leaving ligand in the complex ground state (raising its energy) on the one side, and the π bonding of the amido group to cobalt in the reaction transition state (which lowers its energy) on the other side. The energy difference between the transition state and the ground state is thus lowered, *i.e.*, the free energy of activation is lowered. In addition, the π bonding stabilizes the pentacoordinate intermediate, as illustrated in the following scheme:



If octahedral substitution takes place on a *trans*-isomer, and the mechanism is of the dissociative type, the possible stereo changes are shown in Figure 2.6.7.

One should bear in mind that the energy difference between pentacoordinated species, square pyramid and trigonal bipyramid, is very small. This is the reason why intermediates of either of these geometric forms can occur in octahedral replacements.

We have seen that in a dissociative type octahedral substitution, which takes place over a square pyramidal intermediate, the reaction product retains

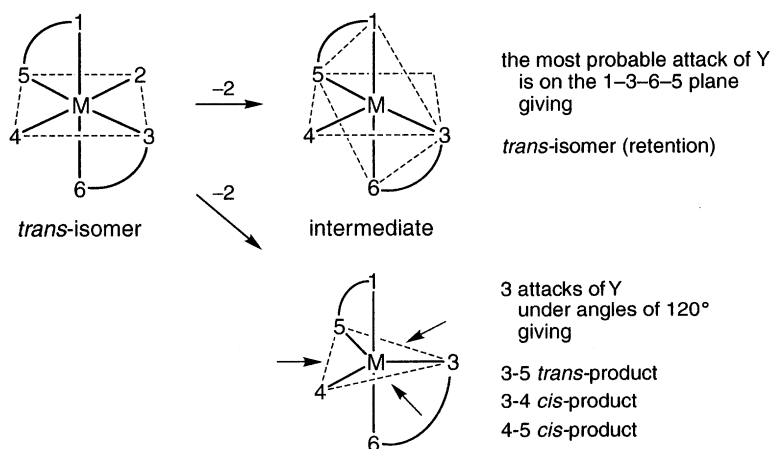


Figure 2.6.7. Possible structural changes in a dissociative type octahedral substitution of X by Y when the starting complex has *trans* configuration.

the starting complex configuration, regardless of whether the starting complex is a *cis*- or *trans*-isomer. On the other hand, if the reaction intermediate has the trigonal bipyramidal structure, the reaction products will always be a mixture of *cis*- and *trans*-isomers.

Table 2.6.4 provides data on the stereochemical changes of acid hydrolyses of some *cis*- and *trans*-[Co^{III}(en)₂(L)(X)]ⁿ⁺ complexes.

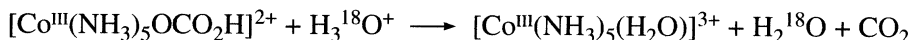
Table 2.6.4. Steric changes in acid hydrolysis of some *cis*- and *trans*-[Co^{III}(en)₂(L)(X)]ⁿ⁺ complexes (according to Basolo and Pearson³⁸)

$[\text{Co}^{\text{III}}(\text{en})_2(\text{L})(\text{X})]^{n+} + \text{H}_2\text{O} \longrightarrow [\text{Co}^{\text{III}}(\text{en})_2(\text{L})(\text{H}_2\text{O})]^{n+1} + \text{X}^-$					
<i>cis</i> -L	X	% <i>trans</i> -fraction in the product	<i>trans</i> -L	X	% <i>cis</i> -fraction in the product
OH ⁻	Cl ⁻	0	OH ⁻	Cl ⁻	75
OH ⁻	Br ⁻	0	OH ⁻	Br ⁻	73
Br ⁻	Cl ⁻	0	Br ⁻	Cl ⁻	50
Cl ⁻	Cl ⁻	0	Br ⁻	Br ⁻	30
Cl ⁻	Br ⁻	0	Cl ⁻	Cl ⁻	35
N ₃ ⁻	Cl ⁻	0	Cl ⁻	Br ⁻	20
NCS ⁻	Cl ⁻	0	NCS ⁻	Cl ⁻	50–70
NCS ⁻	Br ⁻	0	NH ₃	Cl ⁻	0
NO ₂ ⁻	Cl ⁻	0	NO ₂	Cl ⁻	0

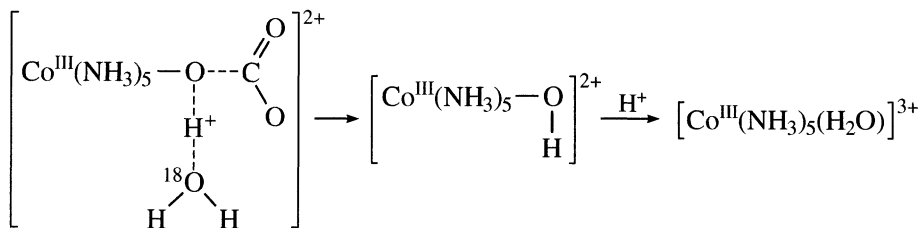
The data shows that *cis*-[Co(en)₂(L)(X)]ⁿ⁺ complexes in all the cited cases react with complete retention of configuration, while *trans*-complexes undergo stereochemical changes, revealing the trigonal bipyramidal geometry of the reaction intermediate in these cases, except for *trans*-L = NH₃ or NO₂. It should be noted that all the quoted ligands, except for NH₃ and NO₂, are good electron donors, the NO₂ “orienting” ligand being an exceptionally good electron acceptor.

2.6.7. Attacks of reactants on ligands (not on metal)

Attacks on ligands, not on the metal, are very rare. Nevertheless, there are such examples, *e.g.*, aquation of the carbonato complex [Co^{III}(NH₃)₅(OCO₂)⁺]. Experiments with isotopically labeled oxygen, H₂¹⁸O, have shown that ¹⁸O does not enter into the cobalt coordination sphere during aquation:



It appears that the mechanism involves the attack of a proton on the oxygen atom bonded to the central cobalt atom, causing CO_2 separation. Simultaneously, protonation of one carbonate oxygen takes place, yielding the final product:



2.6.8. Linkage isomerism

Linkage isomerism has been associated with metal complexes containing ambidentate ligands (from Latin: *ambo* = both). In organic chemistry, it is well known that, for instance, NO_2 can form nitro compounds ($\text{R}-\text{NO}_2$) or nitrites ($\text{R}-\text{O}-\text{N}-\text{O}$), SCN can form thiocyanates ($\text{R}-\text{S}-\text{C}\equiv\text{N}$) or isothiocyanates ($\text{R}-\text{N}=\text{C}=\text{S}$), *etc.* In coordination chemistry, the same groups can behave as ambidentate ligands in bonding to a metal ion. Coordination chemistry knows many ambidentate ligands, *e.g.*, CO , $\text{S}_2\text{O}_3^{2-}$, SO_3^{2-} , $(\text{NH}_3)_2\text{CO}$, $(\text{NH}_3)_2\text{CS}$, $(\text{NH}_3)_2\text{SO}$, and others. Several reviews have been written on this subject.^{39–43}

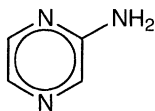
Following the IUPAC (International Union of Pure and Applied Chemistry) recommendations, the corresponding isomers are now marked by the Greek letter “ κ ” (kappa) preceding the bonding atom.⁴⁴ For instance, we talk of κN , or nitro isomer, or of κO , or nitroso isomer.

Ambidentate ligands vary widely, from the simple diatomic species mentioned to poly-*N*-heterocyclic bases, polynucleotides and proteins. A significant observation was noticing that for a given metal (*M*) the bonding site depends on the other ligands in the complex.⁴⁵ For example, the $\text{M}-\text{SCN}$ bonding is in $[\text{Pt}^{\text{II}}(\text{SCN})_4]^{2-}$ and in $[\text{Pd}^{\text{II}}(\text{SCN})_4]^{2-}$, while in analogous phosphine complexes, $\text{M}(\text{PR}_3)_2(\text{NCS})_2$, and in 2,2' bipyridine complexes, the $\text{M}-\text{NCS}$ bonding is involved. It is obvious that the ligand binding atoms do not exhibit the same affinity for a particular metal center, and that this affinity often depends on other ligands, bonded to the metal center. Thermodynamic stability will be decisive in formation of one or the other isomer, but before its rearrangement into a thermodynamically stable isomer, a kinetic (also catalytic) problem can be relevant, since most reactive states are generated far from the thermodynamic equilibrium conditions, and often live long enough to allow the monitoring of their conversion into thermodynamically stable species.⁴⁶ Thus, some forty years ago Basolo *et al.*⁴⁷ designed an experiment to permit the iso-

lation of the unstable M–SCN species before they had time into rearrange to the stable M–NCS isomer.

Linkage isomers have been excessively studied in replacement reactions of pentacyanoferrate(II) complexes, $[\text{Fe}(\text{CN})_5\text{L}]^{n-}$. The reactions are dissociative in nature, as already discussed in section 1.12. The dissociative mechanism enabled formation of the $[\text{Fe}(\text{CN})_5]^{3-}$ intermediate species, which have been used in generation of linkage isomers in the presence of ambidentate ligands, such as aminopyrazine and aminoacids.^{48,49} Linkage isomers have also been observed in the reaction of $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$ with methionine amino acid and methionine sulfoxide.⁵⁰ These amino acids, in the anionic form, can bind pentacyanoferrate(II) ions through the available S and NH_2 groups. The kinetics carried out in the presence of the dmsoligand allowed to discriminate between the κS and κNH_2 linkage isomers.

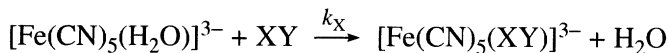
Similar studies, using competitive methods, have been carried out in linkage isomers involving polyaza-heterocyclic ligands, such as 2-aminopyrazine.



2-aminopyrazine

The aminopyrazine ligand has two potential binding sites, represented by the NH_2 group and the opposite N(4) aromatic atom, in addition to a hindered N(1) atom. Using the stopped-flow technique, the initial formation of the κNH_2 and $\kappa\text{N}(4)$ linkage isomers have been observed.⁵¹

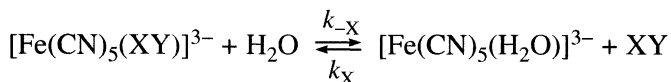
The kinetics of formation of the $[\text{Fe}(\text{CN})_5]^{3-}$ intermediate species is interesting. By using X and Y designation for the linkage isomers, the substitution processes starting from the $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$ involve two parallel reactions:^{46,48–51}



where:

$$k_{\text{obs}}^f = (k_X + k_Y)[\text{XY}]$$

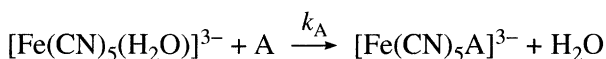
Isomer X, which is more labile, isomerizes to the thermodynamically stable Y form, according to the dissociative scheme:



Linkage isomerization proceeds according to a pseudo-first order kinetics where $k_{\text{obs}}^{\text{isom}}$ is independent of the concentration of the XY ligand, thus:

$$k_{\text{obs}}^{\text{f}} = \frac{k_Y k_{-X}}{k_X + k_Y}$$

The cited authors succeeded in evaluating the kinetic constants involved in the isomerization scheme by introducing a competing ligand, A, which forms a very stable and inert complex with the pentacyanoferrate(II) ion. They found that dimethyl sulfoxide (dmsO) is very suitable for this purpose, because it forms a very stable and inert complex with the pentacyanoferrate(II) ion. For this purpose, in addition to the parallel reactions with rate constants k_X and k_Y , they included the competition reaction:



Thus, the observed rate constant for the substitution reaction in the starting $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$ complex becomes:

$$k_{\text{obs}}^{\text{f}} = (k_X + k_Y)[\text{XY}] + k_A[\text{A}]$$

By plotting $k_{\text{obs}}^{\text{f}}$ versus $[\text{A}]$, with $[\text{XY}]$ in excess, a linear dependence was observed that enabled evaluation of the rate constants k_A and $(k_X + k_Y)$.

2.7. NUCLEOPHILICITY IN INORGANIC CHEMISTRY

It is generally taken that ligand nucleophilicity is influenced by several factors:

(a) *Basicity* of an entering ligand is characterized by its $\text{p}K_{\text{a}}$ value, which often correlates rather well with ligand nucleophilicity towards the central metal atom.

(b) *Polarizability* of a nucleophile is connected with its ability of “soft” approach to the central metal ion, at the moment of approach reducing repulsions between its electron pair and electrons of the central metal atom by sup-

pressing electron density into its empty low energy orbitals. Thus, empty low energy orbitals of an entering ligand are a condition for its “soft” approach. It is obvious that a “polarizable” ligand is expected to be a good nucleophile.

Let us consider an iodide ion, attacking a substrate in which the electrophilic atom is oxygen. Iodide (I^-) can reduce the electron repulsions by forming from its p and d orbitals two pd hybrid orbitals of the d type, with correct symmetry for orbital overlap with the oxygen p orbital, as shown in Figure 2.7.1:

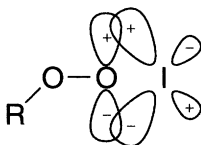


Figure 2.7.1. Hybridization of p and d iodide orbitals yields a d type hybride orbital with correct symmetry for overlap with the oxygen p orbital, in a reaction of iodide with a peroxide.

(c) *Oxidability*. Ligands, which easily undergo oxidation, like to get rid of their electrons and are, therefore, good nucleophiles. This ability is characterized by their standard reduction potentials, or by polarographic half-wave potentials.

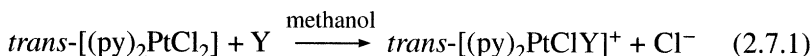
(d) *Solvation energy*. It is expected that better solvated ligands will be weaker nucleophiles, because in order to be bonded to a metal, a nucleophile must be freed of the bonded solvent, a process that requires energy.

(e) *The nature of the metal center*.

The above major factors are difficult to define, which is the reason why nucleophilicity scales in inorganic chemistry are used much less than those in organic chemistry.

2.7.1. n_{Pt} Scale

This scale is based on the reaction:



where n_{Pt} is defined as follows:

$$n_{Pt} = \log \frac{k_Y}{k_{MeOH}} \quad (2.7.2)$$

Some typical values are given in Table 2.7.1.

Unfortunately, this scale can be applied rather well to reactions of platinum(II), very approximately to other metals, and is entirely inapplicable to the metals of the first transition series.

Table 2.7.1. n_{Pt} Nucleophilicity scale of some entering ligands⁵²⁻⁵⁴

Ligand	n_{Pt}
CH ₃ OH	0
Cl ⁻	3.04
NH ₃	3.07
N ₃ ⁻	3.58
Br ⁻	4.18
I ⁻	5.46
CN ⁻	7.14
SCN ⁻	6.65
PPh ₃	8.93

2.7.2. The scale of Swain and Scott

Swain and Scott⁵⁵ showed that the nucleophilic strength is considerably independent of the substrate in reactions of nucleophiles with various compounds of saturated carbon, and they proposed the expression:

$$\log \frac{k_n}{k_0} = sn \quad (2.7.3)$$

where k_n is the rate constant of the reaction of the nucleophile (N) with a carbon compound, k_0 is the rate constant of the standard nucleophile (water), s is the substrate constant, and n is the nucleophilicity constant. Constant n can be determined from the rates of several nucleophiles, and from the rate of H₂O nucleophile with the standard substrate, methyl bromide (CH₃Br). In this way, several equations with unknowns s and n can be obtained. It can be shown that s is practically constant, while n varies.

Even Swain and Scott pointed out that their equations could be applied only to saturated carbon compounds, not to other substrates.

2.7.3. Edwards' scale

Edwards' scale of nucleophilicity⁵⁶ is based on a combination of the reduction potentials of nucleophiles and their basicity:

$$\log \frac{k_n}{k_0} = \alpha E_n + \beta H \quad (2.7.4)$$

where:

$$H = pK_a + 1.74 \quad (2.7.5)$$

$$E_n = E^0 + 2.60 \text{ V} \quad (2.7.6)$$

In expression (2.7.4) k_n is the rate constant of the reaction of a nucleophile (N) with a certain compound, and k_0 is the rate constant of the analogous reaction with water (k_n/k_0 can be replaced by the equilibrium constants of these reactions).

The α and β constants are substrate constants, while E_n and H are the nucleophilicity constants. E^0 is the standard electrode potential, *e.g.*:



According to expression (2.7.6), it follows that E_n for iodide (I^-) is:

$$E_n(\text{I}^-) = -0.54 \text{ V} + 2.60 \text{ V} = 2.06 \text{ V}$$

(see Table 2.7.2). Using expression (2.7.6), it follows:

$$E_n(\text{H}_2\text{O}) = -2.60 \text{ V} + 2.60 \text{ V} = 0$$

which was the purpose of this procedure (see Table 2.7.2).

The polarizability scale of a nucleophile (P) is determined⁶¹ according to the equation:

$$P = \log \frac{R_N}{R_{\text{H}_2\text{O}}} \quad (2.7.7)$$

where R is the molar refraction given by the equation:

$$R = \frac{n^2 - 1}{n^2 + 2} V_m \quad (2.7.8)$$

In this expression n is the refraction index, and V_m is the molar volume.

Table 2.7.2. Nucleophilic strength and polarizability of some entering ligands⁵⁷⁻⁶⁰

Nucleophile	pK_a (25 °C)	$n^{(a)}$	$E_n^{(b)}/V$	$P^{(c)}$
S^{2-}	12.9		3.08	0.611
SO_3^{2-}	9.1		2.57	
$S_2O_3^{2-}$	1.9	6.36	2.52	
$SC(NH_2)_2$	0.4	(4.1)	2.18	
I^-	(-10 to -9.5) ^(d)	5.04	2.06	0.718
CN^-	(9.1 to 9.2)		2.02	0.373
SCN^-	(-0.7)	4.77	1.83	
$C_6H_5NH_2$	4.5	4.49	1.78	
NO_2^-	3.4		1.73	
OH^-	15.7	4.20	1.65	0.143
N_3^-	4.7	4.00	1.58	
Br^-	(-7 to -9)	3.89	1.51	0.539
NH_3	9.5		1.36	0.184
Cl^-	(-4)	3.04	1.24	0.389
C_6H_5N	5.3	(3.6)	1.20	
CH_3COO^-	(4.7 to 4.8)	2.72	0.95	
F^-	3.2		-0.27	-0.150
H_2O	-1.7	0	0	0

(a) Swain and Scott nucleophilicity scale.

(b) Electrode potential scale.

(c) Polarizability scale.

(d) Values in parentheses are estimates.

Assuming that E_n values depend on nucleophile polarizability, we can write:

$$E_n = aP + bH \quad (2.7.9)$$

where P is polarizability, and $H = pK_a + 1.74$ (see eq. 2.7.5). Table 2.7.3 contains data needed for computing the a and b constants.

We can see that the nucleophilic constant E_n can be determined from the electrode potentials and basicities ($E_n^{(a)}$ – see Table 2.7.3) and also from the nucleophile polarizabilities and basicities ($E_n^{(b)}$). Both E_n values are in good agreement.

Molar polarizability is defined by the expression of O. F. Mossotti,⁶² proposed in 1850, and is connected with relative permittivity (dielectric constant), ϵ_r :

$$P = \frac{\epsilon_r - 1}{\epsilon_r + 2} V_m \quad (2.7.10)$$

Table 2.7.3. Data for determination of the a and b constants (eq. 2.7.9) and the nucleophilic constants E_n of eq. (2.7.4)

Donor	$E_n^{(a)}$	H	R_N	P	$E_n^{(b)}$
F^-	-0.27	4.9	2.6	-0.150	-0.23
H_2O	0	0	3.67	0	0
Cl^-	1.24	(-3.0) ^(c)	9.0	0.389	1.21
Br^-	1.51	(-6.0)	12.7	0.539	1.57
OH^-	1.65	17.5	5.1	0.143	1.60
I^-	2.06	(-9.0)	19.2	0.718	2.02
S^{2-}	3.08	14.7	15.0	0.611	3.11

(a) Calcd. by eq. (2.7.6).

(b) E_n values are computed for $a = 3.60$ and $b = 0.0624$ (eq. 2.7.9).

(c) The values in parentheses are approximate.

Since $\epsilon_r = n^2$, where n is the refraction index, the molar polarizability is also defined by eq. (2.7.8). On the other hand, the theory assumes that:

$$P = R_N - R_{H_2O} \quad (2.7.11)$$

Nevertheless, experiments show that the expression (2.7.7) satisfies empirically better, probably because only a part of the total refraction relates to the nucleophilic center.

Relative permittivity is usually measured in an alternating electric field. The field direction steadily changes, depending on the applied potential frequency. If the frequency is not too high, and the relaxation time is short, a molecule will have enough time to change its orientation to respond to the field direction. At very high field frequencies, a molecule will not have sufficient time for orientation and the permanent dipole moment will cease to contribute to the polarization. Only distortion polarization will remain, since even at very high frequencies the electron cloud is sufficiently mobile as to accommodate to the variable electric field causing distortion polarization.

2.7.4. The theory of “hard” and “soft” acids and bases

The theory was proposed by R. G. Pearson in 1963.^{63,64} Acids and bases are qualitatively divided into “soft” and “hard”, the remaining cases being border cases (see Table 2.7.4) Soft acids and bases mainly form covalent bonds in mutual reactions, while hard acids and bases are mainly bonded by ionic forces. The principal rule is that hard acids react most strongly with hard bases, while soft acids react most strongly with soft bases. Hard metal ions react

Table 2.7.4. Classification of some metals and ligands as hard and soft acids and bases (after R. G. Pearson⁶⁵)

Electrophiles	Nucleophiles
<i>Hard acids</i>	<i>Hard bases</i>
H ⁺ , Li ⁺ , Na ⁺ , K ⁺	H ₂ O, OH ⁻ , F ⁻ , SO ₄ ²⁻ , PO ₄ ³⁻
Be ²⁺ , Mg ²⁺ , Ca ²⁺ , Sr ²⁺	CO ₃ ²⁻ , ClO ₄ ⁻ , NO ₃ ⁻ , Cl ⁻
Al ³⁺ , Sc ³⁺ , Ga ³⁺	ROH, RO ⁻ , R ₂ O, NH ₃ , RNH ₂
Cr ³⁺ , Co ³⁺ , Fe ³⁺ , Ce ³⁺	CH ₃ ⁻ , N ₂ H ₄
Si ⁴⁺ , Ti ⁴⁺ , Cr ⁴⁺ , Th ⁴⁺	
<i>Soft acids</i>	<i>Soft bases</i>
Cu ⁺ , Ag ⁺ , Au ⁺ , Tl ⁺ , Hg ⁺	R ₂ S, RS ⁻ , S ₂ O ₃ ²⁻ , CN ⁻
Cd ²⁺ , Hg ²⁺ , Pd ²⁺ , Pt ²⁺	I ⁻ , SCN ⁻ , S ₂ O ₃ ²⁻ , R ₃ P, R ₃ As
Ti ³⁺	H ⁻ , R ⁻
Pt ⁴⁺	
<i>Borderline</i>	<i>Borderline</i>
Fe ²⁺ , Co ²⁺ , Ni ²⁺ , Cu ²⁺ , Zn ²⁺	Cl ⁻ , Br ⁻ , N ₃ ⁻ , NO ₂ ⁻ , SO ₃ ²⁻
Pb ²⁺ , Sn ²⁺ , Ru ²⁺ , Os ²⁺	PhNH ₂
Sb ³⁺ , Bi ³⁺ , Rh ³⁺ , Ir ³⁺	

with ligands similarly to proton reactions with ligands. The proton and all proton donors are classified as hard electrophiles. On the other hand, the hydroxide ion is a hard nucleophile, while iodide is a soft nucleophile. Thus, hydroxide (a hard base) has a strong interaction with the proton, but iodide (a soft base) yields a weak reaction with the proton.

Hard metal ions are small, often bear high charge and have a valence electron shell which cannot be easily distorted. On the other hand, soft metal ions are large, bear low charge, and have a valence electron shell which can be easily distorted and even removed. Soft metal ions bond strongly to highly polarizable ligands; these ligands usually have very small proton affinity. Similarly to metal ions, ligands can be divided into hard ligands, which are not polarizable, and soft ligands, which are polarizable.

The theory remained on qualitative level for about 25 years when Pearson tried to establish a quantitative scale of hardness and softness of bases and acids founded upon the ionization potentials (I) of an M^{n+} ion and electronic affinities (A). The ionization potential (I) of an M^{n+} ion is the energy needed for its conversion into $M^{(n+1)+}$ ion. Analogously, the electron affinity (A) of an M^{n+} ion is the energy release (decrease) in converting it to $M^{(n-1)+}$. It could be shown that I is larger than A ($I > A$), since more energy is needed to convert M^{n+} into $M^{(n+1)+}$ than into $M^{(n-1)+}$. An approximate measure of softness is given by the energy difference of the HOMO (highest occupied molecular

orbital) and the LUMO (lowest unoccupied molecular orbital): the higher the energy of the HOMO or the lower the energy of the LUMO, the softer is the nucleophile or electrophile, respectively. Energies of the HOMO and the LUMO can be approximately determined from measurements of ionization energies and electron affinities, respectively. The attractive force between hard acids and hard bases is mainly caused by the electrostatic attraction. On the other hand, the attraction between soft acids and soft bases is mainly due to the HOMO-LUMO overlap.

Later on, Pearson tried to establish a quantitative scale of absolute hardness and softness.⁶⁵ Absolute hardness is characterized by the value η and absolute electronegativity by the value χ . The absolute hardness (η) is given by the expression $\eta = (I - A)/2$, and the absolute softness (σ) by the expression $\sigma = 1/\eta$. Table 2.7.5. contains a selection of Pearson's absolute hardness parameters.

Table 2.7.5. Absolute hardness $\eta = (I - A)/2$ for some metal ions and ligands (after R. G. Pearson⁶⁵)

	Ionization potential (I/eV)	Electron affinity (A/eV)	Absolute hardness (η/eV)
<i>Metal ions</i>			
Na^+	47.29	5.14	21.08
K^+	31.63	4.34	13.64
Cu^+	20.29	7.73	6.28
Cu^{2+}	36.83	20.29	8.27
Ag^+	21.49	7.58	6.96
Mg^{2+}	81.14	15.04	32.55
Ca^{2+}	50.91	11.87	19.52
Cr^{2+}	30.96	16.50	7.23
Cr^{3+}	49.1	30.96	9.1
Mn^{2+}	33.67	15.64	9.02
Co^{2+}	51.3	17.06	8.22
Co^{3+}	51.3	35.50	8.9
Pd^{2+}	32.93	19.43	6.75
Pt^{2+}	31.94	18.76	8.46
<i>Ligands</i>			
CO	14.0	-1.8	7.9
PF_3	12.3	-1.0	6.7
$\text{C}_5\text{H}_5\text{N}$	9.3	-0.6	5.0
H_2O	12.6	-6.4	9.5
$(\text{CH}_3)_2\text{S}$	8.7	-3.3	6.0
NH_3	10.7	-5.6	8.2

We can see that the differences in absolute hardness of metal ions are small. Exceptions are Na^+ , Mg^{2+} and Ca^{2+} . A similar situation is that of ligands, where the differences in hardness are even smaller. Obviously, further research in the field is to be expected.

In conclusion, we can say that all described scales have some advantages but also deficiencies. An attempt to correlate various scales was made, but with no real success.⁶⁶

2.8. SUBSTITUTIONS ON SQUARE-PLANAR COMPLEXES

The term square-planar is actually a pleonasm. Strictly speaking, square-planar complexes are those complexes whose all four ligands are the same, *e.g.*, $[\text{Pt}^{\text{II}}\text{Cl}_4]^{2-}$, or $[\text{Pt}^{\text{II}}(\text{NH}_3)_4]^{2+}$.

Square-planar complexes are very important for the metal ions Ni^{2+} , Pd^{2+} , Pt^{2+} , Ir^{1+} , and Au^{3+} . By far the largest number of mechanistic studies have been done on Pt^{II} square-planar complexes, because they are very numerous and their substitution reactions proceed at rates that are easy to follow.

Square-planar complexes are often formed when a metal has 8 electrons in d orbitals, as is the case with Pt^{II} , Pd^{II} , Au^{III} , Rh^{I} and Ir^{I} . Such square complexes are always spin paired (diamagnetic).⁶⁷ The reactions of Rh^{I} and Ir^{I} are very fast and have been therefore much less studied. On the other hand, the mechanistic information collected in reactions of the platinum(II) complexes can be in most cases applied to the square-planar complexes of other metals.

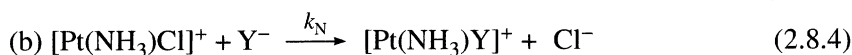
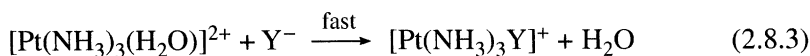
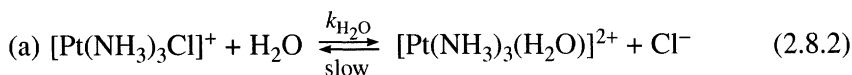
2.8.1. The mechanism of ligand replacements

Almost all substitutions of square-planar complexes follow the kinetic law:

$$-\frac{d[\text{ML}_3\text{X}]}{dt} = k_s[\text{ML}_3\text{X}] + k_Y[\text{ML}_3\text{X}][\text{Y}] \quad (2.8.1)$$

This can be explained by assuming two parallel reaction paths, both following an associative (A) mechanism. The k_Y reaction path involves an attack of nucleophile (Y), with the rate constant (k_Y), on a metal center; the reaction transition state and the reaction intermediate have very probably a trigonal bipyramidal structure. The complex ground state geometry is fully retained, *i.e.*, the *cis* or the *trans* ligand, relative to the ligand being replaced, remain in the trigonal equatorial plane. The k_s reaction path also proceeds over the

trigonal bipyramid, the entering ligand being the solvent. Very extensive experimental data support this mechanism. An associative mechanism should be expected, considering that the coordination number of square-planar complexes is low, as compared to octahedral substitutions. Thus, it has been found that the replacement of Cl^- by Y^- in $[\text{Pt}^{\text{II}}(\text{NH}_3)_3\text{Cl}]^+$ follows two kinetic paths:



Such a mechanism implies the following rate law:

$$\frac{d[\text{Pt}(\text{NH}_3)_3\text{Y}^+]}{dt} = k_{\text{H}_2\text{O}}[\text{Pt}(\text{NH}_3)_3\text{Cl}^+] + k_{\text{N}}[\text{Pt}(\text{NH}_3)_3\text{Cl}^+][\text{Y}^-] \quad (2.8.5)$$

which has been confirmed experimentally.

It should be stressed that neither $k_{\text{H}_2\text{O}}$ in process (a) nor k_{N} in process (b) vary significantly with the complex charge (*e.g.*, replacement of the neutral NH_3 ligand by the Cl^- ligand). If the mechanism were a dissociative one, the

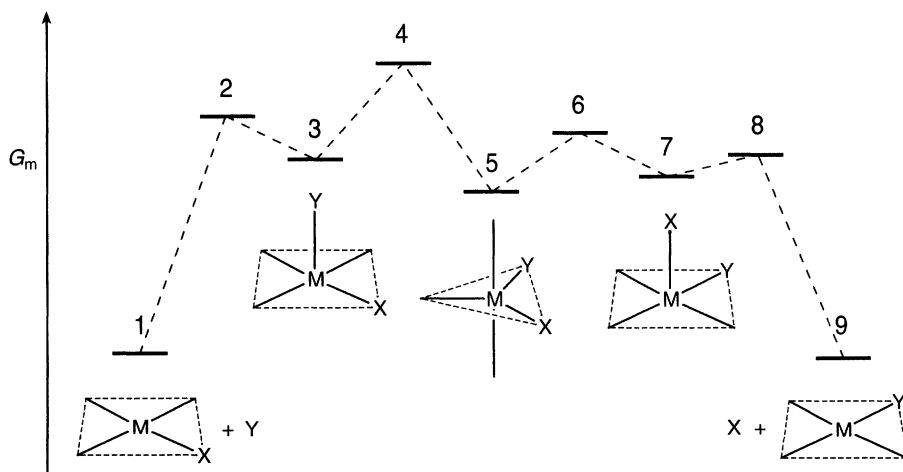


Figure 2.8.1. Energy profile (schematic) and possible steric changes during substitution of X by Y of a square planar complex: energies at 2, 4, 6, and 8 represent the transition states, and the reaction intermediates would have energies shown at 3, 5, and 7.

rate of Cl^- separation from the metal would strongly depend on the metal charge, which is not the case. In addition, steric crowding reduces the rates of both processes, (a) and (b), as expected for an associative mechanism. If the mechanism were a dissociative one, the kinetic effect would be just opposite: the substitution rates would be increased.

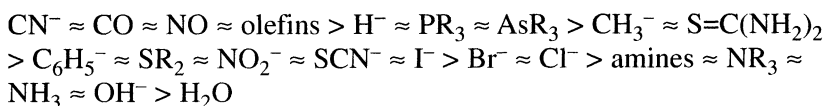
Negative entropies of activation ($\Delta^\ddagger S < 0$), negative activation volumes ($\Delta^\ddagger V < 0$) and the marked dependence of the substitution rate on the nature of entering and leaving ligands support the claim that the square-planar replacements are associative in nature.

Generally speaking, the square planar substitutions proceed with retention of configuration: *cis*-complex yields a *cis*-product and *trans*-complex yields a *trans*-product.

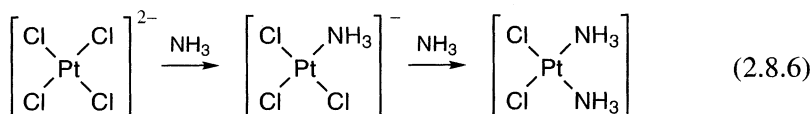
Regarding stereochemical changes, the five coordinate intermediate can be a square pyramid or a trigonal bipyramid. The main intermediate is likely to have the trigonal bipyramid geometry, while a high energy intermediate is probably a square pyramid, as depicted in Figure 2.8.1.

2.8.2. *Trans* effect

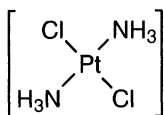
One out of four ligands of a square planar complex is labile and can be replaced by entering ligands. The remaining three ligands are inert; two are in *cis*- and one in *trans*-position to the labile ligand. A ligand in *trans*-position exerts a significant effect upon the dissociation rate of the leaving ligand, which is called *trans* effect. On the other hand, the kinetic effect of a ligand in *cis*-position to the labile ligand is of minor importance. An empirically established and generally accepted order of the *trans* effect is:



The sequence covers the rate effects of a range of 10^6 and is roughly applicable to all square-planar platinum complexes. Based on this sequence, the steric course of a substitution can be predicted, e.g.,

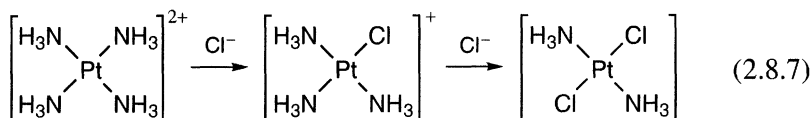


and not



since the *trans* effect of Cl^- is larger than that of NH_3 . This is the way in which the *cis*-complex was prepared.

On the other hand, the *trans*-complex was formed according to scheme (2.8.7), because the *trans* effect of $\text{Cl}^- > \text{NH}_3$.



It is necessary to distinguish between a ligand *trans* effect and a ligand *trans* influence. A ligand *trans* effect is an effect of the *trans*-ligand on the rates of substitution of ligands opposite to it. The ligand *trans* influence is a static ground state effect. This effect influences, *e.g.*, a metal-ligand bond length.

A ligand that is a good σ donor increases the electron density on a metal, thus weakening the bond between the metal and the leaving group. Figure 2.8.2 shows the bonding of the p orbital of an amino ligand with the $d_{x^2-y^2}$ and d_{z^2} orbitals of a metal.

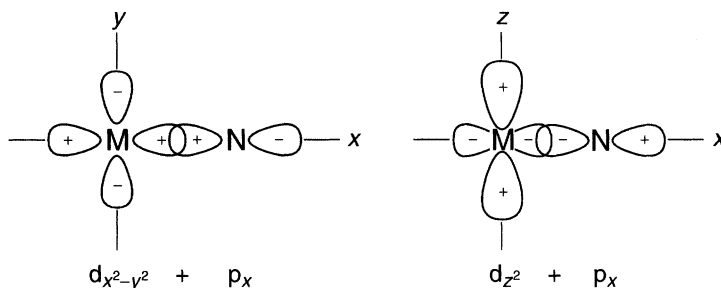


Figure 2.8.2. σ -Bonding of the nitrogen p orbital of an amino ligand and the e_g orbitals of the metal.

The mentioned sequence of ligand *trans* effects reveals a large *trans* effect of H^- ligand for which its σ donation is responsible, while the π bonding appears to be of minor importance. On the other hand, the very high *trans* effects of, *e.g.*, CN^- , CO and NO ligands, and others, are largely due to the π bonding leading to preferential stabilization of the trigonal bipyramidal pentacoordinate species. When the entering ligand (Y) approaches a square planar complex, its donor orbital symmetry is right for the overlap with the empty metal p_z orbital. The entering ligand (Y) and the leaving ligand (X) remain in the

equatorial positions of the trigonal bipyramid. Thus, there are three ligands in the equatorial plane; the out-of-plane π orbital of the *trans*-ligand can interact with the π orbitals of X or Y, or both of them. But, if the intermediate is square pyramidal, such interactions are not possible. On the other hand, we know that steric isomers do occur. It has been found that the thermodynamically unstable isomer (square pyramidal), if formed, is formed most rapidly and then converted to the trigonal bipyramidal intermediate.

Figure 2.8.3 depicts the π bonding of the d_{xz} metal orbital and the p_z orbital of an amine ligand.

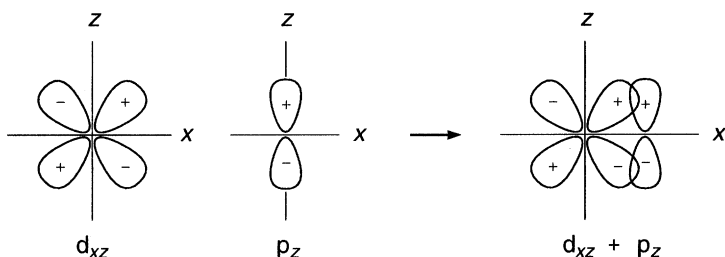


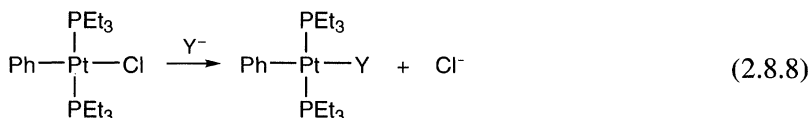
Figure 2.8.3. π Bonding of the d_{xz} metal orbital and the p_z orbital of an entering ligand.

It may be concluded that the *trans* effect of a ligand is a combination of its σ donation and its ability of π bonding. Since the substitutions of square planar complexes are associative in nature, the orienting *trans*-ligand can increase the replacement rate by its contributions to the bond breaking of the metal and the leaving ligand (X) and also by its contribution to the π bond making of the metal and the entering ligand (Y). Very basic orienting ligands contribute to the M–X bond breaking, but their electron donation hampers the bond making with the entering nucleophile (Y^-); the CN^- orienting ligand exhibits a strong *trans* effect, because of its basicity ($pK_a \approx 9.2$), but also because of its polarizability (molecular polarizability = 0.373, see Table 2.7.2), which enables π bonding.

2.8.3. *Cis* effect

The ligands in *cis*-position to the leaving ligand (X) exhibit a small electronic effect and consequently a small replacement rate effect (the acceleration factor is about 2 to 3 while, as already said, the acceleration factor of the *trans* effect can be larger than 10^6). The origin of the *cis* effect is similar to that of the *trans* effect. Molecular orbital calculations show that ligands which weaken bonds to ligands *trans* to them also weaken bonds to ligands *cis* to them, but the effect is much smaller.

On the other hand, bulky ligands in *cis*-position exhibit large steric effects. Thus, in the reaction (2.8.8), the replacement of *trans*-phenyl by *trans*-mesityl (mesitylene = 1,3,5-trimethylbenzene) leads to a rate decrease by a factor of 30, but if phenyl is in *cis*-position the rate decrease factor is about 10^5 :

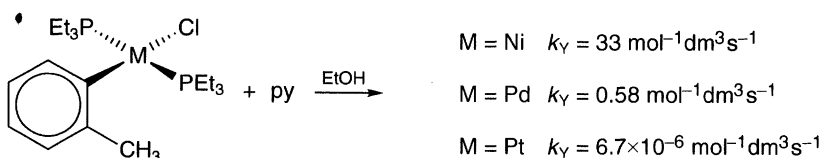


2.8.4. Leaving group effects

The nature of the leaving group affects the rates of the substitution reactions of square-planar complexes. We have previously pointed out that in octahedral substitutions, which are, as a rule, of the dissociative type, the nature of the leaving group (X) exhibits a strong effect on the reaction rate because the bond between the metal and this group is largely broken in the reaction transition state. However, the nature of the leaving group can also influence the substitution rates of square-planar complexes, which are of the associative type. The size of this effect will depend on the degree of bond breaking in the reaction transition state. *E.g.*, by measuring the activation volumes it was established that the bond Pt–Cl in the substitution of Cl^- by Br^- in *trans*-[Pt(PEt₃)Cl₂] remained almost untouched in the reaction transition state.⁶⁸ As already mentioned, the *trans* effect of the orienting ligand depends on the bond strength of the leaving ligand in the reaction transition state, and this bond is a combination of the σ and π bonding.

2.8.5. Effect of the central metal ion

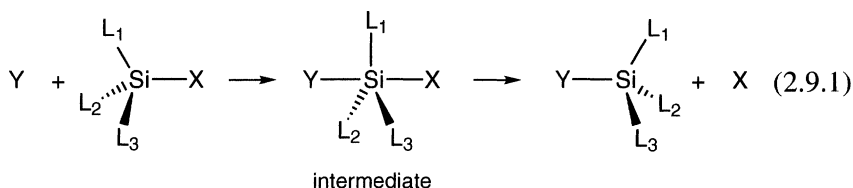
The effect of the central metal ion on the rates of square-planar substitutions can be very strong. Hence, the tendency to undergo substitution is in the same order as the tendency to form pentacoordinate complexes:⁶⁹ $\text{Ni}^{\text{II}} > \text{Pd}^{\text{II}} \gg \text{Pt}^{\text{II}}$. Thus, the substitution rates of chlorine by pyridine in EtOH depend on the metal, as follows:



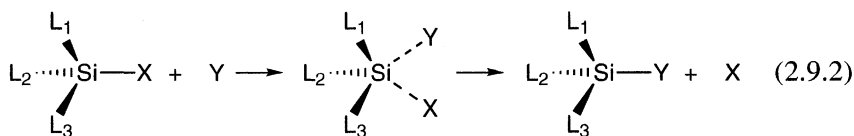
2.9. SUBSTITUTION REACTIONS OF TETRAHEDRAL COMPLEXES

Tetrahedral metal complexes are very frequent. Such complexes can be formed by almost all elements with p electrons in the outer shell. F, Te, Bi, Po, At and the noble gases are exceptions. Almost all transition metals, except Nb, Ta, Sc, Y, La and Ac, build tetrahedral complexes. Substitution mechanisms of the tetrahedral complexes of Si, Ge, Sn and P have been most extensively studied. These substitutions are of the A or I_a type, with an intermediate of the coordination number 5, their possible geometries being a square pyramid or a trigonal bipyramid.

The substitution of X by Y of the silicon L₃SiX complex can proceed *via* a trigonal bipyramid, like in organic chemistry, with configuration inversion (scheme 2.9.1):



In the case of a *cis* attack, the substitution will proceed with the retention of configuration (scheme 2.9.2):

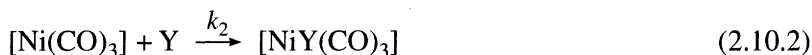


The high spin tetrahedral complexes of the first transition period are very labile. Their substitution reactions are associative in nature. Such complexes are, *e.g.*, [Co^{II}Cl₄]²⁻, [Co^{II}Cl₃Py]⁻, and [Co^{II}Cl₂py₂].

2.10. SUBSTITUTIONS OF CARBONYLS

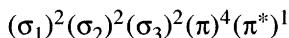
Substitution mechanisms of the carbonyls of organometallic complexes have been most extensively investigated.⁷⁰ These complexes are easy to prepare, are usually very stable and can be well characterized by IR spectra.

Let us consider the $[\text{Ni}(\text{CO})_4]$ complex. Nickel can accept 4 electron pairs from donor ligands. Thus, its valence shell acquires a total of 18 electrons, *i.e.*, the noble gas configuration; the coordination number $Z = 4$. Under such conditions, nickel has no adequate orbitals for accepting an additional electron pair, required for an associative mechanism. Indeed, mechanistic studies have shown that the substitution mechanism of carbonyls is of the dissociative type,⁷¹ as shown by the following reaction scheme:



Reaction (2.10.2) is relatively fast ($k_2 > k_1$).

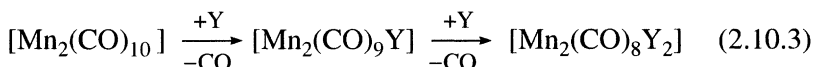
Complexes $[\text{Co}(\text{CO})_3\text{NO}]$, $[\text{Fe}(\text{CO})_2(\text{NO})_2]$ and $[\text{Mn}(\text{CO})(\text{NO})_3]$ are iso-electronic with $[\text{Ni}(\text{CO})_4]$; this is so because the NO ligand is in fact the donor of 3 electrons. Namely, the NO ligand acts as a donor in its NO^+ form. But, NO^+ is a possible electron pair acceptor from the metal, thereby being converted to NO^- . In this way, the coordination saturation (18 valence electrons) is only apparent, but the transfer of two electrons from the metal to the NO^+ opens the possibility of accepting the fifth electron pair, *i.e.*, a pentacoordinate intermediate can be formed, enabling an associative mechanism. It is noteworthy that the structure of NO cannot be depicted in Lewis' way, since the molecule has an odd number of valence electrons. Namely, nitrogen contributes 5 valence electrons, and oxygen 6 electrons, the total number of valence electrons being 11. The NO molecule is paramagnetic. Its electron configuration is



The electron in the π^* orbital is relatively easily released to give nitrosonium ion (NO^+). Since the electron is supplied from an antibonding orbital, the NO^+ ion has a bond distance of 106 pm, which is shorter than the bond distance in the NO molecule (114 pm).

2.10.1. Substitutions of the carbonyls of complexes with a metal-metal bond

Examples of such substitutions are the replacements of CO by Y of the $[\text{Mn}_2(\text{CO})_{10}]$, $[\text{Te}_2(\text{CO})_{10}]$, $[\text{Re}_2(\text{CO})_{10}]$, and $[\text{MnRe}(\text{CO})_{10}]$ complexes, as demonstrated by eq. (2.10.3):



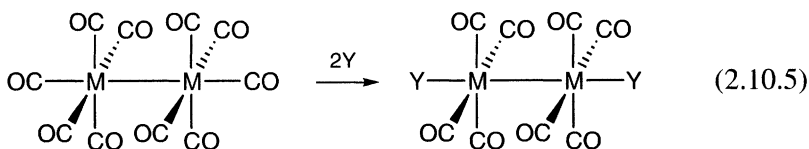
The entering ligand Y occupies the axial, not the equatorial position.

The substitutions follow the kinetic law:

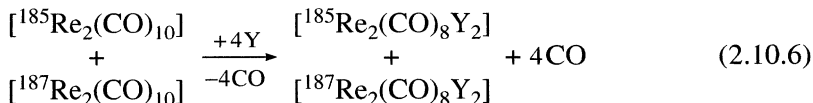
$$\text{rate} = k_1[\text{M}_2(\text{CO})_{10}] + k_2[\text{M}_2(\text{CO})_{10}][\text{Y}] \quad (2.10.4)$$

where $k_1 \gg k_2$. This kinetic expression corresponds most closely to a dissociative interchange mechanism (I_d)⁷² (the substitution of CO by Y is mainly dissociative, since its rate depends very little on the concentration of Y). There were several discussions whether the mechanism involves a CO dissociation^{72,73} or a homolytic cleavage of the M–M bond.^{74,75} Using rhenium isotopes, complexes $[\text{}^{185}\text{Re}_2(\text{CO})_{10}]$ and $[\text{}^{187}\text{Re}_2(\text{CO})_{10}]$ were prepared and used in substitution and exchange reactions. No mixed isotopic species were observed, ruling out the M–M bond homolysis mechanism.⁷⁶

Scheme (2.10.5) shows the structures of the $[\text{M}_2(\text{CO})_{10}]$ complex and its substitution product $[\text{M}_2(\text{CO})_8\text{Y}_2]$.



A definite proof that no homolytic cleavage of the M–M bond is involved was obtained on the Re_2 carbonyls:



No isotopic scrambling was observed, *i.e.*, species $\text{Y}-\text{}^{185}\text{Re}-\text{}^{187}\text{Re}-\text{Y}$ were not observed, which should have been found if homolytic M–M bond cleavage had occurred.

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Chapter 3

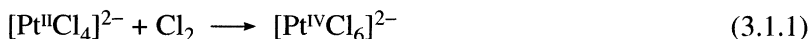
OXIDATIVE ADDITIONS AND REDUCTIVE ELIMINATIONS

Coordinatively unsaturated compounds can generally bind neutral or anionic nucleophiles. Such reactions are called additions. Oxidative additions are reactions that involve an increase of the formal oxidation state and the coordination number. Reductive eliminations are, in principle, opposite processes to oxidative additions. They lead to a reduction of the coordination sphere of the metal and to its formal oxidation state.

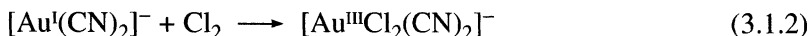
In many cases, oxidative additions and reductive eliminations are microscopic reverses.

3.1. OXIDATIVE ADDITIONS

Halogen oxidation reactions of the type:



or



are obvious oxidative additions.

In reaction (3.1.1), platinum(II) loses two electrons, yielding platinum(IV) ($d^8 \rightarrow d^6$); in reaction (3.1.2), Au^{I} yields Au^{III} ($d^{10} \rightarrow d^8$).

The general form of an oxidative addition process is usually written as:



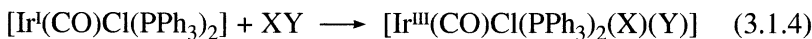
If X and Y are univalent anions (charge number -1), the oxidation state will be formally increased by $+2$, which is the reason why reaction (3.1.3) is called an oxidative addition.

3.1.1. Two-electron oxidative additions

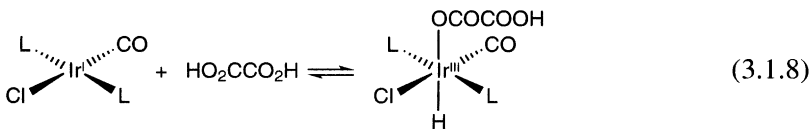
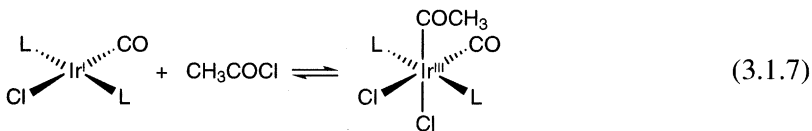
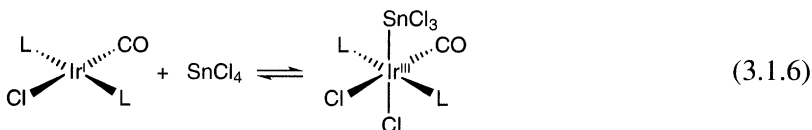
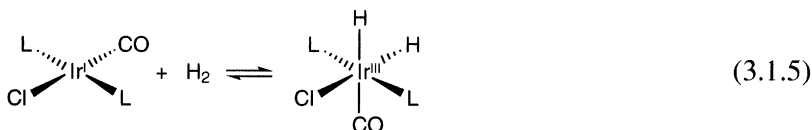
The first oxidative additions of the mentioned general type (3.1.3) are the reactions of Vaska's* compounds,¹ *e.g.*, of compound:



The oxidative addition is:



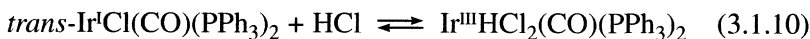
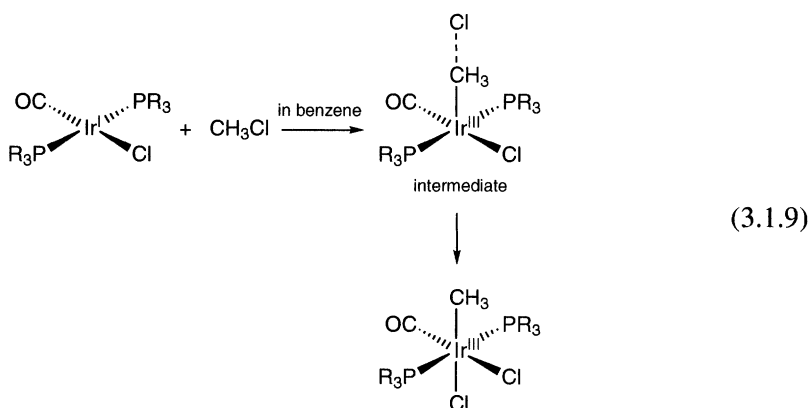
In reaction (3.1.4), XY can be H_2 , R-I ($\text{R} = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, n\text{-C}_3\text{H}_7, \text{etc.}$), HCl , Br_2 , I_2 , Cl-Hg-Cl , $\text{CH}_3\text{CO-Cl}$, $\text{R}_3\text{Si-H}$, and other reactants, *e.g.*,²



* L. VASKA, Estonian-American chemist, professor of chemistry at Clarkson University, Potsdam, N.Y., emigrated to the United States after the Second World War. In his book,^{3a} the late Professor M. L. Tobe called Vaska's compound "a singular compliment in inorganic chemistry where the cult of personality is not encouraged".

Reaction (3.1.9) is a typical *trans* addition. The oxidation number increases by two units, since two ligands are added in the *trans*-positions. The intermediate has a square pyramid structure; the equatorial geometry is preserved. On the other hand, if the reaction is carried out in a more polar solvent, *e.g.*, methanol, the intermediate becomes trigonal bipyramidal, and the products are *cis*- and *trans*-isomers. It is not clear why polar solvents favor the trigonal bipyramidal intermediate. The condition for these reactions is that the complex in its reduced form has the possibility of additional coordination and that it can accept two new ligands.

Examples of oxidative additions (adapted from ref. 2 and other sources):



Oxidative additions involving a two-electron transfer are often very fast and their rates are difficult to measure. It can be generally concluded that oxidative additions of Vaska's compounds follow a second order reaction, *i.e.*,

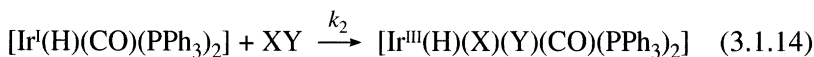
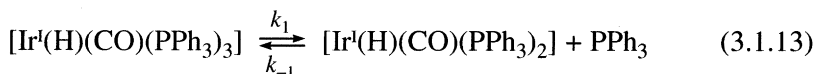
$$\text{Rate} = k_2[\text{Ir}^{\text{I}}][\text{XY}] \quad (3.1.11)$$

The rate equation scheme is valid for the oxidative additions of complexes that are coordinatively unsaturated. Rates of these reactions depend very strongly on the nature of X and Y, but if only complexes of the *trans*-[IrL_{hal}(CO)L₂] type are considered, where L_{hal} is a halogen, and L is a phosphorus ligand-donor (*e.g.*, *trans*-[Ir^ICl(CO)(PPh₃)₂]), then the reactivity is not very dependent on the nature of L_{hal}. Nevertheless, the reaction rate decreases following the sequence Cl > Br > I.

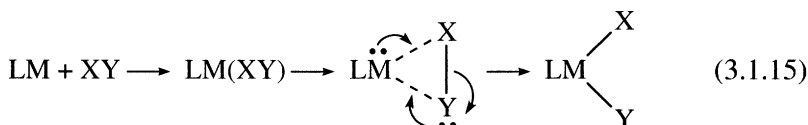
The behavior of the [Ir^IH(CO)(PPh₃)₃] complex is typical. The rate law is:

$$\text{Rate} = \frac{k_1 k_2 [\text{Ir}^{\text{I}}][\text{XY}]}{k_{-1}[\text{PPh}_3] + k_2[\text{XY}]} \quad (3.1.12)$$

This form of the kinetic law has been already mentioned (see eq. 1.12.11). It points to a mechanism where a coordinatively saturated complex must first lose a ligand to become coordinatively unsaturated, and thus be able to undergo an oxidative addition. These steps are shown by the following equations:



One should bear in mind that the oxidizing reagent X–Y provides two ligands. If the complex has no free positions for coordination, then a ligand of the substrate or a potential ligand of the X–Y combination must be freed before or during the oxidative addition, thus enabling the formation of M–X and M–Y bonds. One possibility is that the X–Y are provisionally bonded to the reaction center. The subsequent electron redistribution leads to the X–Y bond rupture and the formation of M–X and M–Y bonds:^{3b}

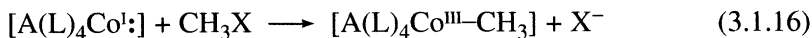


In the oxidative addition scheme (3.1.15), two electrons are transferred from the metal to the X ligand and two electrons from the X–Y bond are transferred to the Y ligand, thus X and Y ligands are ready for coordination to the metal, whose number of electrons is reduced from d^n to d^{n-2} .

It should be expected for both X and Y ligands to be strongly electronegative. Experiments also show that the reaction is stereospecific: X and Y are *cis*, *i.e.*, adjacent in the oxidized complex product.^{3b}

3.1.1.1. Mechanism of oxidative addition of the nucleophilic substitution type

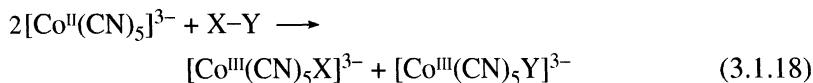
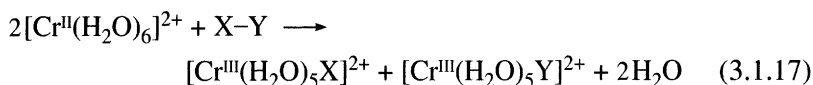
In oxidative additions of this type, the metal electron pair, which has not been previously engaged in chemical bonding, becomes the electron donor pair, *i.e.*, a nucleophile, as in the reaction:



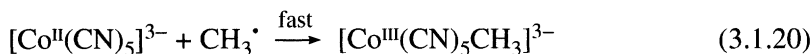
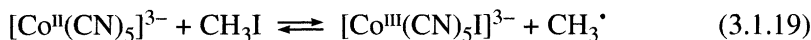
The reaction is a typical S_N2 (A_ND_N) process. Vitamin B_{12} belongs to this category, which will be discussed later.

3.1.2. One-electron oxidative additions

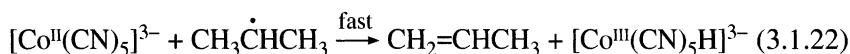
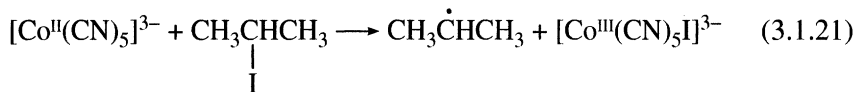
Two important reaction groups involve one-electron oxidative additions. These are the reactions of $Cr^{II} \rightarrow Cr^{III}$ and of $Co^{II} \rightarrow Co^{III}$:



These reactions are analogous to the reactions that involve an inner sphere redox mechanism (to be distinguished from the outer sphere redox mechanism, where the electron transfer takes place without changing the coordination sphere, which will be discussed later), *e.g.*,



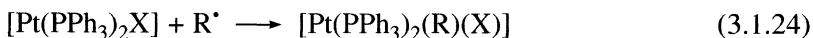
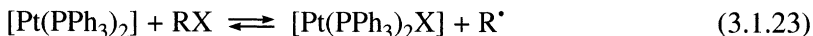
There is strong evidence for the free radical intermediate formation. Thus, it is said that reactions (3.1.19) and (3.1.20) proceed by a one-electron "free radical" mechanism. This category also includes the composite reaction:



Generally speaking, alkyl halides often react by the free radical mechanism, less frequently by the nucleophile attack.^{3b-5} Phosphine ligands, *e.g.*, PMe_3 , PMe_2Ph , $PMePh_2$, are very important in free radical reactions.⁶

It is generally known that the reaction mechanisms involving free radicals exhibit a loss of stereochemical characteristics. The rates of these reactions

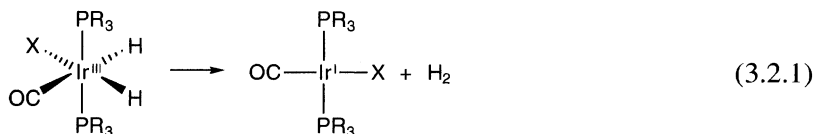
cannot be well reproduced and are slowed down by the free radical inhibitors. All these characteristics apply to the following reactions ($X = \text{halogen}$):⁷



3.2. REDUCTIVE ELIMINATIONS

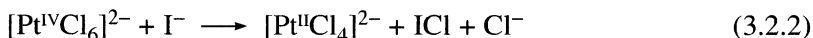
As already pointed out, reductive eliminations are reverse processes to oxidative additions.

Reaction (3.2.1) is an example:



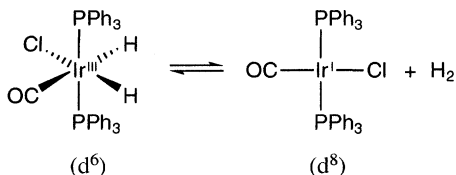
In the reaction, iridium(III) is reduced to iridium(I).

Reaction (3.2.2) is another example:



Reductive eliminations have been generally much less investigated than oxidative additions. Nevertheless, a great deal of information has been obtained from reactions of iridium complexes, *e.g.*, $[\text{Ir}(\text{CO})(\text{R})(\text{R}')\text{L}_2\text{X}]$, where $\text{L} = \text{PPh}_3$ or $\text{P}(p\text{-tolyl})_3$.⁸⁻¹⁴

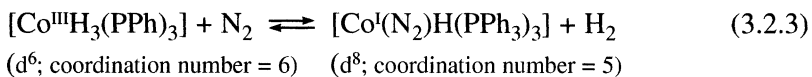
Oxidative additions and reductive eliminations are often reversible processes. Thus, hydrogen addition constitutes a special case of oxidative addition. Despite the high H–H bond energy of 450 kJ mol^{-1} , the oxidative addition of H_2 proceeds readily. The reaction is reversible, since hydrogen can be removed by sweeping with molecular nitrogen or argon, or by applying vacuum:



Regarding the mechanism, it appears that the molecular hydrogen complex is initially formed using the σ^* orbital as an acceptor orbital. This con-

tributes to the polarization and weakening of the H–H bond and to the final formation of two *cis* M–H bonds.¹³

The reversible reaction:



and its reverse, the reductive elimination, were extensively studied in an unsuccessful attempt to find a complex suitable for atmospheric nitrogen fixation under standard temperature and pressure conditions.

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Chapter 4

MOLECULAR NONRIGIDITY

Atoms oscillate approximately harmonically about their equilibrium positions. But, there are appreciable numbers of compounds, especially metal complexes, where vibrations of molecules can carry a molecule from one stereo configuration to another. Such molecules are said to be stereochemically non-rigid (fluxional).

Molecular configuration is an important property of the large majority of compounds. Stereochemistry involves not only the shapes of molecules but also the ways in which they react, because the relative positions of reacting groups have an important effect upon the rate and the result of a reaction.

The interconversion of nonrigid structures is called isomerization. The type of isomerism, where the isomers differ only in the placement of a proton and the corresponding location of a double bond, is commonly referred to as tautomerism. Such isomers are called tautomers. The term fluxional structures is also used.

4.1. PSEUDOROTATION

Let us consider, *e.g.*, compounds PF_5 and $\text{Fe}(\text{CO})_5$, which have a trigonal bipyramidal structure. Out of the 5 ligands, 3 are in the so-called equatorial positions and 2 in axial positions. The distance of axial ligands from the metal center is somewhat larger than that of equatorial ligands. Thus, it could be expected that the ^{19}F NMR spectra would show two maxima, corresponding to the nonequivalent positions of the fluorine atoms of the PF_5 molecule. Analogously, two maxima could be expected in the ^{17}O NMR spectrum of $\text{Fe}(\text{CO})_5$. However, all the mentioned spectra exhibit only one spectral maximum, which corresponds to the statistical average of positions and distances. Using different measuring techniques we can learn that some of these tech-

niques are adequately fast, which will enable us to follow the changes of steric configurations of each tautomer independently. Such methods are electronic spectroscopy and electron diffraction, the time scales of which are less than 10^{-11} s. On the other hand, the NMR spectroscopy scale is about 10^{-5} to 10^{-2} s. These measurements have revealed the nonrigidity of steric configurations of PF_5 and $\text{Fe}(\text{CO})_5$.¹

Coming back to the mentioned PF_5 and $\text{Fe}(\text{CO})_5$ molecules, the fact is that NMR spectra do not register different distances between the central metal atom and the equatorial and axial ligands. The explanation was given by Berry,² and the suggested mechanism was named Berry's mechanism or pseudo-rotation. Figure 4.1.1 is a schematic illustration of Berry's mechanism for the trigonal bipyramid:

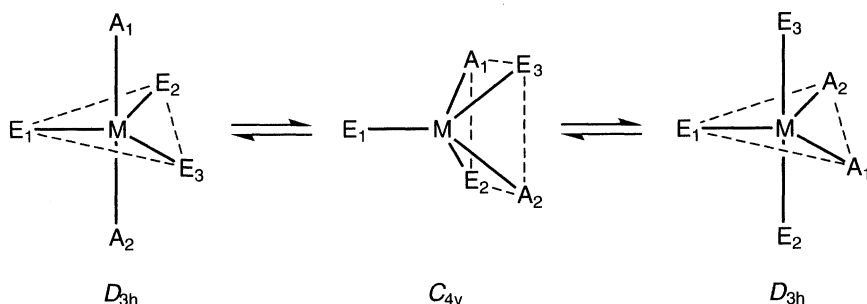


Figure 4.1.1. Berry's mechanism, or pseudo-rotation, for the trigonal bipyramid, including the square pyramidal intermediate.

As already said, in the NMR spectrum all ligands appear equivalent, since they quickly pass between axial and equatorial positions of the trigonal bipyramid (of D_{3h} symmetry). Theory shows that when two nuclei in different positions, of frequencies ν_1 and ν_2 , and their difference $\Delta\nu$, exchange positions at a frequency larger than $\Delta\nu$, then only one frequency will be observed, amounting to $0.5(\nu_1 + \nu_2)$.

Analysis shows that there are only two ways of intramolecular exchange:

- (a) the exchange involves one axial and one equatorial ligand,
- (b) the exchange simultaneously involves two axial and two equatorial ligands.

Experimental data support the latter alternative.

Energies of the square pyramid and trigonal bipyramid stereo structures differ only slightly. Berry has shown that even a small deformation of the oscillation angles can enable an interconversion.

Figure 4.1.1 shows that a decrease of the $A_1\text{--}M\text{--}A_2$ angle below 180° , and an increase of the $E_2\text{--}M\text{--}E_3$ angle by 120° , in such a way that both angles acquire an equal equilibrium value, a square pyramidal intermediate will be

obtained with the base A_1, E_3, A_2, E_2 . The square pyramidal intermediate may revert to the trigonal bipyramid structure (left), or turn into the trigonal bipyramid structure (right), as depicted in Fig. 4.1.1. It should be noted that in both trigonal bipyramidal structures ligand E_1 is in the equatorial position. The final oscillation effect, leading to angle changes, gives an impression of the initial trigonal bipyramidal structure rotation by 90° on the E_1 -M axis (pseudorotation).

In principle, the trigonal bipyramid has slightly lower energy than the square pyramid.

There are several factors influencing the geometry of these two structures:

(a) *Principle of the minimum electronic repulsions*. In the case of the trigonal bipyramid, there are 3 electron pairs in the equatorial plane, which mutually repulse at angles of 120° (3 repulsions at 120°). The 3 electron pairs also repel at 90° angles, with 2 electron pairs in axial positions, above and below the equatorial plane (6 repulsions at 90°). In this case of the square pyramid, there are 8 repulsions at 90° . Though the total number of electron pair repulsions in the trigonal bipyramid structure is 9 (3 at 120° and 6 at 90°), the total electron pair repulsion energy of the square pyramid structure is larger because the repulsions at 90° are larger than those at 120° . We may conclude that, regarding the electron pair repulsions, the trigonal bipyramid structure is slightly more stable than the square pyramid structure.

(b) *Crystal field stabilization energies* (see section 2.4.2).

(c) *Steric interference* (bulky ligands contribute to the structure destabilization).

(d) *Ligand electronic characteristics* (electronegativity of ligands).

An example of the ligand steric influence and the ligand electronic influence on pseudorotation is the $P(CH_3)_2F_3$ molecule. The structure with fluoride ligands in axial (not in equatorial) positions and the methyl groups in equatorial positions, as in Figure 4.1.2, is more stable.

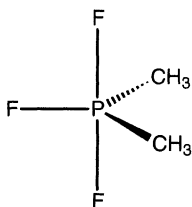


Figure 4.1.2. Strongly electronegative fluorides occupy the axial positions because mutual repulsions are then smallest.

If pseudorotation should occur, at least one CH_3 group would come into an axial position, and two F^- into equatorial positions, thus causing high electron pair repulsions, *i.e.*, a high energy barrier to pseudorotation. This is the

reason why $\text{P}(\text{CH}_3)_2\text{F}_3$ does not undergo pseudorotation, not even at high temperatures.

Figure 4.1.3 depicts a compound of the trigonal bipyramidal structure where pseudorotation is not possible because of the six-membered ring.

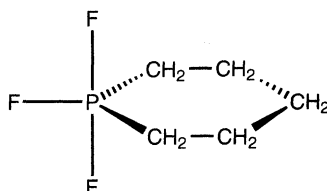


Figure 4.1.3. A trigonal bipyramidal structure where the pseudorotation is not possible for steric reasons.

In metal complexes of the coordination number 4, tetrahedral geometry has lower energy than square planar geometry. Figure 4.1.4. depicts the possible transitions.

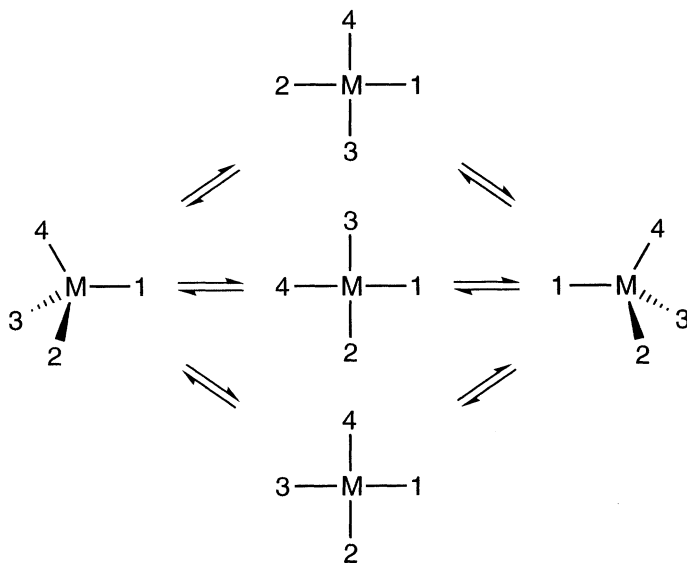


Figure 4.1.4. Inversion and isomerization of a tetrahedral complex over a square-planar transition state.

In carbon compounds, the energy difference between tetrahedral and square-planar structures is large (larger than 350 kJ mol^{-1}). On the other hand, these differences are much smaller in transition metal complexes. Thus, the complexes of transition metals with the coordination number 4 appear in both structures, tetrahedral and square-planar, depending on the nature of the ligands.

Both structures can exist in equilibrium, as is the case of the $[\text{Ni}^{\text{II}}(\text{PPh}_3)_2\text{Br}_2]$ complex.

4.2. NONRIGIDITY OF METAL CARBONYLS

It has lately been definitely established that the dinuclear and polynuclear metal carbonyls exhibit a marked tendency to nonrigidity of their structures, which is known as carbonyl scrambling. It is characteristic of the CO ligand that it can be bonded to one of the two metals as a terminal ligand, or form a bridge between the two metals. On the other hand, if two CO groups are involved, they can be terminal on both metals, or make two bridges, linking the two metals. The energy difference of such structures is small, less than 30 kJ mol^{-1} , as exemplified by the complex $[\text{Cp}_2\text{Fe}_2(\text{CO})_4]$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5^-$).*

The compound exists in solution as a mixture of *cis*- and *trans*-isomers, with CO bridges. For a CO group bridging two metals, the stretching frequency is in the region from 1700 to 1850 cm^{-1} while the stretching frequencies of terminal CO's are generally higher and lie in the region from 1800 to 2140 cm^{-1} .^{1a,1b}

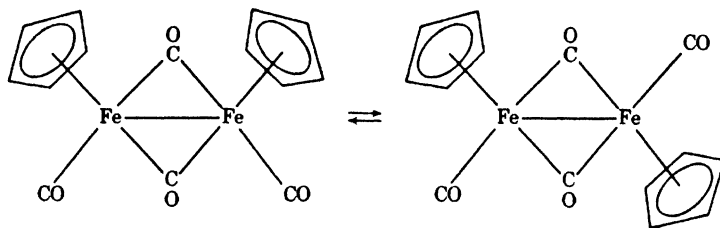


Figure 4.2.1. *Cis*- and *trans*-isomers of the $[\text{Cp}_2\text{Fe}_2(\text{CO})_4]$ complex ($\text{Cp} = \text{cyclopentadienyl}$), ref 1a. Reproduced by permission from F. A. Cotton and of John Wiley & Sons, Inc., © 1988.

The NMR signals of ^1H in the spectrum of cyclopentadienyl rings are expected to appear in different positions, and this is what really happens at -70°C ; however, at room temperature there is only one signal in the intermediate position.^{1a,1b} The ^{13}C NMR for CO groups shows that these groups exchange their bridging and terminal positions. It is taken that the CO bridges break simultaneously in a one-step ("concerted") process. The intermediate $\text{Cp}(\text{OC})_2\text{Fe}-\text{Fe}(\text{CO})_2\text{Cp}$ is thus formed, which can rotate around the $\text{Fe}-\text{Fe}$ bond. Such rotation is impossible as long as rigid CO bridges exist. After

* Symbol η , stands for hapto (from the Greek word *haptein*, meaning fasten); thus, ligand C_5H_5 carries also the name pentahaptocyclopentadienyl group. The use of η is recommended by IUPAC.

rotation, the CO bridges close, yielding a *cis*- or a *trans*-product. Even CO bridges can exchange their initial positions. Nonrigidity of metal carbonyls is specific to this type of compounds.

4.3. [(FULVALENE)TETRACARBONYLDIRUTHENIUM]. STORAGE OF LIGHT ENERGY

Photochemical isomerization of the [(fulvalene)tetracarbonyldiruthenium] complex represents a nonrigid system that can store light energy of relatively long wavelengths (about 350 nm). The illuminated nonrigid complex changes its structure, but after heating at a temperature $> 65\text{ }^{\circ}\text{C}$ the complex reverts to its initial structure, liberating about 12.5 kJ mol^{-1} ($\approx 3\text{ kcal mol}^{-1}$). The interconversion cycle can be repeated more than 40 times with no observable substrate loss. The reaction presents a great challenge to attempts to find its practical application, as it has been pointed out in recent literature.³⁻¹⁰

In the last twelve years, special attention has been devoted to photochemistry of the dinuclear organometallic complexes, since different structures undergo light excitation leading to ligand replacements, disproportionation, or to different redox reactions. Detailed data on the nature of the primary photo reaction and on the reaction intermediates are known and have been published for various metal π complexes,^{3,11,12} including complexes of the $[\text{Cp}_2\text{M}_2(\text{CO})_4]$ type ($\text{M} = \text{Fe}$ or Ru).

Extensive studies of iron dimers suggest at least three independent primary processes:³

- (a) homolysis of the metal-metal bond with formation of two mononuclear radicals;
- (b) loss of CO, resulting in triply-bridged, paramagnetic dinuclear species;
- (c) rupture of the metal-metal bond without fragmentation; a reactive intermediate is bonded with only one CO bridge.

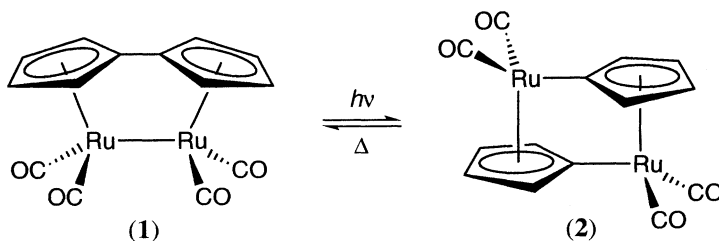


Figure 4.3.1. Photoisomerization of [(fulvalene)tetracarbonyldiruthenium], **1**, and its exothermic reverse, **2**.³ The reaction system effectively stores light energy; after mild heating, above $65\text{ }^{\circ}\text{C}$, the inversion complex reverts to its original structure liberating $\approx 3\text{ kcal mol}^{-1}$ (reproduced by permission from professor K. Peter C. Vollhardt and the American Chemical Society).

It has, however, been shown that $[\text{FvRu}_2(\text{CO})_4]$, **1**, ($\text{Fv} = \eta^5\text{:}\eta^5\text{-bicyclopentadienyl}$) reacts in a different way than the $[\text{Cp}_2\text{Fe}_2(\text{CO})_4]$ complex. The diruthenium complex does not fragmentize under the influence of radiation, since pentadienyls are mutually bonded, but undergoes a reversible isomerization reaction; the reverse reaction is exothermic ($\Delta_r H = -29.8 \pm 1.5 \text{ kcal mol}^{-1}$), see Figure 4.3.1.

*The structure of $[\text{FvRu}_2(\text{CO})_4]$ (**1**).* – The complex has been isolated in the form of yellow crystals.¹³ The IR spectra reveal two strong absorptions of the terminal carbonyls, in contrast to the $[\text{Cp}_2\text{Ru}_2(\text{CO})_4]$ complex which contains equilibrated bridged and terminal carbonyl ligands.^{14,15} The absorption spectrum of **1** in tetrahydrofuran (THF) shows a characteristic maximum at 329 nm, similar to the $[\text{Cp}_2\text{Ru}_2(\text{CO})_4]$ ($\lambda_{\text{max}} = 330 \text{ nm}$), where there is no bridge between cyclopentadienyls. The $[\text{FvRu}_2(\text{CO})_4]$ structure has been confirmed by mass spectroscopy and structural X-ray analysis.

Thermally reversible photoisomerization of complex 1. – Solution of the yellow crystals of **1** in THF, when exposed to light, as described, converts to the complex **2** in 80% yield. The structure of **2** has been confirmed by IR and ^1H NMR spectra, which show that the metal-metal bond is broken, which has been definitively proven by structural X-ray analysis.

The reverse reaction $\mathbf{2} \rightarrow \mathbf{1}$, which takes place in THF at only 65 °C, or in the crystal at 208 °C, causes crystals to bounce a few centimeters high, which is known as “*Hupfeffekt*” (*hüpfen* in German means to bounce); English expression is “thermosalient”.¹⁶ Vollhardt *et al.* carried out 10 cycles of these conversions³ with no noticeable decomposition of the substrate, announcing a possible practical application.

The $\mathbf{1} \rightleftharpoons \mathbf{2}$ interconversion involves a very interesting problem of the metal-metal bond breaking and also Cp–Cp bond breaking (between cyclopentadienyls), and their subsequent bond making with the metal, as $\eta^1\text{-C}_5\text{H}_4\text{-M}$. It should be stressed that **1** absorbs light more effectively than **2**, and that we actually deal with a very unusual oxidative addition $\rightleftharpoons$ reductive elimination reaction. The reaction is claimed to follow a “concerted” mechanism and not to involve intermediates, though the formation of diradicals cannot be excluded.³

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Chapter 5

ELECTRON-TRANSFER REACTIONS

5.1. INTRODUCTION

Electron-transfer reactions are reactions of the oxidative-reductive type. They are of great importance in nature, but also in technology, and have been in the center of interest during the last 50 years, which is evident from several thousands of publications in the field. Many biological processes, *e.g.*, photosynthesis and oxygen transfer in living cells, involve reactions that are governed by electron transfer over distances as large as 1 nm.

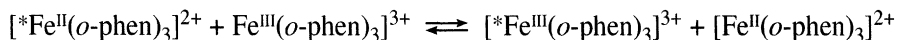
Important progress was made when it was realized that there are, in principle, two types of mechanisms of electron-transfer reactions, outer-sphere and inner-sphere mechanisms.^{1,2}

In outer-sphere redox processes, the interaction between an oxidizing and a reducing agent at the moment of electron transfer is very small. The coordination shell remains intact, though perturbed.

In inner-sphere redox processes, the oxidant and the reductant are “firmly” bonded in the activated complex during electron transfer with at least one ligand, which belongs to the coordination shell of the metal and to the reductant. This ligand serves as a bridge for electron transfer. Electron transfer is often, but not always, the rate-determining step. Our knowledge of the electron-transfer reaction mechanism has been substantially broadened by the use of isotopes and with the development of new techniques for measuring extremely fast reaction rates.

Redox reactions are very exciting from the theoretical point of view; some publications in this field have provided the basis for today's understanding of the electron-transfer mechanisms.³⁻⁹

The metal exchange reaction rates, which are much higher than those of the replacement reactions, often reveal the electron-transfer mechanism. *E.g.*, this holds for the reaction:



(*o*-phen) = *o*-phenantroline, *i.e.*, 1,10-phenanthroline

*, labeled atom

$k \approx 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (25 °C)

This means that 10^{-4} molar complex solutions exchange iron more than 99% in 13 ms.¹⁰

It is generally observed that the electron-transfer reactions are first order with regard to the oxidizing agent and also first order with regard to the reducing agent:

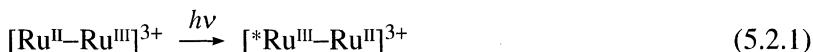
$$\text{rate} = k[\text{oxidant}][\text{reductant}]$$

Thus, the inner and the outer sphere electron-transfer mechanisms cannot be distinguished on the basis of kinetic laws.^{11–15} Activation enthalpies of electron transfer are lower for the outer-sphere electron transfers than for the inner-sphere electron transfers. Both mechanisms have, in principle, negative entropies of activation. These general data show that it is not easy to distinguish between these two mechanisms.

5.2. FRANCK-CONDON PRINCIPLE

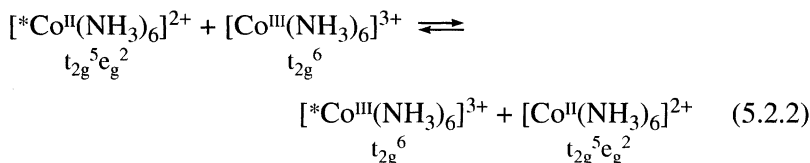
Electron-transfer reactions, which occur either by the inner-sphere or by the outer-sphere mechanism, are subject to restrictions defined by the Franck-Condon principle. The principle explains the distribution of relative intensities of the vibrational structure of an electronic transition. Namely, since the nuclei have a much larger mass than the electrons, electron transition takes place much faster than the nuclei can respond. Thus, the electron transition takes place in about 10^{-15} to 10^{-16} s, while the nuclei need about 10^{-13} s to respond (which is approximately the time of one vibration). This is the reason why electron density is rapidly built up in the new molecular region. The new electron density distribution acts upon the nuclei, which become subject to a new force field, causing them to vibrate. Since the nuclear framework remains unchanged with respect to its geometry during a very fast electronic transition, the expression “vertical transition” is used to describe this situation.

Let us consider the photoreaction of a complex ion of the type:



Assuming that both complex ions are surrounded by the same ligands, we can conclude that the complex product contains Ru^{II} surrounded by ligands with bond lengths and angles of the structure specific to Ru^{II} , while Ru^{III} is surrounded by ligands in an arrangement characteristic of Ru^{II} . This is due to the fast electron transfer influenced by the light energy. According to the Franck-Condon principle, the fast electron transfer is followed by subsequent much slower vibrational relaxation of nuclei, which enables relaxation of the “surroundings”. The differences in the “surroundings” mainly refer to the Ru–N bonds where N belongs to an amine ligand. These differences are small and, consequently, the energy differences caused by different “surrounding” are small as well. Hence, a photon energy of about 100 kJ mol^{-1} is adequate to enable reaction (5.2.1).

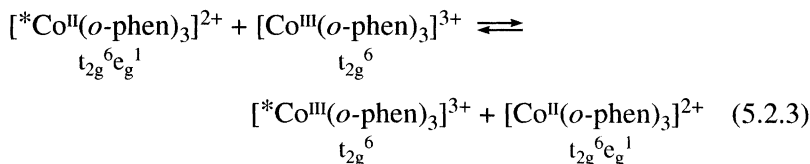
Let us also consider reactions (5.2.2) and (5.2.3):



$$k_{\rightarrow} = 10^{-9} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \text{ (25 } ^\circ\text{C)}$$

The reaction is very slow¹⁰ because it requires a spin change (from the high spin $[\text{Co}^{\text{II}}(\text{NH}_3)_6]^{2+}$ to the low spin $[\text{Co}^{\text{III}}(\text{NH}_3)_6]^{3+}$).

On the other hand, reaction (5.2.3) is fast because the electron transfer proceeds from the e_g orbital of one cobalt atom to the e_g orbital of the other cobalt atom; thus, the outer-sphere electron-transfer mechanism appears very probable:¹⁰



$$k_{\rightarrow} = 1.1 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \text{ (25 } ^\circ\text{C); } o\text{-phen} = o\text{-phenanthroline}$$

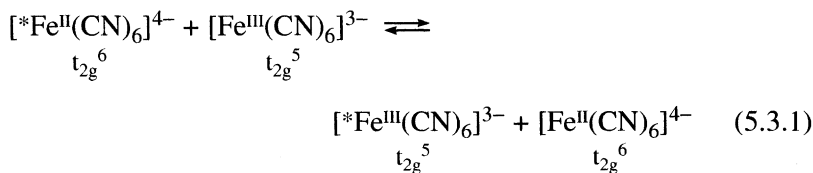
One should bear in mind that the metal-ligand bond distance (M–L) is shorter when the metal is in a higher oxidation state. The shorter M–L bond of the higher oxidation state should not be a consequence of the π back-bonding, because π back-bonding is taken to be of minor importance here, the interaction of the positively charged metal and the ligand electrons being

dominant. On the other hand, if π bonding is important, then the M–L bond can be shortened even in the lower oxidation state. Thus, the V–C bond length is 200.1 pm (2.001 Å), in the $[\text{V}(\text{CO})_6]$ complex, and 193.1 pm^{16,17} in $[\text{V}(\text{CO})_6]^-$ anion derived from the $[\text{HV}(\text{CO})_6]$ hydride.

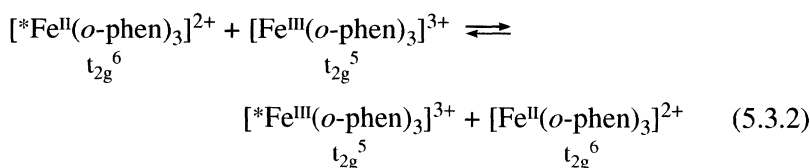
In further consideration we will assume that the metal-ligand bond (M–L) is shorter when the metal is in a higher oxidation state. Prior to the “self-exchange” in an electron-transfer process, a metal in the higher oxidation state must lengthen its bonds towards ligands, while a metal in the lower oxidation state must shorten them. The higher the extent of the reorganization, the higher is the energy needed for this reorganization, and consequently the lower is the electron-transfer rate. If the energy requirements are high, the electron-transfer rate can be very low. We have already seen that the self-exchange in the reaction (5.2.2) is very slow ($k_{\rightarrow} = 10^{-9} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ at 25 °C). It has been mentioned that Co^{3+} has a d^6 low-spin configuration, while Co^{2+} has a d^7 high-spin configuration, so a very slow electron transfer is to be expected. The e_g metal orbitals are antibonding with respect to ligands. Ligands are bonded to a metal by σ bonds. For symmetry reasons, the t_{2g} orbitals are nonbonding. These orbitals can participate only in π bonding with p ligand orbitals, which is presently not considered. A change in the number of e_g electrons has a larger energy effect than a change in the number of t_{2g} electrons. An electron transfer involving e_g orbitals is therefore much slower than an electron transfer involving t_{2g} electrons. If only t_{2g} electrons participate in an electron transfer, these reactions can be exceedingly fast, and most often proceed by an outer-orbital mechanism. This is exemplified by self-exchange (5.2.2).

5.3. OUTER-SPHERE ELECTRON TRANSFER

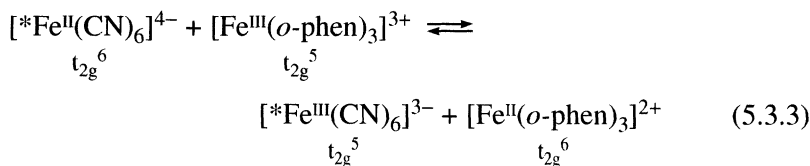
The following reactions are examples of outer-sphere electron transfers:



$$k_{\rightarrow} = 7.4 \times 10^2 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \text{ (25 °C)}$$



$$k_{\rightarrow} = 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \text{ (25 } ^\circ\text{C)}$$



$$k_{\rightarrow} = 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \text{ (25 } ^\circ\text{C)}$$

It is reasonable to expect that electron transfer will occur at a very high rate when two reactants are relatively close to each other. Reactions (5.3.2) and (5.3.3) are very fast indeed. This can be explained by assuming that the *o*-phenanthroline ligand is a ligand in which electrons are strongly delocalized (like in a metallic wire resistor).

Table 5.3.1. Some outer-sphere electron transfer reactions^(a)

Self-exchange	Electron configuration	$k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (25 °C)	Difference in M–L bond length/nm	Ref.
$[\text{Ru}(\text{bipy})_3]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	4×10^8		18,19
$[\text{Ru}(\text{o-phen})_3]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	$\approx 10^7$		20
$[\text{Fe}(\text{o-phen})_3]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	$\approx 3 \times 10^7$		21
		$\approx 10^5$		22
$[\text{Os}(\text{bipy})_3]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	5×10^4		21
$[\text{Mn}(\text{CN})_6]^{4-/3-}$	$\text{t}_{2\text{g}}^5/\text{t}_{2\text{g}}^4$	$\approx 10^6$	very small	23
$[\text{Fe}(\text{bipy})_3]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	$\approx 10^6$	0.000 ± 0.001	23
$[\text{IrCl}_6]^{3-/2-}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	10^3		22
		$\approx 10^6$		23
$[\text{Ru}(\text{en})_3]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	4×10^4		23
$[\text{Ru}(\text{NH}_3)_6]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	4×10^3	0.004 ± 0.001	24
$[\text{Ru}(\text{H}_2\text{O})_6]^{2+/3+}$	$\text{t}_{2\text{g}}^6/\text{t}_{2\text{g}}^5$	20	0.009 ± 0.002	24,25
$[\text{Fe}(\text{H}_2\text{O})_6]^{2+/3+}$	$\text{t}_{2\text{g}}^4 \text{e}_\text{g}^2/\text{t}_{2\text{g}}^3 \text{e}_\text{g}^2$	4	0.014 ± 0.002	24,26

^(a) en = ethylenediamine; *o*-phen = *o*-phenanthroline; bipy = 2,2'-bipyridine.

5.3.1. Marcus theory of outer-sphere electron transfer

Electron-transfer reactions have been attracting interest of theoretical chemists for many years. An important contribution to the theory of outer-sphere electron transfer is that of R. A. Marcus.*

In 1954 Marcus, Zwolinski and Eyring^{4,27} developed a theory of electron transfer based on the hypothesis that the mechanism involves electron tunneling (sections 1.14 and 1.15). They assumed that solvents and ligands form a barrier through which electrons must pass. Taking Eyring's transition state theory into account, their results could be formulated using the expression

$$k = \frac{\kappa k_{\text{B}} T}{h} e^{(-\Delta_{\text{r}}^{\ddagger} G^{\circ}/RT - \Delta_{\text{c}}^{\ddagger} G^{\circ}/RT)} \quad (5.3.4)$$

where κ is the transmission coefficient, which also involves the probability of the electron passing through the barrier, $\Delta_{\text{r}}^{\ddagger} G$ is the free energy of activation of reorganization of the solvent and coordination shells, and $\Delta_{\text{c}}^{\ddagger} G$ is the free energy of activation needed to overcome electric repulsions between ions. The transmission coefficient, which is always less than 1, increases when reaction partners approach one another, thus causing an increase in the reaction rate. On the other hand, increased electron repulsions increase the energy of activation, thus contributing to the reaction rate decrease. These opposing rate effects lead to an optimum distance of the reacting partners of about 6 Å, when the exchange rate is at its maximum.

Weiss²⁸ took tunneling into account in 1954, while Marcus did it in 1956.²⁹ Several investigators have tried to compute $\Delta^{\ddagger} G$, notably Marcus³⁰ and Hush.³¹ Marcus and Hush arrived at essentially the same results, correctly predicting the electron transfer rates to within an order of magnitude. This is quite satisfactory considering that the rates studied vary by a factor of 10^{14} . Later on, several reviews of the field were published.^{32–36} They contain numerous relevant references, describing different theoretical approaches. The essence of the Marcus theory of electron transfer is based on the observation that a large majority of electron-transfer reactions have some defined energies of activation. It was previously mentioned that in outer-sphere electron-transfer reactions covalent bonds are neither broken nor formed. Thus, if an electron just “drops downhill”, why is all the activation necessary at all? Marcus claimed that there must be a difference in the solvation of reactants and products, which

* RUDOLPH A. MARCUS, Canadian-born American chemist received the 1992 Nobel Prize for chemistry “for his contribution to the theory of electron transfer reactions in chemical systems”. The Marcus theory has shed light on diverse and fundamental phenomena of the outer-sphere electron transfer.

causes the energy barrier; the electron transfer itself is isoenergetic and therefore very fast; after electron transfer, a solvation relaxation of the reaction products must take place.

Marcus gave his theory a quantitative form. Gibbs free energy changes in a bimolecular outer-sphere electron transfer are represented in Figure 5.3.1: W_r is the work needed to bring the reactants from the ground state to the appropriate reaction distance. Analogously, $-W_p$ is the work required to bring the newly formed products from the reaction distance into the product equilibrium distance in the bulk solvent, which then becomes the product ground state. This work is, of course, negative; (λ_r) is the Gibbs energy required to achieve the distorted configuration of the reagents in the reaction transition state, while $(-\lambda_p)$ is the Gibbs energy change due to the equilibrium relaxation of the newly formed reaction products.

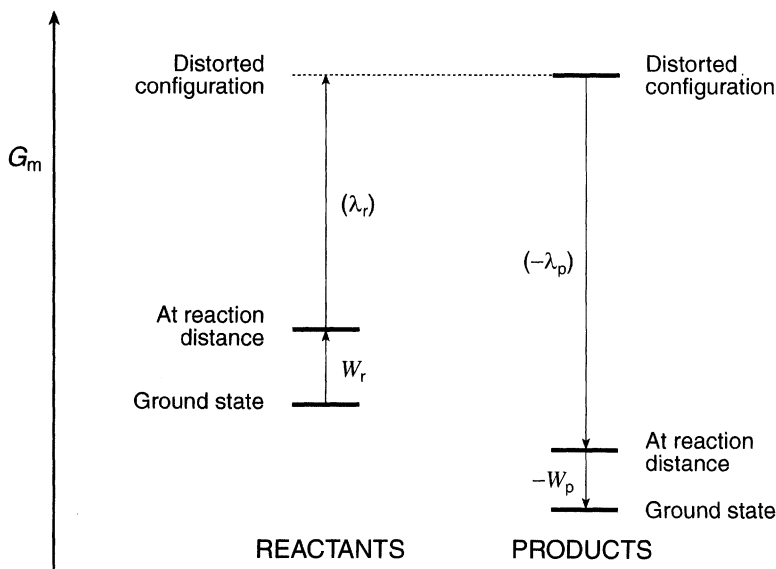


Figure 5.3.1. Schematic changes of Gibbs energy in a bimolecular electron-transfer reaction.^{38,39}

Based on these ideas Marcus derived eq. (5.3.5), which is used for reactants and products of the same size and charge type. In this equation K_{12} is the equilibrium constant of the redox system, obtained from emf (electromotive force) measurements, and k_{11} and k_{22} are rate constants.

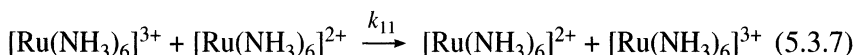
$$k_{12} = \sqrt{k_{11}k_{22}K_{12}} \quad (5.3.5)$$

If the size and charge requirements are not met, an additional factor, f_{12} , must be added, so that eq. (5.3.5) acquires the form:

$$k_{12} = \sqrt{k_{11}k_{22}K_{12}f_{12}} \quad (5.3.6)$$

Factor f_{12} is a function of collision frequency, which is considered to be constant. Its value is usually less than 1.

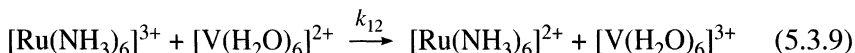
Let us consider two reactions having rate constants k_{aa} (where $a = 1$ or 2):



and



A possible reaction is, *e.g.*, the so-called cross-reaction:



The equilibrium constant for (5.3.9), obtained from electromotive force measurements is K_{12} . The values of k_{11} and k_{22} are determined as 4×10^3 and $1.2 \times 10^{-2} \text{ mol dm}^{-3} \text{ s}^{-1}$, respectively, and $K_{12} = 1.07 \times 10^6$. It follows from these data⁴⁰ that the calculated value of k_{12} is $7.2 \times 10^3 \text{ mol dm}^{-3} \text{ s}^{-1}$. The experimental value is $4.2 \times 10^3 \text{ mol dm}^{-3} \text{ s}^{-1}$, which is considered a good agreement, since rate constant variations can span 9 orders of magnitude.

A detailed description of the Marcus theory and the derivation of eq. (5.3.6) can be found in refs. 39 and 41, and in original Marcus' publications (see refs. 27–38).

The usefulness of equations (5.3.5) and (5.3.6) is great. Determination of the rate constant k_{12} is important because the calculated value can be compared with the experimental one, and if these values differ significantly, the outer-sphere electron-transfer mechanism is very probably not involved. What is most important is that the theory enables calculation of rate constants of a large number of various interactions in solutions if the kinetic parameters of involved reactants are known. A list of about 30 such parameters enables prediction of the rate constants of about 450 various reactions.^{42,43}

The theory has been successfully applied to electron-transfer reactions in biological systems, which is discussed in the next section.

5.3.2. Long-range electron transfers in biological systems

Experiments have confirmed that electron-transfer reactions can occur at rather high rates even when the reactants are separated much beyond “collisional” distances, often over 1 nm (10 Å). Long-range electron-transfer reactions are often encountered in biological systems.

According to Marcus’ theory, the rates of long-range electron transfers are primarily determined by the relative relation of the reaction standard Gibbs energy, $\Delta_r G^\circ$, and the reorganization energy, λ . A maximum rate is obtained when $\Delta_r G^\circ$ equals the “reorganization energy”. Indeed, many biological reactions approach these conditions.

Further increase in $\Delta_r G^\circ$ causes a rate decrease. The inverted effect is now established with certainty. It corresponds to the region in which $\Delta_r G^\circ > \lambda$. These ideas were strongly supported by P. L. Dutton,⁴⁴ professor at the University of Pennsylvania, Philadelphia. Dutton studied electron-transfer reactions in bacterial photosynthetic centers. The first step in bacterial photosynthesis is a light excitation in bacteriochlorophyll. The excited electron is first transferred to bacteriopheophytin and then to a quinone, and again to another quinone. Electron transfer to the first quinone occurred at a distance of about 1 nm. Dutton and coworkers systematically changed quinones as electron acceptors and thereby also reaction distances. Additional distances were 0.46 and 2.34 nm. A variation of 2 nm (20 Å) in the distance between electron donors and acceptors in protein changed the electron-transfer rate by a factor of 10^{12} . A linear distance dependence of the maximum electron trans-

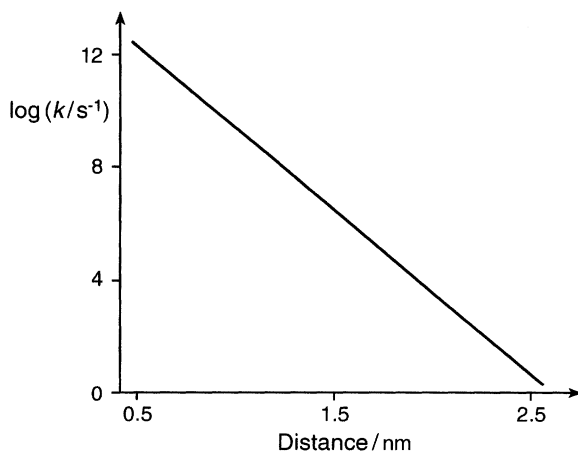


Figure 5.3.2. Dependence of the maximum electron transfer rate ($\Delta_r G^\circ = \lambda$) on the distance between the atom donor center to the atom acceptor center for 18 different biological systems (schematic), adapted from ref. 44.

fer rate ($\Delta_r G^\circ = \lambda$), expressed as $\log k$ vs. reaction distance, was observed. Dutton and coworkers used 18 different systems to determine the line on this plot. Figure 5.3.2.⁴⁴ depicts these results schematically.

The authors concluded that proteins constitute a uniform electron barrier to electron tunneling. They further found that the selection of the distance, the free energy and reorganization energy are sufficient parameters to define the rate and directional specificity of a biological electron transfer, which is in accordance with the Marcus theory.

About 40 years ago it was taken that the electron transfer between a cytochrome *c* and a light activated bacteriochlorophyll in the bacterium *Chromatium vinosum* occurred even at 80 K. A few years later it was reported that the electron transfer was temperature-independent from 120 K down to 4 K, suggesting that the electron transfer proceeds through a quantum mechanical tunneling mechanism (see section 1.15), probably taking place over a distance as large as 30 Å.⁴⁴

A different viewpoint was put forward by R. M. Baum.⁴⁵ Along with a group of chemists, he questioned the possibility of redox centers, separated by such long distances as 25 Å, or even more, and consequently weakly bonded, being capable of an effective transfer of electrons. They claim that there are proteins that specifically promote electron transfer. The fact that the rate of electron transfer in proteins rapidly decreases with the redox center distance strongly suggests the involvement of tunneling. J. N. Betts *et al.*, of the California Institute of Technology, and J. N. Onuchic *et al.*, of the California University at San Diego,⁴⁶ developed a model system for computation of electron transfer by tunneling. Their results indicate that the long-distance electron transfer is controlled by protein structure. The covalent σ bonds and hydrogen bonds mainly serve as a bridge for electron transfer. Here and there, an electron may jump through empty space.^{47–49} The electron jump through typical free space is equivalent to about 10 covalent bonds. Not so long ago, J. Kraut, professor at the University of California in San Diego, with his coworker H. Pelletier prepared a 1:1 complex between cytochrome *c* and cytochrome *c* peroxidase. Both cytochromes are natural partners in electron transfer. They established that the combination of these two cytochromes is a much better way of electron transfer than the way through two proteins. Their work is considered very important. H. B. Gray, professor at the California Institute of Technology in Pasadena, and his coworkers also maintain that proteins, as mediators in electron transfer, exhibit special properties.⁴⁸ Electron transfer takes place between prosthetic groups linked by proteins (the distances are often larger than 1 nm). Though the electron donor and electron acceptor are loosely bonded, the electron transfer is very fast and markedly specific for a particular system.⁴⁸ The simplest models describing the long-range elec-

tron transfer treat the medium between the electron donor and electron acceptor as a one-dimensional square tunnel barrier. Consequently, the electron-transfer rate constant should exponentially decrease with increasing distance.^{45,50,51} It is generally observed that tunneling is more efficient over bonding orbitals than through free space, where the potential energy barrier is higher. One should bear in mind that the electron path from the electron donor to electron acceptor over proteins is much longer than the direct way through free space. Some authors think that the resistance to electron transfers *via* a hydrogen bond is twice the resistance *via* a covalent bond.⁴⁶ This view has found substantial support.⁵²

Cytochromes are hemoproteins that enable electron transfer in the respiratory chain and in many complex biological processes. There are more than 50 known cytochromes with different structures and physical properties. Cytochromes contain prosthetic groups similar to heme. Prosthetic groups, also called coenzymes, are compounds required by an enzyme to catalyze a particular reaction. Cytochromes assist electron transfer in the membranes of cell mitochondria and chloroplasts. Each cytochrome is associated with a protein structure called apoenzyme, with apoenzyme protein bound to the prosthetic group. The *a*-type cytochromes show very high redox potentials. They are important in the reduction of oxygen to water in the cytochrome *c* oxidase. Cytochromes *b* have the protoporphyrin IX structure; their proteins are not covalently bonded to the porphyrin. Cytochromes *a* contain hemes with a formyl group as a substituent of the ring. Cytochromes *b* and *c* have the same prosthetic groups, but the cytochrome *c* protoporphyrin IX vinyl groups are condensed with cysteinyl SH groups. Cytochrome *c* is soluble in water and assists in the electron transfer between cytochrome reductase and cytochrome oxidase. The nomenclature *a*, *b*, and *c* stems from the early recognized spectral differences that enabled their identification (see, e.g., W. Kaim and B. Schwederski, *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*, John Wiley and Sons, Inc., New York, 1996, pp. 107–118).

The mentioned results of Pelletier and H. Kraut⁴⁷ support the claim of H. B. Gray that the proteins taking part in electron transfer between the electron donor and electron acceptor cannot be looked upon, at least not in all cases, as a bridge of identical repeating units.

It appears that many proteins behave specifically, analogously to cytochrome *c*. Calculations on models indicate that the cytochrome *c* structure is a very effective way of electron transfer.^{45,47}

Figure 5.3.3, (a) and (b), schematically depicts the cytochrome *c* structure. The central iron atom is bonded to four pyrrole nitrogens. Like in hemoglobin, the prosthetic group resides in a protein pocket, where the fifth coordination position is occupied by an imidazole nitrogen of a histidyl side chain, while the sixth axial position is occupied by the sulfur atom of the

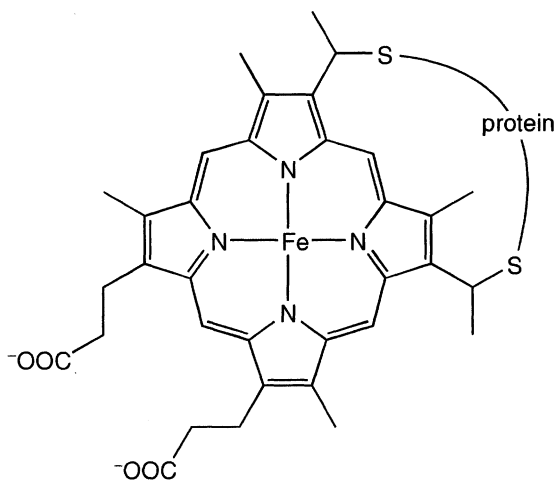


Figure 5.3.3. Schematic structure of cytochrome *c* (adapted from refs. 23 and 53).

methionyl side chain, like in hemoglobin and myoglobin.⁵³ The central iron atom is a $\text{Fe}^{2+}/\text{Fe}^{3+}$ redox system, enabling the electron transfer.

The important chemical role of cytochrome is the oxidative phosphorylation of ADP (adenosine diphosphate) to ATP (adenosine triphosphate). This is a process in which the ATP is formed when electrons are transferred from NADH (the reduced form of nicotinamide adenine dinucleotide (NAD^+) when this compound accepts ($\text{H}^+ + 2\text{e}^-$), which is equivalent to the acceptance of the H^- ion). NADH is a very strong reducing agent ($E^\circ = -0.32 \text{ V}$). Many reactions occurring in living systems are not spontaneous, *i.e.*, these reactions have $\Delta_r G^\circ > 0$. (We know that reactions which proceed spontaneously in a thermodynamic sense must have $\Delta_r G^\circ < 0$). In biological systems, the reactions that have $\Delta_r G > 0$ are called endergonic, and reactions where $\Delta_r G < 0$ are called exergonic (in Greek *ergon* = work; *endon* = inside). In biological systems, endergonic reactions can be coupled to reactions that are strongly exergonic for the mentioned thermodynamic reason. Adenosine triphosphate (ATP) is an example to the point. *E.g.*, the hydrolyses of ATP to ADP and ATP to AMP (adenosine monophosphate) are strongly exergonic reactions. In fact, these reactions are very complicated because they do not occur only at a phosphorus center but a certain enzyme also requires a metal ion for its catalytic function.⁵³

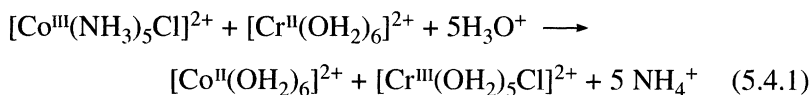
In conclusion, it can be said that the electron transfer through proteins is a partly solved problem, which remains in the center of interest of the most prominent world laboratories of coordination chemistry, and of international conferences on coordination chemistry.

5.4. INNER-SPHERE ELECTRON TRANSFER

In the outer-sphere mechanism, the oxidant and the reductant have very little communication. The stable polynuclear complexes, in which a firm ligand bridge is present at the moment of electron transfer, are well known and described.⁵⁵

A clear demonstration of such a mechanism was given by Henry Taube^{1,2,57-59} (see also Chapter 2, section 2.3). Taube showed that, in an intermediate reaction stage, a chemical bond must form between one of the ions and a ligand that is still bonded to the other ion. This ligand acts as a temporary bridge between the two ions, and its bond to the original ion can later break in such a way as to indirectly effect the electron transfer that completes the reaction.

Stable polynuclear complexes linked by a ligand bridge are now well known and described.⁵⁵ If such a complex contains two equal metal atoms in different oxidation states, then these complexes are most often intensively colored, suggesting electron exchange between these two metal atoms. It is, therefore, no wonder that the oxidant and the reductant build a bridge over a common ligand, through which the electron transfer takes place. The first thoroughly investigated reaction of this type was the reaction:



It is characteristic of this reaction that the cobalt(III) complex is inert while the chromium(II) complex is labile.

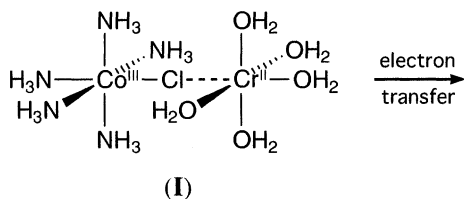


Reaction (5.4.1) is fast ($k_{25^\circ\text{C}} = 6 \times 10^5 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$). Instead of chloride, some other ligands can be analogously transferred, *e.g.*, F^- , Br^- , I^- , SO_4^{2-} , N_3^- , NCS^- , PO_4^{3-} , OH^- , *etc.*, but also carboxylates (RCO_2^-).

The rate of reaction (5.4.1) is proportional to the concentrations of both complexes, *i.e.*,

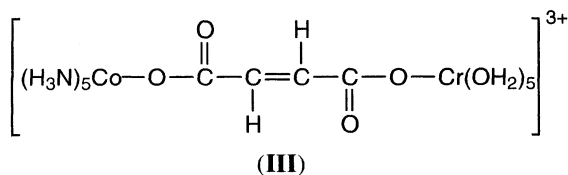
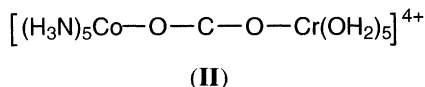
$$\text{Rate} = k[\text{Co}^{\text{III}}(\text{NH}_3)_5\text{Cl}^{2+}][\text{Cr}^{\text{II}}(\text{OH}_2)_6^{2+}] \quad (5.4.3)$$

It seems very likely^{1,2,57-59} that the activated complex in the reaction (5.4.1) has structure **I** in which cobalt and chromium are bridged by chlorine:



In reaction (5.4.1), the electron is transferred from the chromium atom to cobalt while chloride is, so to say, transferred to chromium. However, this would not be reasonable to claim since the transfer of the atomic nuclei is relatively slow, compared to the very fast electron transfer. Taube^{1,2} pointed to the importance of the fact that the reaction product is $[\text{Cr}^{\text{III}}(\text{OH}_2)_5\text{Cl}]^{2+}$ and not $[\text{Cr}^{\text{III}}(\text{OH}_2)_6]^{3+}$. Namely, as soon as the chromium(II) is oxidized, it becomes inert and the changes in its coordination sphere are slow. Taube concluded that the chlorine-chromium bond must be formed at the moment or prior to the moment of chromium oxidation. He also concluded that all chlorine in the $[\text{Cr}^{\text{III}}(\text{OH}_2)_5\text{Cl}]^{2+}$ product must be that from the $[\text{Co}^{\text{III}}(\text{NH}_3)_5\text{Cl}]^{2+}$, because when the reaction (5.4.1) was carried out in solution containing radioactive $^*\text{Cl}^-$, no $^*\text{Cl}^-$ was found in the $[\text{Cr}^{\text{III}}(\text{OH}_2)_5\text{Cl}]^{2+}$ product. In this way, it was established that the chlorine atom was transferred from cobalt to chromium, because chlorine was the bridging ligand in the electron transfer.⁵⁶ Taube's experiments explained why the reaction between $[\text{Co}^{\text{III}}(\text{NH}_3)_6]^{3+}$ and $[\text{Cr}^{\text{II}}(\text{OH}_2)_6]^{2+}$ is 10^{10} times slower than reaction (5.4.1). Namely, unlike all the other mentioned ligands, including carboxylates, the NH_3 ligand has no available electrons to form a bridge towards chromium.

The carboxylato bridge is of special interest because the electron transfer takes place over oxygen and carbon atoms (as in **II**), and also over a long conjugated system (as in **III**) if the bridge is fumarate.



It is interesting to note that the reaction rate with fumarate is higher than that with acetate. This is explained by assuming that Cr^{2+} attacks carboxylate at the end most distant from Co^{3+} , whereby the repulsions of the nuclei get

reduced, while the electron passes through the conjugated system of the activated complex.

Water can also have the role of a bridge between cobalt and chromium. It is most probable, however, that the OH^- is the bridging ligand, since the reaction rate decreases with increasing hydrogen ion concentration. Besides, there is a substantial energy difference between the two oxygen electron pairs in the water molecule. One is practically 2s, and the other 2p; 2s will not be accessible for such bridging.

Reaction $[\text{Co}^{\text{III}}(\text{NH}_3)_5\text{L}]^{2+} + [\text{Cr}^{\text{II}}(\text{OH}_2)_6]^{2+}$ has been studied also for various ligands (L), which were differently substituted carboxylates. The results are shown in Table 5.4.1. It can be seen that the rate constants vary only little, though the enthalpies of activation ($\Delta^\ddagger H^\circ$) differ by as much as 30 kJ mol^{-1} (recall that 5.86 kJ mol^{-1} corresponds to a reaction rate change by a factor of 10, see expression (1.3.12)).

Table 5.4.1. Activation parameters for reaction $[\text{Co}^{\text{III}}(\text{NH}_3)_5\text{L}]^{2+} + [\text{Cr}^{\text{II}}(\text{OH}_2)_6]^{2+}$ for some carboxylato ligands (L) at 25°C (adapted from ref. 60)

L	$k / \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$	$\Delta^\ddagger H / \text{kJ mol}^{-1}$	$\Delta^\ddagger S / \text{J mol}^{-1}$
Acetato	0.18	14.64	-209
Chloroacetato	0.10	33.05	-155
Cyanoacetato	0.11	16.74	-205
Benzoato	0.14	20.50	-192
<i>p</i> -Chlorobenzoato	0.21	41.84	-117
<i>p</i> -Hydroxybenzoato	0.13	40.17	-126
<i>p</i> -Cyanobenzoato	0.18	31.38	-155

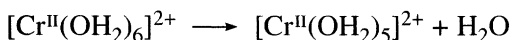
Using Table 5.4.1, we can calculate the Gibbs energy changes ($\Delta^\ddagger G^\circ$), *e.g.*, for the first and the fifth reaction, whose enthalpies of activation differ appreciably:

$$\text{acetato ligand:} \quad \Delta^\ddagger G^\circ = \Delta^\ddagger H^\circ - T\Delta^\ddagger S^\circ = 76.92 \text{ kJ mol}^{-1}$$

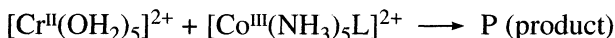
$$p\text{-chlorobenzoato:} \quad \Delta^\ddagger G^\circ = \Delta^\ddagger H^\circ - T\Delta^\ddagger S^\circ = 76.71 \text{ kJ mol}^{-1}$$

We see that both ligands give almost equal Gibbs energies of activation. Since the Gibbs energy of activation determines the rate constant (eq. 1.4.14), the rates with both ligands are practically equal (0.18 and 0.21), as shown in Table 5.4.1.

A question might arise how the Gibbs energies can be so small, because if the reaction rate were determined by the dissociation:



and further by reaction:



the energy of activation (E_a) would be equal to the sum of energies of activation of both processes. It is estimated that the first process alone requires an energy of activation of at least 42 kJ mol^{-1} , and hence the above mechanism should be rejected.

It is important to bear in mind that bridge formation is a bimolecular process and both complexes participate in the transition state, thus lowering the energy of activation. If a bridge forming ligand is a good electron donor, its electron donation will assist the bridge formation to chromium, but it will at the same time hamper the ligand separation from cobalt. This is why the $\Delta^\ddagger G^\circ$, and hence the specific rates of reaction (5.4.1), are similar for various ligands, as already shown in Table 5.4.1. (variations in $\Delta^\ddagger H^\circ$ are compensated by variations in $\Delta^\ddagger S^\circ$).

It is known that electron transfer is the slowest process in a composite reaction (5.4.1), which is most often the case in reactions of this type. If the bridge is changed, the rate increases in the order: $\text{NCS}^- < \text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^-$. Table 5.4.2 illustrates these changes.

Table 5.4.2. Inner sphere electron transfer rates of reaction $[\text{Co}^{\text{III}}(\text{NH}_3)_5\text{L}]^{2+} + [\text{Cr}^{\text{II}}(\text{H}_2\text{O})_6]^{2+}$ over various bridging ligands in aqueous solution at 25°C (adapted from ref. 61)

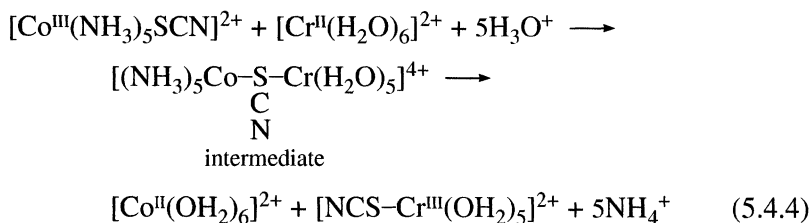
L	$k / \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$
NCS^-	19 ^(a)
SCN^-	1.9×10^5
F^-	2.5×10^5
N_3^-	3.0×10^5
Cl^-	6.0×10^5
Br^-	1.4×10^6
I^-	3.4×10^6

^(a) Remote attack.

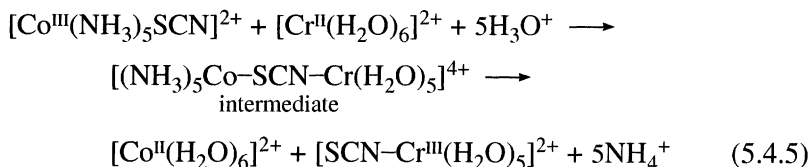
The sequence $\text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^-$ can be considered normal, because this is the polarizability order, *i.e.*, the order of “soft approach” to a metal ion, in the above case to the chromium(II) (see section 2.7). This sequence is also the electronegativity decrease sequence, but it is not always obeyed, since it

depends on the nature of the reductant metal and its polarizability. Thus, the rates of bridging halides for the Fe^{2+} -reductant are $\text{Br}^- < \text{Cl}^- < \text{F}^- < \text{NCS}^- < \text{SCN}^-$. The SCN^- and NCS^- bridges are especially interesting because the rate difference is large, as seen from Table 5.4.2. Thiocyanate is an ambidentate ligand and can use either S or N as donor atoms.⁶² Distinction can be achieved by ^{14}N NQR (nuclear quadrupole resonance) or by MAS ("magic-angle spinning") ^{13}C NMR spectra.⁶³ The way of bonding depends on the nature of the metal, on steric factors and on the nature of other ligands. Heavier metals are usually bonded over sulfur, and in such cases the $\text{M}-\text{SCN}$ bond is often bent.⁶⁴ Reaction schemes (5.4.4) and (5.4.5) show these two possibilities of bonding. If both metals are bonded over sulfur, we talk of an adjacent (neighboring) attack. In this attack sulfur atom is the sole bridge between the two metals. If, on the other hand, the other metal is bonded to nitrogen, then we talk of a remote attack.

Adjacent attack:



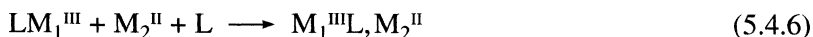
Remote attack:



It can be concluded that the bridge forming ligand acts as a Lewis base towards both metal centers and must, therefore, have two electron pairs to be able to donate one electron pair to each metal center.

In principle, the following reaction steps should be considered:

(a) association of two complexes:



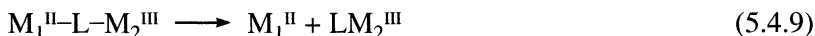
(b) bridge formation:



(c) electron transfer:



(d) dissociation:



Any of these steps can be the rate-determining one. Figure 5.4.1 depicts a possible activation profile, most frequently encountered, in which the electron transfer is the rate-determining step.

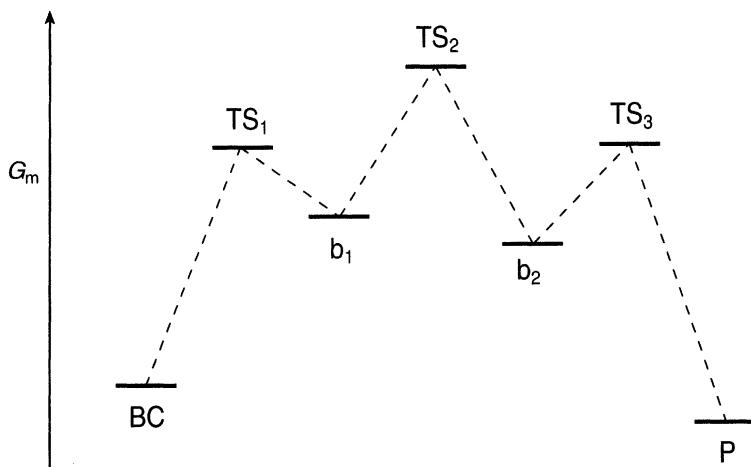


Figure 5.4.1. Possible activation profiles of an inner-sphere electron transfer, most frequently encountered, in which the electron transfer is the rate-determining step; BC = basic complex; b_1 = bridging complex 1 before electron transfer; b_2 = bridging complex 2 after electron transfer; P = products; TS are transition states; G_m = molar Gibbs energy (see eq. 5.4.8).

A highly illuminating article on the bridged inner-sphere electron transfer mechanism is that of A. Haim.⁶⁵ The ability of a ligand to take part in such a mechanism is associated with the symmetry requirements of the metals and the ligand involved. If the symmetries of the metal ions, electron donor and electron acceptor, and of the bridging ligand are adequate, then such a ligand constitutes a bridge of relatively low energy for electron passage.⁶⁶ Thus, if the electron donor metal gives an e_g electron into the e_g ($d_{x^2-y^2}$ or d_{z^2}) orbital of an electron acceptor metal, then, *e.g.*, the bridging chloride ligand (σ donor), will be a better bridging ligand than, *e.g.*, azide (see Fig. 2.8.2). On the other hand, an electron transfer involving a metal t_{2g} orbital will be advantageous if azide were the bridging ligand, because in this case the t_{2g} metal orbital will

overlap with the π -system of the azide (see Fig. 2.8.3). This explanation is supported by experimental results.

5.5. REACTIONS WITH SOLVATED ELECTRONS

Hydrated electrons are very strong reducing agents, with a redox potential of about 2.7 V. These chemical species are very short-lived with half-lives ($t_{1/2}$) of 10^{-3} s, and can be obtained by the pulse radiolysis, a highly specialized technique requiring special equipment, including an electron accelerator.

Solvated electrons can be obtained in concentrations up to 10^{-4} mol dm $^{-3}$. Reactions with solvated electrons are very fast second-order reactions, with rate constants between 10^8 to 5×10^{10} mol $^{-1}$ dm 3 s $^{-1}$, which means that their rates are close to the diffusion control. A reaction is diffusion-controlled when the reaction rate is dependent upon the rate at which reactants diffuse toward one another. A diffusion-controlled reaction must have a small activation energy, because if E_a is high ($E_a/RT \gg 1$), then the reaction rate is controlled by the number of molecules with energy higher than the activation energy, not by the diffusion rate. Reactions with high E_a are activation-controlled.

One should have in mind that in previous discussions of the transition-state theory high energies of activation were assumed, which justified the assumption of the *quasiequilibrium* between reactants and the activated complex. Analogously, in discussing the collision theory, the assumption was that the reactive collisions are relatively rare, a situation corresponding to high activation energy.

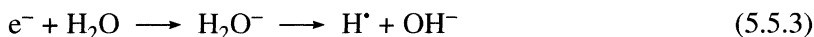
Pulse radiolysis has been used with great success in studies of the hydrated electron $e^-(aq)$. If the pulse of electrons from a linear accelerator (5–15 MeV) is passed through an aqueous solution, several chemical species are produced. The spectral changes in solution can be followed spectrophotometrically, either at a definite time after the electron pulse with a spectroscopic flash and a spectrograph, or continuously at a fixed wavelength with a steady light source and a photomultiplier. Instead of the electron beam of an accelerator, X-rays* pulse can be applied for one or two microseconds.⁶⁷

It is of the utmost importance to remove even traces of solution impurities, since they can interfere with the reaction. The hydrated electrons (aqueous electrons) produced upon irradiation disappear with time, but the rate of this disappearance slows down after successive pulses, suggesting that the

* WILHELM CONRAD RÖNTGEN, 1845–1923, German physicist, is recipient of the first Nobel Prize for physics in 1901 for the discovery of X-rays, which heralded the age of modern physics and revolutionized medical diagnostics.

hydrated electrons react with the impurities. The solutions are pulsed until a reproducible rate of hydrated electron decay is reached. This usually requires about 20 irradiations. Literature should be consulted for further information on the technical procedures in pulse radiolysis and laser photolysis.^{68,69}

A very great number of publications are devoted to radiolyses, mostly in aqueous solutions. Until 1987, 4600 papers were published, mainly addressing $e^-(aq)$, and $OH^\bullet$ and $H^\bullet$ radicals. The following reactions are described:



Electrons that are produced by absorption of ionizing radiation are quickly thermalized (their kinetic energy approaches the value $k_B T$) and then get solvated, because the dipoles of surrounding molecules become oriented due to the negative electron charge. The so-called trapped electron can be relatively long-lived.

Hydrated electron was discovered independently by Hart and Boag and by Schulte-Frohlinde and Eiben.⁷⁰ Its maximum absorption is at 720 nm.^{71,72}

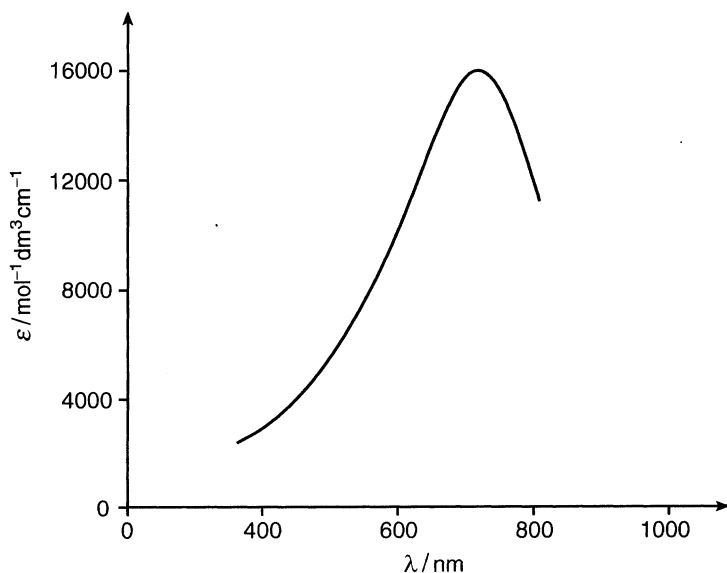
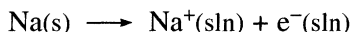


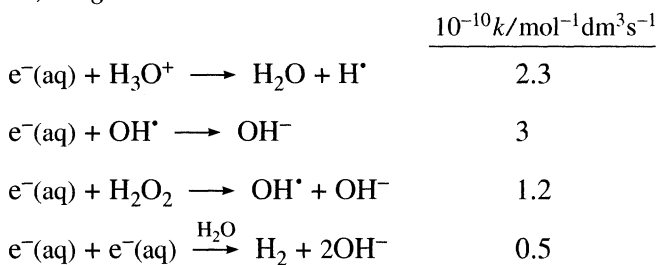
Figure 5.5.1. Absorption spectrum of the hydrated $e^-(aq)$; $\epsilon_{\max} = 1.58 \times 10^4 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$; $\lambda_{\max} = 720 \text{ nm}$ (refs. 72 and 73).

If an alkali metal is dissolved in liquid ammonia, the solution acquires a dark-blue color from solvated electrons:



The obtained spectrum is similar to that in Figure 5.5.1.

In water radiolysis, H_3O^+ , $\text{OH}^\bullet$, $\text{e}^-(\text{aq})$, and H_2O_2 are dominant chemical species. Reactions of $\text{e}^-(\text{aq})$ with H_3O^+ , $\text{OH}^\bullet$, and H_2O_2 have very high rate constants,⁶⁸ *e.g.*:



The production of $\text{e}^-(\text{aq})$ is usually performed in the presence of methanol or some other $\text{OH}^\bullet$ scavenger (*e.g.*, N_2O) in order to prevent elimination of $\text{e}^-(\text{aq})$ by the $\text{OH}^\bullet$ radical: ($\text{OH}^\bullet + \text{e}^-(\text{aq}) \longrightarrow \text{OH}^-$). Table 5.5.1 presents the reduction rate data of some metal complexes with $\text{e}^-(\text{aq})$.

Table 5.5.1. Second order rate constants for reductions of some metal complexes with the hydrated electron, $\text{e}^-(\text{aq})$ (data compiled from refs. 75 and 76)

Complex	$10^{-9}k/\text{dm}^3\text{mol}^{-1}\text{s}^{-1}$ (20–25 °C)
$[\text{Co}^{\text{III}}(\text{NH}_3)_6]^{3+}$	90
$[\text{Co}^{\text{III}}(\text{en})_3]^{3+}$	73
$[\text{Cr}^{\text{III}}(\text{H}_2\text{O})_6]^{3+}$	60
$[\text{Co}^{\text{III}}(\text{NO}_2)_6]^{3-}$	58
$[\text{Cr}^{\text{III}}(\text{edta})]^-$	29
$[\text{Co}^{\text{III}}(\text{CN})_5\text{Cl}]^{3-}$	18
$[\text{Cr}^{\text{III}}(\text{CN})_6]^{3-}$	15
$[\text{Co}^{\text{III}}(\text{CN})_5(\text{NO}_2)]^{3-}$	8
$[\text{Co}^{\text{III}}(\text{CN})_6]^{3-}$	2.7
$[\text{Al}^{\text{III}}(\text{H}_2\text{O})_6]^{3+}$	2
$[\text{Co}^{\text{II}}(\text{edta})]^{2-}$	0.51

Hexadentate edta^{4-} ligand, mentioned in Table 5.5.1, bonds to a metal as shown in Figure 5.5.2.

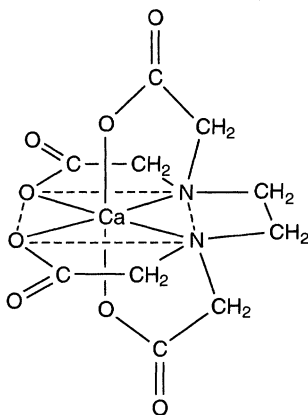
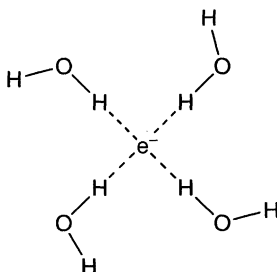


Figure 5.5.2. Structure of $[\text{Ca}(\text{edta})]^{2-}$.

It is taken that $e^-(\text{aq})$ undergoes further hydration within 10^{-11} s, and is likely to be surrounded by four water molecules,⁷⁷ its formula being H_8O_4^- :



It may be concluded that $e^-(\text{aq})$ is an important reductive species. Comparison of the reaction rates of the solvated electron and solvated proton points to the conclusion that the solvated proton reacts faster, since its diffusion coefficient is almost twice as large as that of the solvated electron (the values being 9.29×10^{-9} and $4.9 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, respectively).

The rate constants of the reactions of metal complexes and $e^-(\text{aq})$ do not correlate with the redox potential of the metal ion, and neither with the affinity of the free ion for the electron. It is therefore inferred that the reaction of $e^-(\text{aq})$ with a metal complex does not involve a direct metal-ligand bond. It appears that the electron can quickly tunnel out of the solvent cage into an empty, in energy terms, most suitable d orbital. In such a case, the reduction rates with $e^-(\text{aq})$ approach diffusion control. It was assumed in earlier works that all these rates are diffusion-controlled since the corresponding energies of activation amounted to only 14.6 kJ mol^{-1} ($\approx 3.5 \text{ kcal mol}^{-1}$), but subsequent more precise measurements have shown that the reactions with $e^-(\text{aq})$ are still too slow to be diffusion-controlled.⁷⁹

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Chapter 6

REACTIONS OF FREE RADICALS

When a substance is heated, the kinetic energy of atoms and molecules increases. *E.g.*, if methane is heated, the kinetic energy of translation, vibration and rotation of methane molecules increases, as discussed in section 1.2. As heat is applied, higher vibrational states are increasingly populated. In higher vibrational quantum states, the average C–H bond distance increases until finally the C–H bond breaks. The result is the formation of a methyl radical and a hydrogen atom.



The enthalpy of this reaction ($\Delta_r H^\circ$, 25 °C) amounts to about 435 kJ mol⁻¹.

The energy of 435 kJ mol⁻¹ is rather high and reveals that the C–H bond in methane is quite strong. A temperature of about 1000 °C is needed to achieve a significant rate. The enthalpy of the C–H bond in ethane is somewhat less and amounts to 418.4 kJ mol⁻¹; for the C–C bond breakage, $\Delta_r H^\circ$ amounts to only 368 kJ mol⁻¹. Thus, when ethane is heated, the C–C bond rupture is somewhat faster and the reaction is usually carried out at 700 °C.

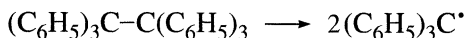


It can be generally taken that in pyrolysis the bond rupture takes place on the weakest bond. Free radicals thus formed contain an odd number of electrons. At room temperature, alkyl radicals can exist only in small concentrations; nevertheless, they have been identified by different spectroscopic methods.

Free radicals are very important primarily in organic reactions, but also in inorganic reactions.

6.1. CHAIN REACTIONS

In 1900, Moses Gomberg discovered that hexaphenylethane in solution dissociates into two triphenylmethyl radicals:



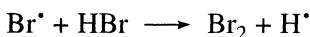
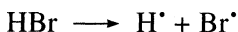
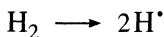
In 1907, Bodenstein* and Lind¹ studied the kinetics of the gas reaction $\text{H}_2 + \text{Br}_2 \longrightarrow 2\text{HBr}$ in the temperature interval from 200 to 300 °C. They experimentally established the kinetic law and formulated it as follows:

$$\frac{d[\text{HBr}]}{dt} = \frac{k[\text{H}_2][\text{Br}_2]^{1/2}}{1 + k' \frac{[\text{HBr}]}{[\text{Br}_2]}} \quad (6.1.1)$$

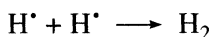
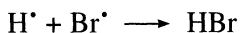
Thirteen years later, equation (6.1.1) was explained by Cristiansen, Herzfeld and Polanyi.²⁻⁴ They assumed the following mechanism:



and showed that this mechanism leads to the kinetic law (6.1.1). They ignored the possible reactions:



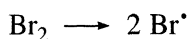
* ERNEST AUGUST MAX BODENSTEIN, 1871–1942, was professor of chemistry in Leipzig, Hannover, and Berlin. He is a great name of the German and world chemical kinetics, especially in the field of gas reactions, where he discovered several basic kinetic laws.



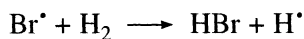
because these reactions are relatively slow due to high energy requirements or low concentrations of the reactants involved.

Reactions (6.1.2) to (6.1.6) exhibit a chain mechanism in which 4 reaction steps are important:

(a) Initiation step (6.1.2):



(b) Propagation step (6.1.3):



Br atoms are reactive intermediates, the so-called chain carriers, because Br reacts with the H_2 molecule yielding the reaction product, HBr, but atom H, a second chain carrier, is also produced (reaction 6.1.3). Atom H reacts with Br_2 (6.1.4) yielding an additional product molecule (HBr), but the initial $\text{Br}^\bullet$ chain carrier is also produced, reacting again with the H_2 molecule, and the chain reaction continues.

(c) Inhibition step

Since the concentration of HBr is reduced in the reaction



this step is taken to be the inhibition step. But the chain reaction is continued, since $\text{Br}^\bullet$ radicals are also produced.

(d) Termination step

Termination occurs whenever two radicals collide:

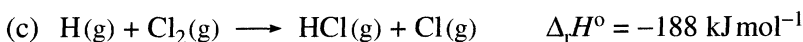
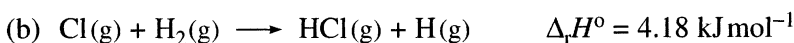


In practice, the chain process involves about 10 000 cycles before it is terminated.

The gas reaction $\text{H}_2(\text{g}) + \text{Cl}_2(\text{g})$ follows a similar mechanism. The gases do not react in the dark, but a very strong chain reaction takes place under the influence of light. The first step is the dissociation of a chlorine molecule into atoms, which is the slowest and therefore the rate-determining step:

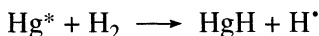


The first step is followed by the two-step chain reaction:

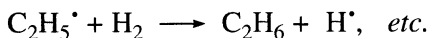
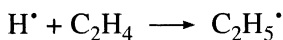


Repeating of steps (b) and (c) accounts for the formation of hydrogen chloride and the net evolution of energy ($\Delta_r H^\circ = -184 \text{ kJ mol}^{-1}$). It can be calculated that light of a wavelength of 490 nm is capable of supplying this energy.

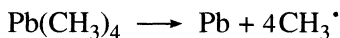
The work of H. S. Taylor⁵ is often quoted as the first observation that simple radicals can be chain carriers. Taylor exposed a mixture of hydrogen and mercury vapor to ultraviolet light ($\lambda = 253.7 \text{ nm}$), which initiated the reaction:



Then, he added ethene (ethylene) to the reaction mixture. A fast reaction took place, which yielded ethane, butane and higher polymeric hydrocarbons. Taylor believed that hydrogen reacted with ethylene producing the C_2H_5^* free radical, which initiated the chain reaction:

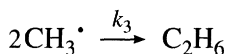
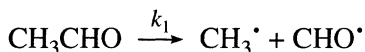


Among the early works on free radicals, the importance of experiments of F. Paneth and W. Hafeditz⁶ is often quoted. They supplied evidence that aliphatic free radicals occur in the decomposition of metallic alkyls, such as dimethylmercury ($\text{Hg}(\text{CH}_3)_2$), and tetramethyl- or tetraethyllead ($\text{Pb}(\text{CH}_3)_4$ or $\text{Pb}(\text{C}_2\text{H}_5)_4$). Paneth saturated⁶ a stream of nitrogen with $\text{Pb}(\text{CH}_3)_4$ vapor. The vapors were then heated to 450°C . Decomposition of $\text{Pb}(\text{CH}_3)_4$ deposited a lead mirror on the heated part of the tube. When the vapors from the decomposition passed over the deposited lead mirror at 100°C , the mirror slowly disappeared. It was concluded that the following reaction had taken place:



Tetramethyllead decomposed to lead and methyl radicals. The stream of nitrogen carried methyl radicals for some time before they recombined to stable hydrocarbons. Free radicals removed the lead mirror by reacting with lead to form volatile alkyls of lead (but also of other metals, *e.g.*, zinc and antimony, if they were involved).

In 1934, Rice and Herzfeld⁷ showed that the kinetics of acetaldehyde decomposition ($\text{CH}_3\text{CHO} \longrightarrow \text{CH}_4 + \text{CO}$), which proceeds *via* free radicals, can be kinetically treated by applying the steady state approximation principle. The following reactions should be considered:



The chain carrier is $\text{CH}_3\cdot$, which is regenerated in the second process. The steady-state approximation treatment leads to the following equation:⁸

$$[\text{CH}_3\cdot] = \sqrt{\frac{k_1}{2k_3}} [\text{CH}_3\text{CHO}]^{1/2}$$

It follows that the rate law based on CH_4 formation, involving free radicals, is:

$$\frac{d[\text{CH}_4]}{dt} = k_2[\text{CH}_3\cdot][\text{CH}_3\text{CHO}] = k_2 \sqrt{\frac{k_1}{2k_3}} [\text{CH}_3\text{CHO}]^{3/2}$$

The predicted reaction order of 3/2 was confirmed by experiments.⁸

6.2. STABILITY OF THE METAL-CARBON σ BOND

Monomolecular dissociation of metal-alkyl complexes in which the metal-carbon bond is broken, often assisted by solvent, is considered to be one of the most important reactions of metal complexes:



This reaction can compete with the homolytic dissociation:



or both reactions are entirely independent. The metal-carbon σ bond can largely differ in stability.^{9,10} Thus, tetramethyltitanium in ether disintegrates at -65°C , yielding methane. On the other hand, the metal-carbon σ bond in the $[\text{Pt}(\text{PPh}_3)_2\text{Cl}(\text{CH}_3)]$ complex, as well as in other Pt(II) complexes, is very strong. The cobalt-carbon bond in vitamin B₁₂ is also very strong, which will be discussed in section 7.2.

The metal-carbon bond is also strong in the $[\text{Cr}(\text{CH}_2\text{PhMe}_2)_4]$ and $[\text{Mo}_2(\text{CH}_2\text{SiMe}_3)_6]$ complexes.¹¹⁻¹³

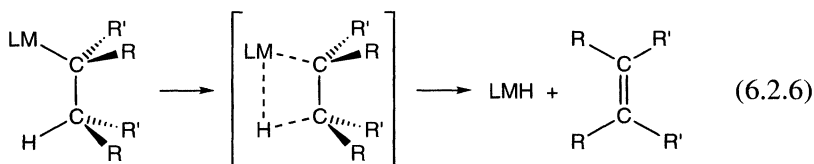
It was first considered that the metal-carbon σ bond is, by its nature, unstable in the thermodynamic sense, and if kinetic stability is present, it is due to the π bonding of large ligands.

However, it has been shown that the metal-carbon σ bond of the transition metal complexes is thermodynamically more stable than that of the main group metals.¹⁴ It was concluded that kinetically unstable complexes with the metal-carbon σ bond can find a reaction path of low energy barriers.

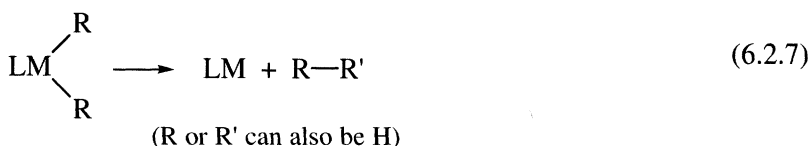
The metal-carbon bond rupture can occur: (a) by a mechanism involving free radicals, or (b) by a mechanism that does not include free radicals.^{15,16} Thus, free radicals are involved in the carbon-mercury bond breakage of the pyrolysis of diphenylmercury in alcoholic solutions, the products being benzene and an aldehyde:



The one step “concerted” mechanism, which does not include free radicals, is encountered in β eliminations of olefins, especially when metals of higher atomic weights are involved:^{17,18}



The following reaction also belongs to this class:



Alkylcopper also disintegrates by a mechanism that does not include free radicals:¹⁹



Free radicals do not participate in disintegration of ethylsilver either.^{20,21}

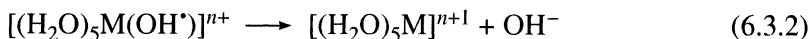
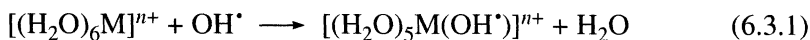


Reactions (6.2.8) and (6.2.9) are typical reductive eliminations. They involve two molecules of an alkylmetal.

6.3. OXIDATION OF TRANSITION METAL COMPLEXES BY HYDROXYL RADICALS

Oxidation of transition metal complexes by hydroxyl radicals can proceed by different mechanisms: (a) by the inner-sphere mechanism in which a ligand of the metal complex is replaced by the hydroxyl radical, the replacement being followed by electron transfer; (b) by the outer-sphere mechanism; (c) by abstraction of the hydrogen atom of $\text{OH}^\bullet$, or in some other way.

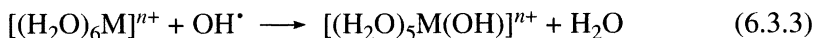
The inner-sphere electron transfer mechanism (a) by the OH radical is represented by expressions (6.3.1) and (6.3.2):



The reaction rate can be determined by either of these two reactions. In many cases, the dissociation of the coordinated water (6.3.1) is the slowest and thus the rate-determining step.

Oxidation of Ti^+ by the hydroxyl radical takes place by the inner-sphere mechanism.²²

Many hexaaquametal ions, *e.g.*, of Fe^{2+} , Mn^{2+} , Cu^{2+} , react with hydroxyl radicals by abstracting a hydrogen atom of the coordinated water, this being the slowest and therefore the rate-determining step:



The abstraction of a hydrogen atom from water by the hydroxyl radical occurs relatively easily ($k \approx 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 25°C), while the “absorption” of a hydrogen atom of a non-coordinated water by $\text{OH}^\bullet$ is a much slower process ($k \approx 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 25°C). Thus, it can be concluded that the O–H bond in coordinated water is much weaker than in non-bonded water. This is to be expected since oxygen electrons in coordinated water are engaged in metal bonding, whereby the electron density at hydrogen atoms is reduced.²³

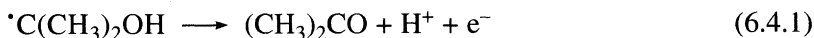
If a complex is substitutionally inert, an outer-sphere electron transfer can take place.²⁴ In the reaction of $[(\text{NH}_3)_5\text{Co}^{\text{III}}\text{py}]^{3+}$ by OH radical, the radical is added to pyridine ligand, forming a ligand-radical, from which the electron transfer to metal takes place.

6.4. REDUCTION OF TRANSITION METAL COMPLEXES BY ORGANIC RADICALS

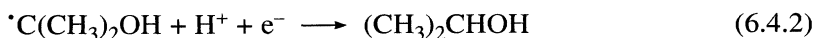
Reductions of transition metal complexes by organic radicals are very frequent. Of special importance is the 1-hydroxy-1-methylethyl radical, $^\bullet\text{C}(\text{CH}_3)_2\text{OH}$. This radical is presumably derived from isopropyl alcohol in which a hydrogen atom is removed from the carbon bearing the OH group. These free radicals were used by many researchers, *e.g.*, at the Ames Laboratory and Department of Chemistry, Iowa State University, Ames, Iowa, and at the Rugjer Bošković Institute, Zagreb, Croatia.^{25a–25f}

The first papers of this type were published in 1982.²⁶ Two review articles by J. H. Espenson are very informative.^{27,28}

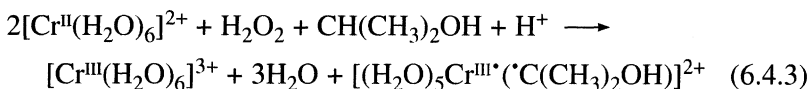
The 1-hydroxy-1-methylethyl radical acts as a reducing agent ($E^\circ \approx -1.2 \text{ V}$), *e.g.*,



but, under certain conditions, it can also act as an oxidant:



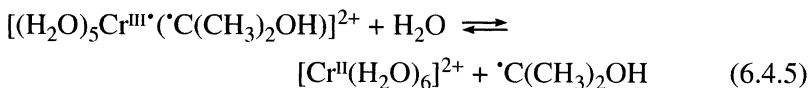
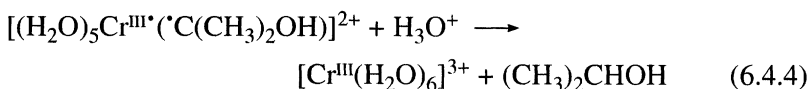
The mentioned authors^{25a–25f} prepared the $^\bullet\text{C}(\text{CH}_3)_2\text{OH}$ radical from the $[(\text{H}_2\text{O})_5\text{Cr}^{\text{III}}\text{C}(\text{CH}_3)_2\text{OH}]^{2+}$ complex, obtained in the reaction of $[\text{Cr}^{\text{II}}(\text{H}_2\text{O})_6]^{2+} + \text{H}_2\text{O}_2$, in an acidic aqueous solution containing 2-propanol:



$$\lambda_{\text{max}}^1 = 311 \text{ nm}; \quad \varepsilon = 2500 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$$

$$\lambda_{\text{max}}^2 = 407 \text{ nm}; \quad \varepsilon = 700 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$$

The decomposition of $[(\text{H}_2\text{O})_5\text{Cr}^{\text{III}}(\cdot\text{C}(\text{CH}_3)_2\text{OH})]^{2+}$ takes place in two parallel reactions, one being acidolysis (6.4.4), and the other homolysis (6.4.5), producing $\cdot\text{C}(\text{CH}_3)_2\text{OH}$:



Homolysis (6.4.5) is a reversible reaction and, in excess of the hexaaquachromium(II) ions, the only reaction that follows is acidolysis. If the substrate considered reacts fast enough with $\text{Cr}(\text{H}_2\text{O})_6^{2+}$ and with the radical, the rate constant becomes the sum of k_{A} (acidolysis) and k_{H} (homolysis).

Besides temperature, changes in the reaction rate are caused by small variations of k_{H} values. The homolysis rate is reduced by introducing electron attracting groups (F, Br, CF_3), and increased by introducing branched alkyl groups. The chosen substrate should not react with the hexaaquachromium(II) ions, or, at least, this reaction should be substantially slower than the reaction with the $\cdot\text{C}(\text{CH}_3)_2\text{OH}$ radical. The kinetic analysis is then based on the quantitative determination of the reaction products.²⁹

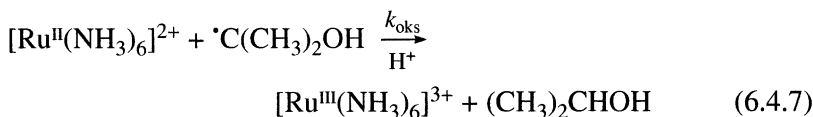
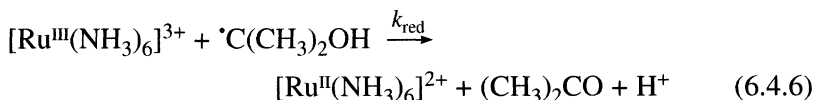
The second method allows the homolysis to proceed in the presence of two substrates, which competitively react with the $\cdot\text{C}(\text{CH}_3)_2\text{OH}$ radical. As seen from eq. (6.4.5), fast elimination of $[\text{Cr}^{\text{II}}(\text{H}_2\text{O})_6]^{2+}$ will foster the homolysis. Supposing that the rate of one competing substrate is known, the other rate can be calculated from the ratio of the reaction products.²⁹

The rates of electron transfer to a series of pentaammine(pyridine)-cobalt(III) complexes, $[\text{Co}^{\text{III}}(\text{NH}_3)_5(\text{NC}_5\text{H}_4\text{X})]^{3+}$ ($\text{X} = 3\text{-CN}, 3\text{-Cl}, \text{H}, 4\text{-CH}_3, 4\text{-C}(\text{CH}_3)_3$, and $4\text{-N}(\text{CH}_3)_2$) were determined using the mentioned competition method. The homolytic scission of the chromium-carbon bond in $[(\text{H}_2\text{O})_5\text{CrC}(\text{CH}_3)_2\text{OH}]^{2+}$ was used to estimate the rate constants for the reducing agent $\cdot\text{C}(\text{CH}_3)_2\text{OH}$, whereas direct measurements were carried out for the reductions by $\text{V}(\text{H}_2\text{O})_6^{2+}$ and $\text{Ru}(\text{NH}_3)_6^{2+}$.^{25f,26} Arguments have been put forward that in each case the reactions proceed by a direct outer-sphere

electron transfer to cobalt(III) and not by an inner-sphere mechanism involving prior electron transfer to the pyridine ring.

It was already mentioned that the 1-hydroxy-1-methylethyl radical can also act as an oxidizing agent (see 6.4.2), though its reducing ability is dominant. Thus, it is difficult to study oxidations with this radical, since the oxidized metal complex would be immediately reduced by the same radical. Nevertheless, the oxidation of Eu^{2+} by $\cdot\text{C}(\text{CH}_3)_2\text{OH}$ was successfully studied at a Eu^{2+} concentration much higher than that of Eu^{3+} .²⁹

On the other hand, this is not so in the reaction of $[\text{Ru}(\text{NH}_3)_6]^{3+}$ with $\cdot\text{C}(\text{CH}_3)_2\text{OH}$, because the reduction rate constant with this radical is much larger than that of oxidation with the same radical.³⁰



$$k_{\text{red}} \gg k_{\text{oks}}$$

Free radicals play an important role in the activity of the vitamin B_{12} coenzyme, which will be discussed in the next section.

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Chapter 7

MECHANISM OF VITAMIN B₁₂ ACTION

7.1. INTRODUCTION

Vitamin B₁₂ was one of the last vitamins to be isolated (in 1948). It is water-soluble, has the highest molecular weight (1355) of all vitamins, and is absorbed by a very complex mechanism.

Deficiency of vitamin B₁₂ [cyanocobalamin (R = CN), or some other important cobalamins, *e.g.*, adenosylcobalamin (R = adenosyl), hydroxocobalamin (R = OH), methylcobalamin (R = CH₃)], see Figures 7.1.1 and 7.1.3, causes a slow-developing disease, called *pernicious anemia*, in which the production of red blood cells is impaired. Absence of hydrochloric acid in gastric secretions (achlorhydria) is also characteristic of this condition. Without medical treatment, the disease will end in death in about 2 to 3 years.

Since vitamin B₁₂ is found only in animal food, pure vegetarians risk its deficiency over the course of several years. The requirement of vitamin B₁₂ is (with vitamin D) the smallest of all vitamins – only two micrograms per day, with liver stores usually enough to last for five years of deprivation. Vitamin B₁₂ participates in DNA synthesis with folic acid. Humans are unable to synthesize folic acid and therefore it is considered a vitamin that must be supplied in the diet. Deficiency of vitamin B₁₂ or folic acid leads to similar anemia symptoms. There is a separate effect of vitamin B₁₂ deficiency on the nervous system.¹

Pernicious anemia is one of many types of anemia, a disease marked by a reduction in red blood cells, or in the oxygen-carrying substance hemoglobin found in these cells. Red blood cells need vitamin B₁₂ to mature properly in the bone marrow. In pernicious anemia, vitamin B₁₂ is unavailable due to lack of the so-called intrinsic factor, a glycoprotein responsible for the intestinal absorption of the vitamin. For this reason, oral application of vitamin B₁₂ is ineffective.² Vitamin B₁₂ must be injected directly into the circulatory

system (in the form of cyano- or hydroxocobalamin). The organism can convert these cobalamins into adenosylcobalamin or methylcobalamin.

Pernicious anemia most often occurs in persons over 40 years of age. It is practically unknown among black people. In England, approximately 1 of 1000 persons suffers from this disease.¹ The World Health Organization recommends a daily dose of only $1\text{ }\mu\text{g}$ (10^{-6} g) of vitamin B_{12} . Human body stores about 5 mg of the cobalamins. Neither plants nor animals can synthesize cobalamins. This vitamin is unique in that it is synthesized only by certain microorganisms, notably anaerobic bacteria.

The sick person notices difficulties in the late stage. The general symptoms are those of anemia. When the level of hemoglobin falls below 4 g per 100 ml of blood, mortal danger is high (normal values of hemoglobin are about 16 g per 100 ml of blood for men and 14 g for women). As soon as 48 hours after first intravenous application of 1 mg of hydroxocobalamin, the bone marrow exhibits a sudden change from the megaloblastic to normoblastic stage. The disease usually appears in families. A person suffering from pernicious anemia is at an increased risk of getting cancer of the digestive tract.³

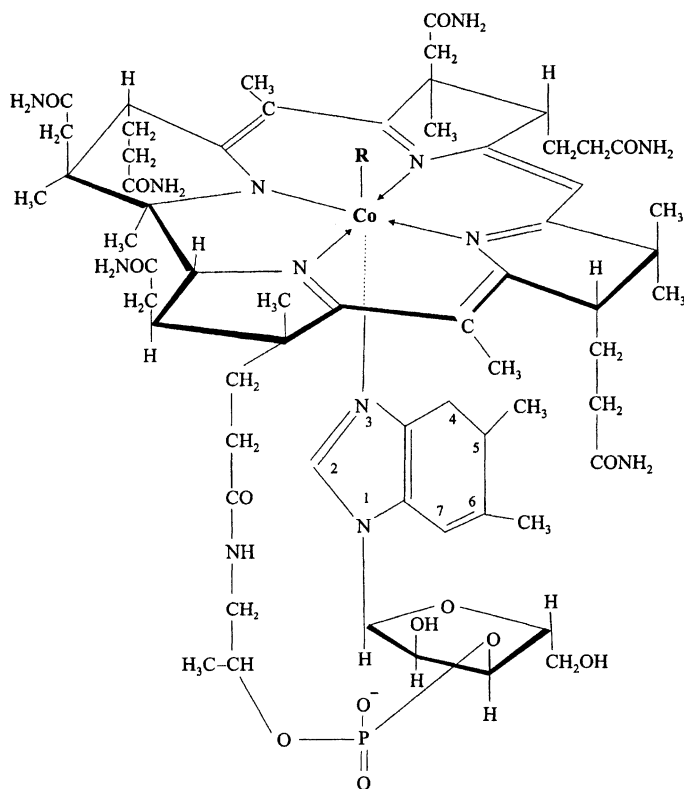


Figure 7.1.1. Structure of cobalamin.

Adenosylcobalamin and methylcobalamin are rare examples of organo-metallic compounds with a cobalt-carbon σ bond occurring in nature. These compounds are basically tetrapyrrole macrocycles. The structure is called a corrin structure, Figure 7.1.2. The corrin ring is similar to the porphyrin ring. Both rings are tetradentate (see next chapter), but the corrin ring is less regular, with one of the bridges between pyrrole rings being a direct ring-to-ring bond instead of an HC or CH₃C unit. The corrin ring appears to be more flexible than the porphyrin ring and is therefore probably preferred to the porphyrin ring in catalytic activity. The carbon atoms positioned at the periphery of the corrin ring are saturated. They bear seven amide groups: three are acetamides and three are propionamides. The remaining one is an N-substituted propionamide. The amide substituent is a propyl group bonded to a ribonu-

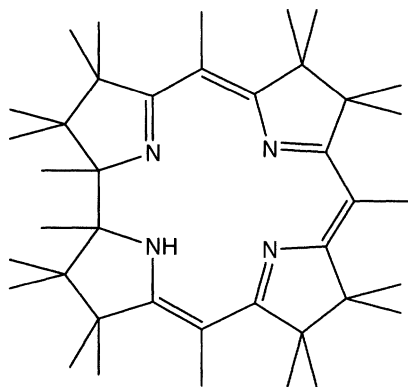


Figure 7.1.2. Corrin ring.

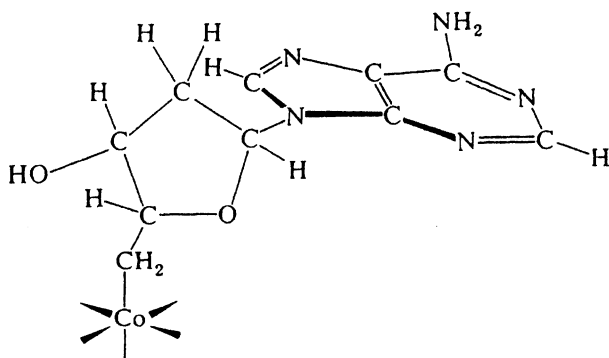


Figure 7.1.3. Structure of 5'-deoxyadenosine; if 5'-deoxyadenosine = R in Figure 7.1.1, the complex is called vitamin B₁₂ coenzyme. The carbon atom of the CH₂ group is directly coordinated to the cobalt atom, the only known example of the carbon-metal bond in a biomolecule.

cleotide, its basic unit being 5,6-dimethylbenzimidazole. The whole structure, including benzimidazole and ribose phosphate, is called cobalamin.

In vivo, R in Figure 7.1.1 is 5'-deoxyadenosine (known as the enzyme cofactor). The compound is then called 5'-deoxyadenosine cobalamin, broadly known as vitamin B₁₂.

Figure 7.1.3 depicts the structure of 5'-deoxyadenosine, bonded to cobalt in the upper axial position, as shown in Figure 7.1.1. In the opposite axial position, cobalt is bonded to the imidazole nitrogen of the 5,6-dimethylbenzimidazole.

The synthesis of vitamin B₁₂ was completed in 1971 by a team of organic chemists headed by R. B. Woodward* of Harvard University and Albert Eschenmoser of the Swiss Federal Institute of Technology in Zürich (Eidgenössische Technische Hochschule, ETH). The synthesis was an impressive achievement, probably the most impressive organic synthesis ever done. In his well-known textbook *Introduction to Organic Chemistry* (Macmillan Publishing Co., Inc. New York 1976), A. Streitwieser pointed out that more than 90 separate synthetic reactions were required and dozens of highly trained chemists labored for years to bring the synthesis to completion. This notable effort should be compared with the ease with which nature can prepare this highly complex molecule.

7.2. MECHANISM OF VITAMIN B₁₂ ACTIVITY

Cyanocobalamin (vitamin B₁₂) is not physiologically active. Physiologically active cobalamins are adenosylcobalamin and methylcobalamin, which are produced *in vivo* from vitamin B₁₂.⁴⁻⁶

In human body, vitamin B₁₂ enables two enzymatic reactions, which otherwise do not take place:

(a) The action of methylmalonyl coenzyme A mutase (= coenzyme A),

* ROBERT BURNS WOODWARD, 1917–1978, American chemist, best-known for his syntheses of complex organic substances, including quinine (1944), cholesterol and cortisone (1951), and vitamin B₁₂ (1971). In 1954, he completed the syntheses of strychnine and lysergic acid, and two years later the synthesis of reserpine, followed by syntheses of chlorophyll (1960), tetracycline (1962), colchicine (1963), and cephalosporin C (1965), and finally vitamin B₁₂ (cyanocobalamin). The structures of complex natural products deduced by Woodward also include penicillin, patulin, strychnine, oxytetracycline, cevine, carbomycin, gliotoxin, ellipticine, calycanthine, oleandomycin, streptonigrin, and tetrodotoxin. Woodward was awarded the Nobel Prize in 1965 “for his outstanding achievements in the art of organic chemistry”. Woodward’s later work on vitamin B₁₂, in collaboration with Roald Hoffmann (shared the Nobel Prize for chemistry in 1981 with Kenichi Fukui), led to the recognition of the concept of orbital symmetry conservation, probably the most important theoretical achievement in organic chemistry of the 1960s.

which enables the conversion of R-methylmalonyl coenzyme A mutase into R-succinyl coenzyme A.

(b) The action of methionine synthetase, which converts *S*-hemocysteine into *S*-methionine. This reaction requires the presence of methylcobalamin.

It is generally considered that the reactions mentioned in (a) and (b), in the absence of cobalamin, cause pernicious anemia.

Unlike inorganic catalysts, enzymes are highly selective. A particular enzyme generally interacts with only one type of substrate, for instance, it acts only on certain proteins, and only at very specific sites. Like all catalysts, enzymes lower the required activation energy, so that the kinetic energy of many substrate molecules becomes sufficient to enable the reaction. Enzymes may cause hundreds of thousands of molecules of the substrate to yield the product each second. Most enzymes are conjugate proteins, *i.e.*, they contain a non-protein part and a protein part. Nonprotein groups attached to some proteins are called prosthetic groups. Prosthetic groups may be as simple as a single metal ion bonded to the polypeptide chain, or they may be sugars, or some lipids or carbohydrates. In any case, prosthetic groups alter significantly the properties of the protein. If a non-protein group can be easily separated from a conjugate protein, it is called a coenzyme.

Neither coenzymes alone nor proteins alone are active catalysts. Prosthetic groups and coenzymes enable the formation of active centers for enzyme activity. Many enzymes require the presence of metal ions (Co²⁺, Fe²⁺, Zn²⁺, Cu²⁺, Mg²⁺) for their activity. Coenzyme A is one of the central molecules in metabolism. It has been noticed that many enzyme-catalyzed acetylations need a heat resistant factor, which is called coenzyme A, where A indicates acetylation. The substance was isolated a few years later and its structure was determined.

Figure 7.2.1 depicts the structure of coenzyme A (usually referred to as CoA):

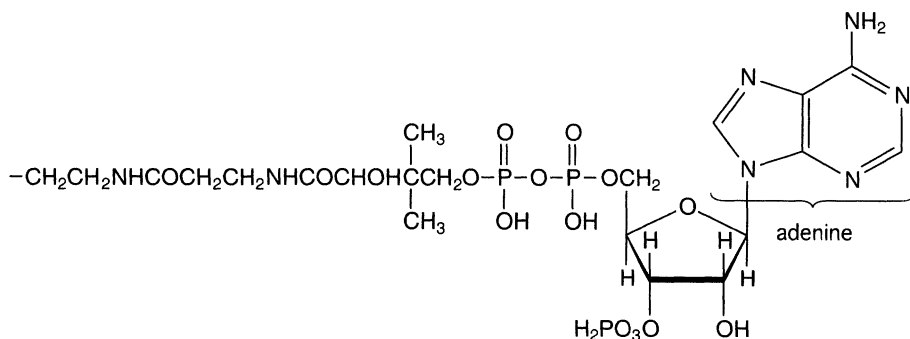
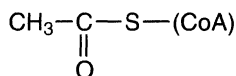
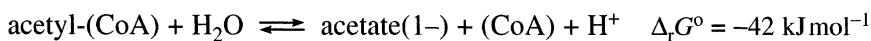


Figure 7.2.1. Structure of coenzyme A (CoA); the substrate is bonded to the terminal CH₂ group (left) by the SH group.

The reactive center is the SH group. Through this group the acyl groups are bonded to coenzyme A by a thioester bond. Such derivatives are most often the acetyl-(CoA) derivatives:

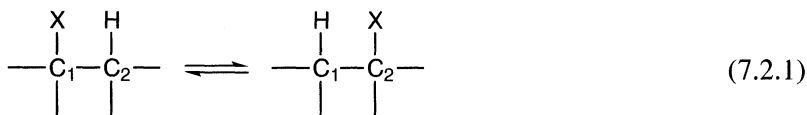


The standard Gibbs energy $\Delta_r G^\circ$ for the acetyl-(CoA) hydrolysis is very negative:

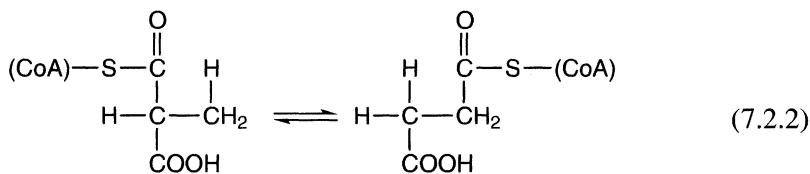


This means that the acetyl-(CoA) species are very effective in transferring acetyl groups and are therefore called acetyl carriers, or acetyl transmitters. Coenzyme A is said to be an acyl carrier, so its biological function is similar to ATP (adenosine triphosphate), a phosphoryl carrier. Thus, the biological functions of (CoA) and ATP are similar.

Reaction 7.2.1 is one of the several known reactions in which the replacement of a substituent X with H takes place, the two substituents being positioned at adjacent carbons:



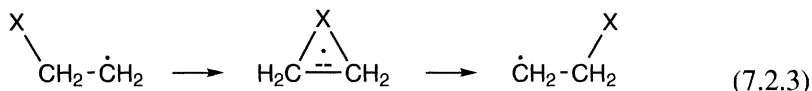
An example is reaction (7.2.2):



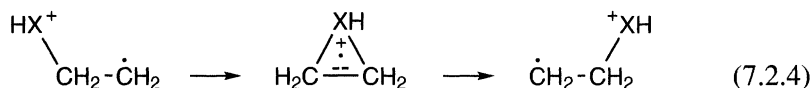
Reaction (7.2.2) is a very unusual reaction,⁷ which most probably proceeds by a free radical mechanism.^{8,9}

Intramolecular atomic shifts require very high energies of activation. There is no doubt that enzymes catalyze such 1,2- atomic shifts. It is known that such shifts, if they proceed *via* carbocations, proceed relatively fast;¹⁰ those shifts which involve free radicals are very rare.^{11,12} Attempts have been made to increase the cationic character of the reacting species, expecting a rate increase.

Thus, Golding and Radom¹⁰ investigated the effect of protonation of the group which migrates in a 1,2-intramolecular shift (see reactions 7.2.3 and 7.2.4):



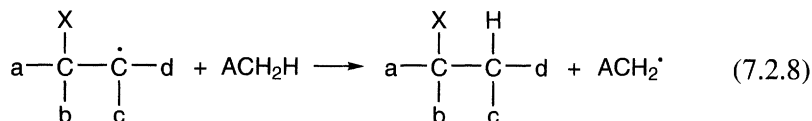
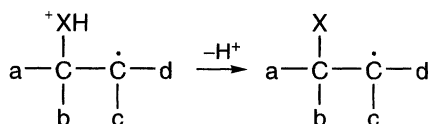
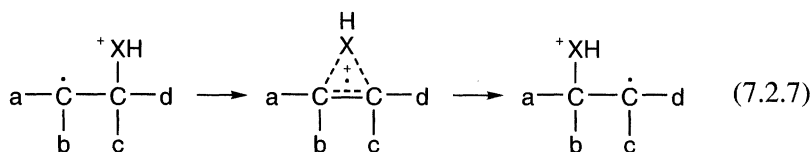
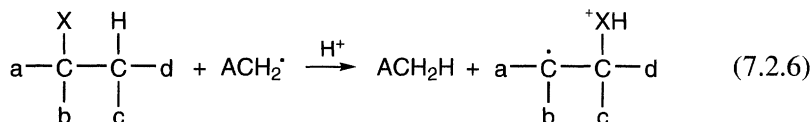
and in the case of protonation, we have:



It was found that protonation facilitates the 1,2-shifts in several reactions involving free radicals.¹³ Based on molecular-orbital calculations, Golding and Radom¹⁰ proposed the following general scheme for the intermolecular rearrangement catalyzed by adenosine cobalamin (eqs. 7.2.5 to 7.2.8):



Reaction (7.2.5) is a homolysis of adenosine cobalamin (ACH₂ stands for adenosine, Fig. 7.1.3, and [Co] stands for cobalamin, Fig. 7.1.1):





Formation of bridged cations is well documented in the cases when X contains a π system (*e.g.*, X = phenyl).^{11,14-16} However, if atom X is hydrogen or a hydride of an element of the first period, the bridged structure includes one electron in the antibonding orbital. In such cases, the 1,2 shift has not been confirmed yet,^{11,12} with the exception of one observation.¹⁷

Summarizing the essential steps of the mechanism depicted in equations (7.2.5) to (7.2.9), it can be concluded that the following steps are mechanistically essential:

(a) Enzyme induced homolytic dissociation of the cobalt-carbon bond in coenzyme B₁₂, yielding the cobalamin radical and the 5'-deoxyadenosine radical (ACH₂^{*}) (scheme 7.2.5);

(b) Separation of an H atom from the substrate, with the formation of the substrate free radical and 5'-deoxyadenosine (ACH₃) (scheme 7.2.6);

(c) Rearrangement of the substrate-radical, yielding (directly or through the bridged intermediate) the corresponding product-radical (scheme 7.2.7);

(d) Separation of an H atom from the ACH₃ caused by the product-radical, resulting in the exchange of the H and X positions (scheme 7.2.8);

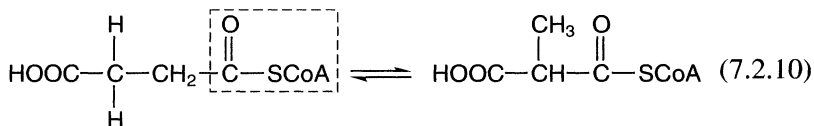
(e) Restoration of 5'-deoxyadenosine cobalamin (vitamin B₁₂ coenzyme), (scheme 7.2.9).

These steps were confirmed using deuterium labeling, thus showing that the two methylene H atoms of ACH₂ are scrambled, suggesting that all the three ACH₃ atoms have become equivalent during the reaction, because ACH₃ is the reaction intermediate.

Additional support for this mechanism was obtained from electron paramagnetic resonance measurements, showing the presence of free radicals.

It should be pointed out that the given reaction scheme (7.2.5–7.2.9) is a general scheme. In reality, the mechanisms can vary in details.

Coenzyme B₁₂ (shortened ACH₂-B₁₂) is a cofactor in various enzymatic reactions. Reaction (7.2.10) is an example. The enzyme is methylmalonyl-coenzyme A mutase; the migrating group is framed. For additional and more complete information, see the article by J. Halpern.¹⁸



The ability of cobalt to induce molecular rearrangements of the covalently bonded organic species has been studied by several authors using alkyl-cobalooximes.¹⁹ In such reactions, studied at low temperatures in cyclo-

propane, the ESR spectra revealed the existence of free radicals.²⁰⁻²² On the other hand, the reactions carried out at higher temperatures in benzene gave products whose structures reveal their formation involving free radicals. However, there are observations suggesting the involvement of organo-cobalt intermediates derived from the substrate and coenzyme B₁₂, but no adequate proof has been offered.^{23,24}

It can be concluded that a large body of data strongly suggests that the rearrangements discussed (migration of X) proceed by way of free radicals. At least this is so in the case of methylmalonyl-CoA mutase (reaction 7.2.10). Free radicals can be formed because the cobalt-carbon bond is weak. It is hard to believe that some other organic molecule could form a very reactive radical under so mild reaction conditions as those of the substituent X migration. The role of coenzyme B₁₂ in biological systems can be looked upon as a reversible source of free radicals (5'-deoxyadenosine radical), produced under very mild reaction conditions. This viewpoint is advocated by J. Halpern¹⁸ who makes a comparison with the action of hemoglobin and myoglobin that enable reaction (7.2.11):



The O₂^{·-} superoxide radical will be discussed in Chapter 8.

7.3. DIFFICULTIES IN DISTINGUISHING D AND I_d MECHANISMS

Difficulties in distinguishing D and I_d mechanisms in reactions of aquacobalamin (vitamin B_{12a}) with azide and hydrazoic acid, yielding azidocobalamin, have been described by Marques *et al.*²⁵ The authors followed the replacement rates of water by stopped-flow spectrophotometry, and also by measuring the volume of activation for the reaction with azide. They concluded that they were not able to distinguish between these two mechanisms. Other authors also emphasize that their results can be equally well interpreted by either of these two mechanisms.^{26,27} On the other hand, some authors favor the limiting D mechanism, in which the monomolecular dissociation of water from the coordination sphere of cobalt(III) is the slowest and thus the rate-determining step.²⁸⁻³² However, there are publications that favor the I_d mechanism, with participation of the entering group in the reaction transition state. It was recently established³³ that the *pseudo* first-order rate constants for the replacement of water in the aquahydroxocobamide by azide, *N*-methylimidazole, pyridine, or cyanide exhibit a clear tendency to limiting rates. This observation sup-

ports the claim that all these reactions follow a dissociative mechanism, *i.e.*, the reaction activation is of a dissociative nature. In addition, the fact that the $\Delta^\ddagger H$ and $\Delta^\ddagger S$ activation parameters of these reactions depend on the nature of the entering ligand L reveals that L participates in the transition state. The conclusion was that the mechanism of water replacement in aquahydroxocobamide is an I_d process. A further support for this claim is found in the replacement reactions of coordinated water with the anionic ligands I^- , $S_2O_3^{2-}$, NO_2^- , SCN^- , and N_3^- .³⁴ Meier and van Eldik³⁵ also support the claim that the replacement of water in aquacobalamin (vitamin B_{12a}) is an I_d process (thus correcting their earlier claim that the replacement is of the D type³¹). They found³⁵ that the activation volumes for the forward reactions and their reverses have values between +6 and +10 $\text{cm}^3 \text{mol}^{-1}$, the corresponding entropies of activation being positive, as expected for an I_d mechanism (see section 2.6.2).

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Chapter 8

KINETICS AND MECHANISMS OF METALLOPORPHYRIN REACTIONS

8.1. INTRODUCTION

Coordination chemistry of metalloporphyrins is a very large research field. The porphyrin macrocyclic ligand forms complexes with all transition metals, with many main group metals and many lanthanides. Metalloporphyrins easily bind various ligands in the axial positions above and below the porphyrin plane. The number of publications in the field amounts to several thousands a year. Fortunately, several review articles and monographs help manage this enormous research area.¹⁻¹³

Such a large interest in this field is primarily caused by the biological importance of iron porphyrin complexes as oxygen carriers in hemoglobin and

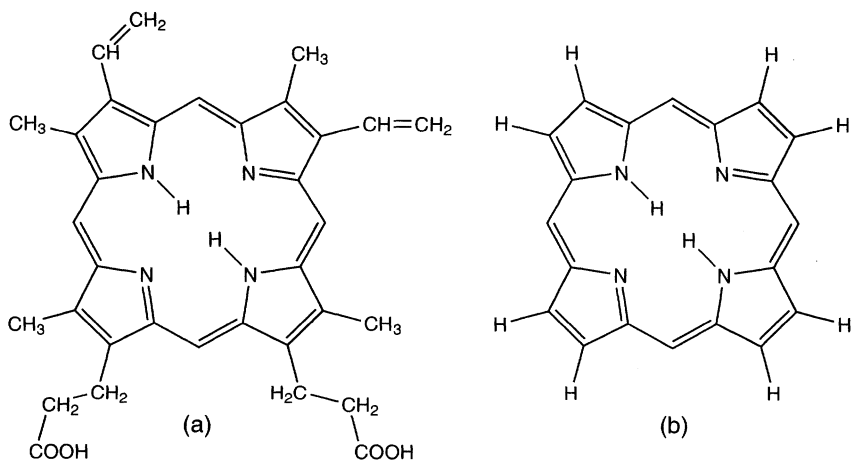


Figure 8.1.1. (a) Structure of protoporphyrin IX; (b) Structure of porphyrin.

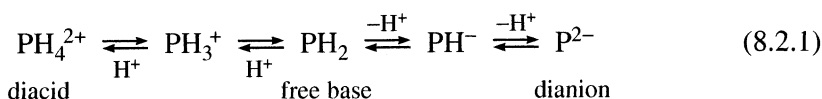
myoglobin, and as mediators in electron transfer reactions of cytochromes; the magnesium type porphyrins, chlorophylls, enable the synthesis of glucose from CO_2 and H_2O by a photo-excited chlorophyll.

The porphyrin complexes of iron were found in the excrements of reptiles, the so-called coprolites, several tenths of millions years old, suggesting that the mechanism of oxygen transfer did not basically change during this vast period of time up to our days.

Figure 8.1.1 depicts: (a) the structure of protoporphyrin IX, and (b) the structure of porphin from which porphyrins are derived. Porphin is an unsubstituted tetrapyrrole connected at α -carbons by CH bridges. Porphyrins are substituted porphins, among which protoporphyrin IX is one of the most important because it is a constituent of hemoglobin and myoglobin.

8.2. MECHANISM OF METAL INCORPORATION INTO THE PORPHYRIN COMPLEX

Scheme 8.2.1 given below shows the most important reactants of metalloporphyrins (MP). In reality, the possible reactions are more numerous than those depicted in the scheme. The free base (PH_2) can add protons, forming the monocation (PH_3^+) and the dication (PH_4^{2+}). But, the free base can also lose two protons, thus forming the monoanion (PH^-) and the dianion (P^{2-}). Most porphyrins are in the form of the free base, PH_2 (up to $\text{pH} \approx 14$).



The formation of the complex between the free base (PH_2) and the metal ion has been extensively studied. It was found that the complicated metal incorporation mechanism can be best interpreted for the reaction of the dipositive metal ion and the neutral chelating ligand. However, this does not mean that the anionic porphyrin species (PH^- and P^{2-}) are not reactive. In fact, they are present in very small concentrations, so small that they can hardly be detected. On the other hand, the cationic porphyrin species are definitively unreactive. Earlier works, of some twenty years ago, preferred the mechanism of metal incorporation which assumes a pre-equilibrium between the free base (PH_2) and the dissociated protons of pyrrole nitrogens, so that the metal cation would actually react with the P^{2-} dianion. Later works, however, indicate the existence of the so-called SAT (sitting-atop) complex intermediate, which was already foreseen in 1960 by Fleischer and Wang.¹⁴ It was later shown¹⁵ that the SAT metal-ion intermediate can deform porphyrin, thus

enabling proton dissociation. Another metal ion can then be incorporated from the axial (distal) side. The metalloporphyrin (MP) is thus formed. The latest works strongly suggest that the following steps are involved:

(a) Deformation of the chelate ligand (K_D):



Pasternack, Sutin and Turner¹⁶ determined the rate constants of deformation of 5,10,15,20-tetra[(4-*N*-methylpyridil)porphin], (H_2TMpyP), and found that in aqueous solution k_1 amounts to $4.6 \times 10^7 \text{ s}^{-1}$, and k_{-1} to $1.2 \times 10^9 \text{ s}^{-1}$. As can be seen, both processes are very fast, the latter being very near diffusion control.

(b) Formation of the outer-orbital complex:



(c) Formation of the first bond:



(d) Formation of the second bond (SAT):



(e) Metalloporphyrin formation:



It is generally accepted that the SAT intermediate formation is the slowest step in the metallation process,¹⁷ and that the proton dissociation in (8.2.6) is an I_d process,¹⁸ which means that the energy for proton dissociation is supplied by the chelating ligand itself, the position thus freed being simultaneously filled by the metal ion. The assumption is that the metal-porphin bond is easily formed but also easily broken. Under such conditions, it is very probable that the pyrrole ring can rotate, thus exposing its free electron pair to the second metal ion, M' , approaching from the opposite axial position. In this way, a new metalloporphyrin is formed in which M' has replaced M . Most unexpected in this SAT mechanism is the moment in which metal M , which has formed the SAT complex, does not "fall" into the porphyrin ring, but the other metal, M' , is needed to form metalloporphyrin. It appears that the rigidity

of the porphyrin ring causes resistance to the metal ion bonding and that the foregoing deformation of the porphyrin ring is absolutely necessary. These ideas found a strong experimental support. Thus, the Li^+ ion forms the SAT complex in the presence of Cu^{II} and Zn^{II} , but metalloporphyrin is not formed,¹⁵ the Li^+ ion being only a catalyst for the metalloporphyrin formation with Cu^{II} and Zn^{II} .

Probably the strongest support for the existence of the SAT complex is the fact that the free base, PH_2 , is the reactive form of the porphyrin, which follows from the dependence of the reaction kinetics on pH.^{4,19,20} It was already mentioned that porphyrins are such weak acids that the PH^- concentration is extremely small, and PH_3^+ and PH_4^{2+} ions are not reactive.

The metalloporphyrin formation is an interesting and illustrative example of a sterically controlled replacement reaction.

8.3. METALLOPORPHYRINS AS OXYGEN CARRIERS

Coordination of Fe^{2+} to four nitrogen atoms of protoporphyrin IX gives heme (at pH = 7 heme has a negative charge due to ionized carboxyl groups). In aqueous solution, the iron(II) heme is irreversibly oxidized to iron(III). Such a complex is called hemin. This is the reason why heme cannot function as an oxygen carrier in biological processes. Nature avoids this situation by surrounding heme with hydrophobic groups of amino acids. Thus, heme is embedded in peptides (see the structure of hemoglobin and myoglobin²¹).

The role of the peptide part of hemoglobin is to prevent an irreversible oxidation of Fe^{2+} . Irreversible oxidation would mean biological death. The surrounding of the embedded heme has a low permittivity (mainly hydrocarbons) and therefore acts as a nonpolar solvent, preventing charge separation in the transition state of an oxidation process of the type $\text{Fe}^{2+} \rightarrow \text{Fe}^{3+}$. There are also steric reasons that prevent the formation of the μ -oxo-heme dimer, which appears to be a necessary intermediate in the irreversible oxidation. The μ -oxo dimer is preceded by a μ -peroxo dimer, as suggested in the scheme (Figure 8.3.1).

In model systems, artificially formed obstacles can prevent the bimolecular reaction and the formation of oxo complexes. Thus, "picket fence" porphyrins allow bonding of the small O_2 molecule and no space is left for formation of the μ -peroxo and μ -oxo dimers. This is the reason why oxygen bonding remains a reversible process, which is characterized as oxygenation, rather than oxidation.

One of the first "picket fence" porphyrins that could reversibly transfer oxygen was prepared by Collman and coworkers,²⁴⁻²⁶ Figure 8.3.2.

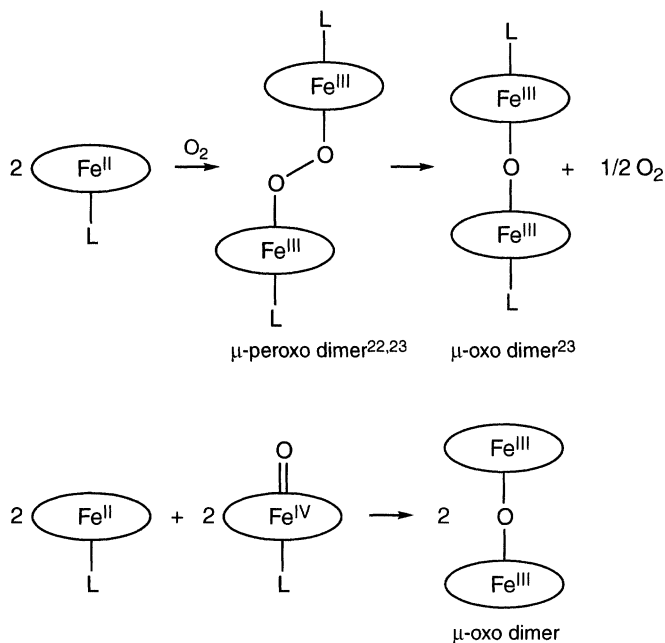


Figure 8.3.1. Unwanted metalloporphyrin dimerization; L is a nitrogen base, e.g., imidazole.

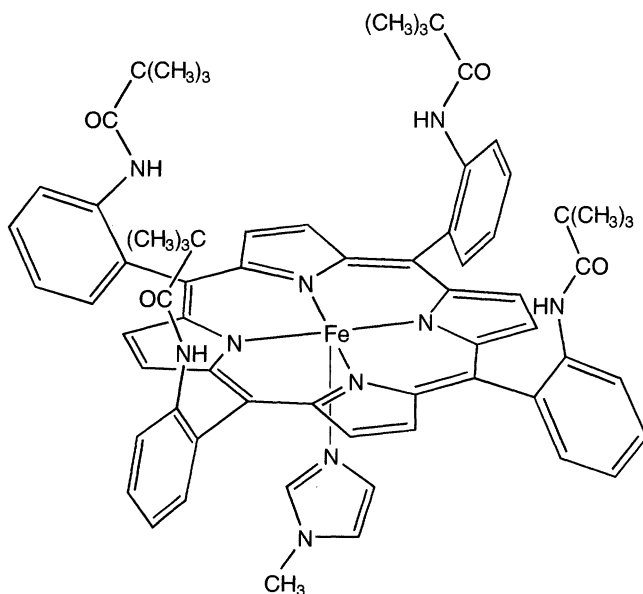


Figure 8.3.2. "Picket fence" porphyrin of Collman *et al.*²⁴⁻²⁶ enables reversible bonding of molecular oxygen.

The mentioned authors synthesized the iron(II) *mezzo*-tetra($\alpha,\alpha,\alpha,\alpha$ -*o*-pivalamidephenyl)porphyrin (pivalic acid is trimethylacetic acid), and then introduced an amine ligand, *e.g.*, 1-methylimidazole, pyridine or piperidine, into the axial position. In excess of these ligands, the bonding of oxygen is reversible. Such picket fence porphyrin accepts molecular oxygen into a hydrophobic surrounding (pocket). The oxygen molecule accepts an electron, producing an $O_2^{\bullet -}$ radical. Protonation of the $O_2^{\bullet -}$ radical into the more stable HO_2 radical is inhibited, and so is the reduction of O_2 by formation of a porphyrin-Fe- O_2 -Fe-porphyrin complex. In this respect, the article of Suslick and Reinert²⁷ on the synthetic analogs of O_2 -binding heme proteins is very informative and provides many details.

Artificial oxygen carriers are also “capped” porphyrins.²⁸ The cover is made of large tetraaldehydes and is tailored to accept the small O_2 molecule, but not an amine ligand (L), Figure 8.3.3. In the presence of an amine ligand, O_2

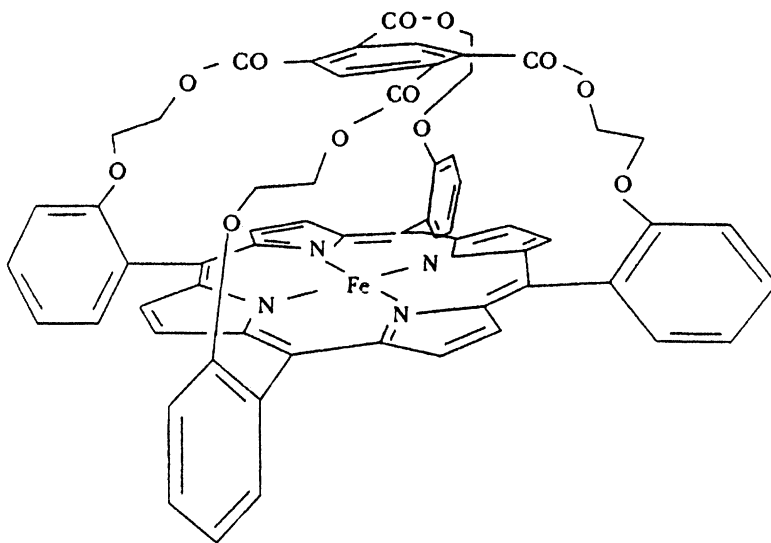


Figure 8.3.3. A capped porphyrin of iron protected by large tetraaldehydes.

will fit under the cover but L will stay outside, in the opposite distal position. Since O_2 is covered and protected, μ -oxo complexes cannot be formed, thus the reaction reversibility is assured. However, if the amine ligand is not present, O_2 can be bonded outside the cover and the μ -oxo complex is formed, causing an irreversible oxidation (Figure 8.3.4).

There have been indications that picket fence porphyrins and capped porphyrins could be a temporary substitute for blood in emergencies but no noticeable success has been achieved.

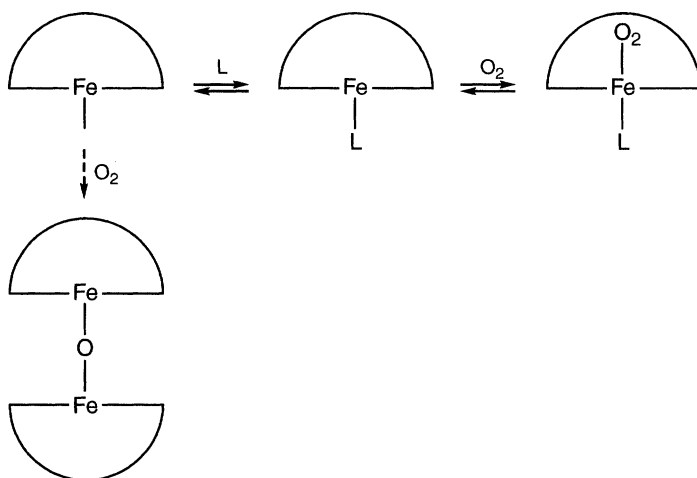


Figure 8.3.4. Scheme of the reaction of a capped porphyrin in the presence of amine ligand (L) and in its absence.

The nature of the bond between iron and the imidazole nitrogen of the proximal histidine in hemoglobin and myoglobin has been the subject of numerous investigations. Hemoglobin and myoglobin have similar structures. The molecular mass of hemoglobin is about 64 000; it contains four heme groups. Myoglobin is similar to a quarter of the hemoglobin molecule containing one heme group of hemoglobin. Its molecular mass is just under 18 000, which is roughly one fourth of the molecular mass of hemoglobin. The structure of myoglobin was solved in 1958 by Sir J. C. Kendrew, using the X-ray structural analysis. Two years later, M. F. Perutz analogously solved the structure of hemoglobin. Perutz and Kendrew shared the 1962 Nobel Prize for chemistry.*

Hemoglobin is a globulin protein (globulins are a group of proteins, insoluble in water but soluble in diluted alkalies). Hemoglobin is a constituent of the red blood cells (erythrocytes) of vertebrates, which transport oxygen to

* Sir JOHN COWDERY KENDREW, English chemist and biochemist, received his education at Trinity College, Cambridge. He served as deputy chairman of the Medical Research Council Laboratory for Molecular Biology at Cambridge.

MAX FERDINAND PERUTZ, 1914–2002, Austrian-born British biochemist, was educated at the University of Vienna and at the University of Cambridge, where he received his Ph.D. in 1940. He founded the medical Research Council Unit for Molecular Biology at Cambridge, where he made the first X-ray diffraction pictures of hemoglobin. Kendrew and Perutz continued their investigation of hemoproteins, Kendrew specializing in the molecular structure of myoglobin, and Perutz concentrating on the hemoglobin molecule. By 1959, Perutz had shown that hemoglobin was composed of four separate polypeptide chains. He subsequently showed that in oxygenated hemoglobin the four chains are rearranged, which solved the role of hemoglobin in the respiratory mechanism.

the tissues. Hemoglobin forms an unstable, reversible bond with oxygen; in the oxygenated state, it is called oxyhemoglobin and is bright red; in the reduced state, it is purple-blue.

Hemoglobin develops in bone marrow cells, which become red blood cells. Each hemoglobin molecule is made up of four heme groups surrounding a globin group. Heme, which accounts for only 4 percent of the weight of the molecule, contains all the iron and gives the red color to the molecule. Globin consists of two linked pairs of polypeptide chains. The amino acid sequences in these chains are fully known. Each of the four chains enfolds a complex prosthetic group called heme, which has an iron atom at its center. As said, each of the iron atoms in a hemoglobin molecule can combine loosely with one molecule of oxygen. When hemoglobin binds with the first O_2 molecule, structural changes that increase the affinity of hemoglobin for oxygen take place. These structural changes cause additional changes in the neighboring heme subunits, lowering their energies of activation for additional O_2 bonding. Thus, the conformational changes involved in the bonding of the first oxygen molecule are considered a “trigger” for the further oxygenation process.

The bonding of hemoglobin with O_2 is loose and depends on environmental conditions. Thus, the conditions in the lungs favor oxyhemoglobin formation. On the other hand, the conditions in the capillaries of the systemic blood circulation favor release of O_2 and the reversion of oxyhemoglobin to hemoglobin. The critical condition in determining whether hemoglobin will bond oxygen or release it is the partial pressure of O_2 .

Hemoglobin has two important roles: (a) it binds oxygen molecules to the iron atoms and carries them to the cell, while myoglobin transports oxygen into the cell for glucose oxidation; (b) Hemoglobin then uses certain amino acids to bind carbon dioxide and transports it back to the lungs.

Myoglobin is found in muscle cells. It functions as an oxygen-storage unit, providing oxygen to the working muscles. Seals and whales have more myoglobin in their muscles than other animals, and are able to remain submerged for long periods of time.

Myoglobin has been obtained in pure crystalline form from many sources. Though the heme portion of all myoglobins is the same, the protein portion varies considerably between species.

Heme is bonded to proteins in hemoglobin and myoglobin by imidazole nitrogen of histidine amino acid, the imidazole nitrogen being coordinated to iron (proximal histidine). In the *trans*-position towards the coordinated histidine, a water molecule is bonded in deoxyhemoglobin and an oxygen molecule in oxyhemoglobin. In oxyhemoglobin, the iron electron of heme is not fully transferred to O_2 (the process is oxygenation, not oxidation), so the irreversible formation of O_2^- radical is avoided because of the hydrophobic medium and the low dielectric constant, as already discussed.

At higher oxygen pressures hemoglobin binds oxygen equally well as myoglobin does, but at lower pressures, like in muscle cells, hemoglobin binds oxygen less efficiently than myoglobin, so that oxygen passes from hemoglobin to myoglobin. In addition, the need for O_2 in muscles increases with simultaneous CO_2 production. The increase of CO_2 concentration lowers the pH, causing an increased transfer of oxygen to myoglobin (the so-called Bohr's effect²⁹).

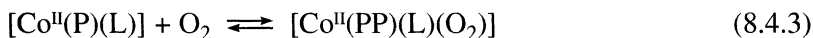
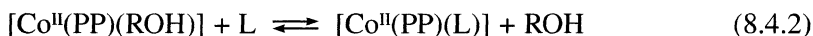
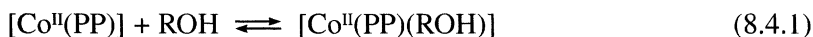
It is now known that deoxyhemoglobin contains high spin iron(II),³⁰⁻³² having two electrons in the e_g orbitals. Under such conditions, the iron atom diameter is too large and iron does not fit into the equatorial plane, but remains above the plane by about 50 pm (0.5 Å); the Fe–N bond of iron towards histidine is some 8° off the perpendicular position and amounts to 220 pm (2.2 Å). Thus, the iron atom is pentacoordinated and has a square pyramidal configuration, with four pyrrole nitrogens in the base of the square pyramid, and the imidazole nitrogen in its apex. But, when O_2 binds into the opposite axial position, the iron atom acquires the low spin state, its electrons occupying the t_{2g} level. The $d_{x^2-y^2}$ orbital is then empty, the iron atom diameter becomes smaller and almost fits into the equatorial plane, and the Fe–N bond becomes almost perpendicular. The lowering of iron almost into the equatorial plane causes a lowering of the imidazole nitrogen bonded to iron. This shift is then transferred to the entire helix of bonded amino acids of the four hemoglobin units, making the overall oxygenation process easier.

The nature of the bonding between iron and the imidazole nitrogen of the proximal histidine is also important. Thus, the increase of pK_a of a ligand bound to iron can change the ratio of its σ/π bonding to the metal,^{33,34} which will be discussed in the next chapter.

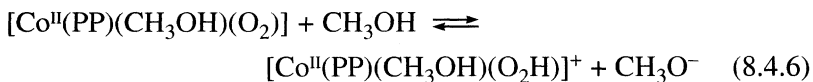
8.4. SUBSTITUTIONS ON METALLOPORPHYRINS

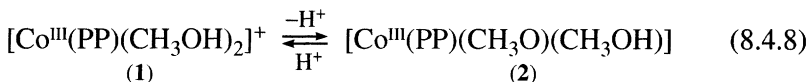
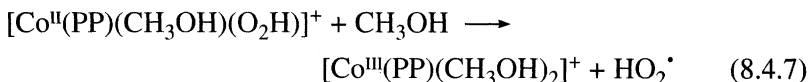
Several ligands can be easily coordinated in the axial position of Co^{III} porphyrins in a variety of aprotic and mixed protic-aprotic solvents.³⁵⁻³⁸ On the other hand, binding of amine ligands in the sixth axial position of Co^{II} porphyrins is very unfavorable³⁹ because cobalt(II), a d^7 system, does not fit into the equatorial plane determined by four porphyrin nitrogen atoms, and is placed by about 50 pm (0.5 Å) above the equatorial plane, as already mentioned. For example, the binding of amine ligands in the sixth axial position of Co^{II} porphyrins in toluene takes place at high ligand concentrations only (e.g., with piperidine a 10^5 -fold excess over complex concentration is required); with ligands coordinating less strongly than piperidine, there is practically no binding to the sixth position at room temperature.³⁹

In alcoholic solutions (usually methanol, with a few volume percent of chloroform to increase the complex solubility), in the presence of molecular oxygen, and in the presence of various amine ligands ($L = \text{pyridine (py)}, 3\text{CN-py}, 4\text{CN-py}, 4\text{CH}_3\text{-py}, \text{imidazole, etc.}$), the oxidation of cobalt(II) protoporphyrin IX dimethyl ester (in further text = $[\text{Co}^{\text{II}}(\text{PP})]$), proceeds readily by way of the reaction intermediate $[\text{Co}^{\text{II}}(\text{PP})(L)(\text{O}_2)]$, the involvement of which has been widely recognized.^{40–47} The product is $[\text{L}_2\text{Co}^{\text{III}}(\text{PP})]^+$.³⁶ It is formed through the intermediate $[\text{L}^{\delta+}\text{Co}^{\text{II}}(\text{PP})(\text{O}_2^{\delta-})]$, which is stabilized by polar and protic properties of the alcoholic solvent. A protic solvent enables elimination of the superoxide radical-anion, $\text{O}_2^{\cdot-}$, in the form of the $\text{HO}_2^{\cdot}$ radical, followed by coordination of the applied amine ligand. If the reaction medium does not contain a source of protons, the oxidation does not take place and $[\text{L}_2\text{Co}^{\text{III}}(\text{PP})]^+$ is not formed. Amine ligand acts as an electron donor, promoting electron transfer from Co^{II} to O_2 . The following equilibria are most probably involved in the oxidation process:



Formation of the intermediate $[\text{Co}^{\text{II}}(\text{PP})(L)(\text{O}_2)]$ was confirmed on several occasions.^{40–47} It was also shown⁴⁸ that $[\text{Co}^{\text{II}}(\text{PP})]$ in methanol undergoes oxidation even in the absence of amine ligands, the methoxo-methanol complex, $[\text{Co}^{\text{III}}(\text{PP})(\text{CH}_3\text{O})(\text{CH}_3\text{OH})]$, being the reaction product. The mechanism is essentially analogous to that in the presence of an amine ligand, with the difference that methanol has taken over the role of the orienting ligand – electron donor. However, since methanol is a much weaker electron donor than amine ligands, the rate of oxidation is about 1000 times lower. This proved useful because the probable reaction steps (8.4.5) to (8.4.8) could be separately studied:⁴⁸





If no acid or alkali is extra added to methanolic solutions, the methoxo-methanol species (2) widely predominates, as revealed by its absorption spectra: Soret, 416 nm; α , 531 nm; β , 565 nm. Stage (8.4.6) shows the importance of the protons of the protic solvent in the oxidation of cobalt(II) and elimination of superoxide radical ($\text{HO}_2^\cdot$).

Methanolic solutions of $[\text{Co}^{\text{III}}(\text{PP})(\text{CH}_3\text{O})(\text{CH}_3\text{OH})]$ can be also prepared by dissolving $[\text{Co}^{\text{III}}(\text{PP})(\text{Cl})]$ (dark violet-red crystals) in methanol. Upon dissolution, the complex releases its chloride practically instantaneously and equilibrates,⁴⁸ as shown by (8.4.8) where species 2 predominates. The spectra of $[\text{Co}^{\text{III}}(\text{PP})(\text{CH}_3\text{O})(\text{CH}_3\text{OH})]$ prepared either from $[\text{Co}^{\text{II}}(\text{PP})]$ in methanol in the presence of O_2 or from $[\text{Co}^{\text{III}}(\text{PP})(\text{Cl})]$ in methanol are identical.

If $[\text{Co}^{\text{II}}(\text{PP})]$ is dissolved in an aprotic solvent which does not coordinate (*e.g.*, chloroform, methylene chloride, benzene), the solutions are stable in air and can be kept as stock solutions.³⁶ On the other hand, alcoholic solutions of $[\text{Co}^{\text{II}}(\text{PP})]$ are stable only in an oxygen-free atmosphere. The equilibrium (8.4.5) is quickly established. The fact that the absorption spectra of the solution of $[\text{Co}^{\text{II}}(\text{PP})]$ in methanol in the presence and absence of oxygen (argon atmosphere) are identical can be explained by: (a) supposing that the equilibrium (8.4.5) is shifted far to the left, so that the O_2 complex cannot be detected spectrophotometrically, or (b) by the assumption that there are no observable differences in absorption spectra of the species shown in (8.4.5). The intermediate $[\delta^+\text{Co}^{\text{II}}\text{P}(\text{CH}_3\text{OH})(\text{O}_2^{\delta-})]$ should exhibit an EPR signal, due to the partial electron transfer to O_2 and its partial conversion to the superoxide radical. Indeed, the freshly prepared solution of $[\text{Co}^{\text{II}}(\text{PP})]$ in methanol, in the presence of air, at 77 K, gave an EPR signal, but only in the initial reaction stage. When the oxidation is completed and the $[\text{Co}^{\text{III}}(\text{PP})(\text{CH}_3\text{O})(\text{CH}_3\text{OH})]$ is predominantly formed, the EPR signal disappears, as expected.⁴⁸

8.4.1. Imidazole, an essential component of many biological systems; the nature of metal bonding

The imidazole ring is an essential component of many biological systems: in proteins as part of the side chain of the amino acid histidine (hemoglobin and myoglobin), in nucleic acids as part of the purine ring of adenine and

guanine, in cytochromes, in vitamin B₁₂ coenzyme as benzimidazole, in metalloenzymes, *e.g.*, in carbonic anhydrase, in microperoxidase-8 (a heme octapeptide which catalyzes the reduction of H₂O₂, enabling the oxidation of substrates not in direct vicinity of the active site).

Imidazole is a ligand electron donor in the σ and π sense. It is a much better electron donor than are most of the other nitrogen heterocycles.⁴⁹ The majority of imidazoles are especially good σ donors, and moderately good π donors.⁵⁰ It has been recently shown that imidazole with an aldehyde group in 2-position, (2-CHOimH) is a very strong π acceptor, comparable to pyrazine.^{51,52}

Imidazole has different roles in the mentioned biological systems, *e.g.*, as proton donor or proton acceptor in hydrogen bonding; imidazole can function as a specific base or a nucleophilic catalyst, or it can function as a ligand for metal coordination.^{53–57} Imidazole is the bonding site for various metalloproteins, such as Mn²⁺, Fe²⁺, Fe³⁺, Cu⁺, Cu²⁺, and Zn²⁺.^{56–58} It is known that 1-methylimidazole has a strong affinity for Mg²⁺.^{59–62} It is assumed that Mg²⁺ coordinates to *N*-methylhistidine found in myosin, the main constituent of thick filaments.^{63,64}

Each thick filament is composed of about 250 myosin molecules. Myosin has two important roles: a structural one as the building block for thick filaments; and a functional one as the catalyst of the breakdown of adenosine triphosphate (ATP) during contraction and its interaction with actin as part of the muscle force generator. Actin is an important constituent of the thin filament. The molecular mass of myosin is about 500 000; it contains two major protein chains and four small ones, the entire molecule being about 160 nm long, and has a coiled-coil structure. The interaction of actin and myosin provides a basis for molecular models of force generation and contraction in living muscle.

Asher *et al.*⁴⁹ pointed out that our knowledge of the imidazole ability of π bonding is important for understanding its effect on the physical and chemical properties of hemoproteins.

8.4.2. Comparison of the bonding modes of imidazole and pyridine to a metal

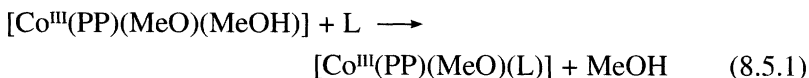
Imidazole is a considerably poorer π acceptor than pyridine.⁶⁵ There are cases where imidazole π -donation is important and those where it is not important. For example [(NH₃)₅Co^{III}(5-CH₃-imH)]³⁺ is a case where π donation is not important.^{66,67} Co^{III}, a low spin d⁶ ion, has no empty π orbitals at low energy and cannot be an effective π acceptor.⁶⁸ Unlike Co^{III}, low spin Fe^{III} and Ru^{III} can accept π -electron density from a donor atom.⁶⁶ In contrast to the

good π -donor properties of imidazole, pyridine is a much weaker π donor, since pyridine does not have a high energy HOMO (highest occupied molecular orbital) as does imidazole.⁶⁵ The π -acceptor properties of pyridine are moderate because its LUMO (lowest unoccupied molecular orbital) is not as low in energy as, *e.g.*, that of pyrazine, known as a good π acceptor.⁶⁸ Since Co^{III} has no empty π orbitals at low energy and cannot be an effective π acceptor, it can be concluded that the modes of bonding of entering ligands into Co^{III} -porphyrin complexes are limited to σ bonding and cobalt to ligand π bonding only.

It can be concluded that substitutions in metalloporphyrins mainly follow the I_d mechanism. However, a D mechanism can be encountered when the "orienting ligand" (an expression used by C. K. Ingold)⁶⁹ is a strong electron donor, *e.g.*, methoxide in the axial position of a metalloporphyrin.^{34,48,70} If a D mechanism is involved, limiting rates should be expected for all entering ligands, but individual rates at certain concentrations of the entering ligands should differ, revealing that the pentacoordinate intermediate lives long enough to discriminate between the entering ligands. On the other hand, if specific limiting rates depend on the nature of the entering ligand, because this ligand participates in the reaction transition state, then the mechanism is defined as I_d (interchange of the dissociative type).

8.5. NATURE OF THE BOND OF AMINE LIGANDS TO COBALT(III) IN PORPHYRINS; THE RELATION OF σ TO π BONDING

The $[\text{Co}^{\text{III}}(\text{protoporphyrin IX dimethyl ester})(\text{MeO})(\text{MeOH})]$ complex is very suitable for the study of the nature of bonds of strongly bound entering amine ligands, which easily replace the weakly bonded outgoing methanol. Replacements of both ligands, MeO^- and MeOH , can be followed spectrophotometrically in methanol solvent using the stopped-flow technique.³⁴ Replacements of MeOH and MeO^- ligands proceed consecutively in this order (eqs. 8.5.1 and 8.5.2):



Differences in the rates of the two replacements are large enough to permit independent spectrophotometric determination of the first step at 417 nm.

When the replacement rates of MeO^- by L ($4\text{CN-py} < \text{py} < 4\text{Me-py} < 4\text{NH}_2\text{py}$) were carried out at about 50 times larger concentrations of L than those in replacements of MeOH, it was found that the more basic the entering ligand, the faster was the replacement,³⁴ in agreement with the literature.³ On the other hand, it was a great surprise that the rate of replacement of MeOH by L according to (8.5.1) showed a different kinetic behavior, *i.e.*, the least basic amine ligand L exhibits the highest rate of entry.³⁴ The reactions follow a D $[\text{S}_{\text{N}}1(\text{lim})]$ mechanism. The observed rate constant (k_{obs}) is given by eq. (8.5.3):

$$k_{\text{obs}} = \frac{k_1 k_2 [\text{L}]}{k_{-1} [\text{MeOH}] + k_2 [\text{L}]} \quad (8.5.3)$$

where k_1 and k_{-1} are rate constants of dissociation and association of the MeOH ligand, respectively, and k_2 is the rate constant of the reaction of the intermediate $[\text{Co}^{\text{III}}(\text{PP})(\text{MeO})]$ with L (see section 1.12, eq. 1.12.12). Since the concentrations of L are low and the concentration of MeOH is high (MeOH is the solvent),

$$k_{\text{obs}} = \frac{k_1 k_2 [\text{L}]}{k_{-1} [\text{MeOH}]} \quad (8.5.4)$$

Consequently,

$$\frac{k_{\text{obs}}^{\text{L}_1}}{k_{\text{obs}}^{\text{L}_2}} = \frac{k_2^{\text{L}_1}}{k_2^{\text{L}_2}} \quad (8.5.5)$$

must also hold.^{34,71} It follows that $E_{\text{a}(\text{obs})}^{\text{L}_1} - E_{\text{a}(\text{obs})}^{\text{L}_2} = E_{\text{a}(k_2)}^{\text{L}_1} - E_{\text{a}(k_2)}^{\text{L}_2}$.

Eq. (8.5.3) can be modified into:

$$\frac{1}{k_{\text{obs}}} = \frac{k_{-1} [\text{MeOH}]}{k_1 k_2 [\text{L}]} + \frac{1}{k_1} \quad (8.5.6)$$

from which the k_2/k_{-1} values can be determined.

By plotting the dependence of $\ln(k_2/k_{-1})$ on $\text{p}K_{\text{a}}$ values of entering pyridine ligands LH^+ , a minimum reaction rate is observed at $\text{p}K_{\text{a}}$ of about 5, as shown in Figure 8.5.1.

An analogous plot to that in Fig. 8.5.1. is shown in Fig. 8.5.2. for the entering imidazole type ligands. We can see that for $\text{p}K_{\text{a}}$ between 6.5 and 8 the reaction rates are practically independent of $\text{p}K_{\text{a}}$ of entering imidazoles. This is supported by a statistical treatment.³⁴ Since the imidazole ligand itself is

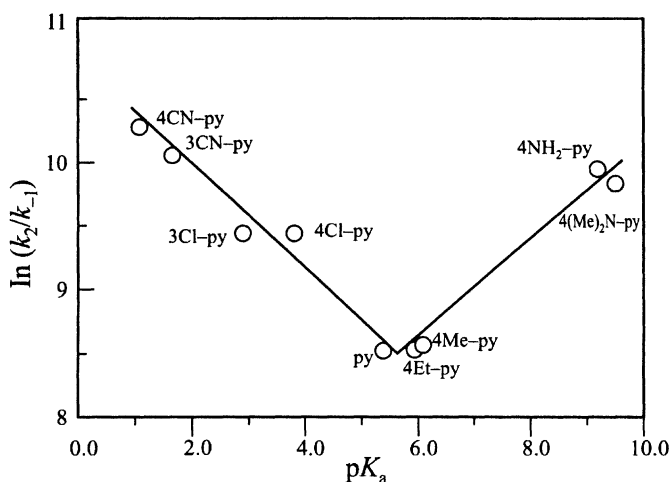


Figure 8.5.1. Dependence of $\ln(k_2/k_{-1})$ in replacement of MeOH of $[\text{Co}^{\text{III}}(\text{PP})(\text{MeO})(\text{MeOH})]$ (5×10^{-6} M) by various pyridine type ligands (2×10^{-3} M) on their pK_a values at 25 °C. The descending branch is inferred to correspond to the decrease in metal $\rightarrow$ ligand π bonding and the ascending branch to the increase of σ bonding.³⁴

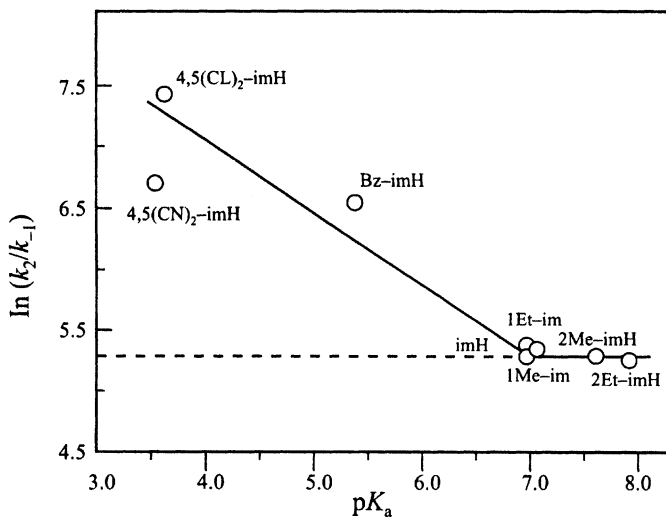


Figure 8.5.2. Plot analogous to that in Figure 8.5.1 but for the entering imidazole type ligands. For pK_a between 6.5 and 8 the reaction rates are practically independent of the pK_a of entering imidazoles.³⁴

already quite basic, relative to the pyridine ligand, the basicity increase of the substituted imidazoles is not likely to have an additional effect on the rate.

As already mentioned for pyridine and imidazole entering ligands and their derivatives, we should primarily consider ligands exhibiting σ and cobalt(III)

→ ligand π bonding. Since electron-withdrawing ligands will promote π bonding, while electron-donating ligands will favor σ bonding, stabilization of the transition state between the reaction intermediate $[\text{Co}^{\text{III}}(\text{PP})(\text{MeO})]$ and the entering ligands L should have its minimum at a certain $\text{p}K_{\text{a}}$ of LH^+ . It can be inferred from Fig. 8.5.1. that the cobalt(III) → ligand π bonding in the transition state is more important (higher rates) than the ligand σ bonding.

The equilibrium constants K for the substitution of coordinated water in the iron(III) porphyrin microperoxidase-8 (Fig. 8.5.3.) by various azoles have been determined⁷² in aqueous MeOH (vol. fraction 20%) and a linear relationship between $\log K$ and $\text{p}K_{\text{a}}(\text{LH}^+)$ (L = entering azole) was found. (The iron(III) porphyrin microperoxidase-8 was obtained from proteolytic degradation of horse heart cytochrome).*

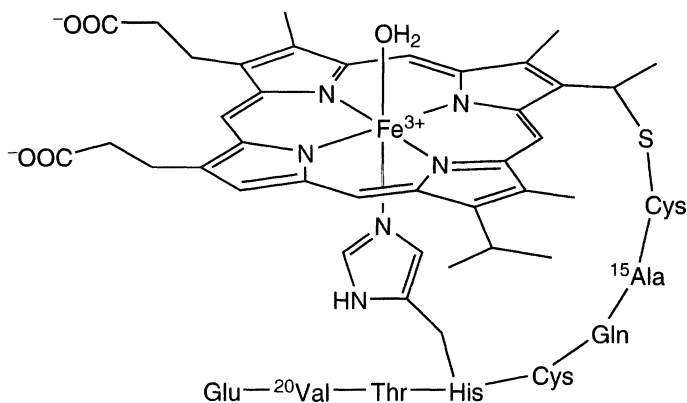


Figure 8.5.3. Microperoxidase-8 is a heme octapeptide: Glu (glutamic acid), Val (valine), Thr (threonine), His (histidine), Cys (cysteine), Gln (glutamine), Ala (alanine).

The authors⁷² have pointed out that the important factors, which determine the preference of iron(III) porphyrins for imidazole (as histidine) over pyridine and amines, are group-specific factors > basicity > π bonding.

The equilibrium constant K for the substitution of coordinated H_2O in the cobalt(III) corrinoid aquacyanocobamide (vitamin B_{12}) by various amines and six-membered heterocycles in aqueous solution was determined by the same authors;⁷³ the results have special relevance to the mentioned work.³⁴ In the quoted paper,⁷³ the CN^- ligand is firmly held and can be considered inert (at least in the dark), while the H_2O ligand is kinetically very labile; in addition, the reaction took place in aqueous solution and is of dissociative nature (I_{d} type⁷⁴). Analogously, in the (MeOH) and (MeO) replacements³⁴ methoxide

* Proteolytic enzymes catalyze the hydrolysis of the peptide bond. The majority of proteolytic enzymes also catalyze different but akin reactions, e.g., hydrolysis of the ester bond.

is firmly held while the MeOH ligand is kinetically labile. The solvent is methanol, and the mechanism is also dissociative (D type). Of course, the chelate is different and, what appears to be most important, the orienting ligand *trans* to the leaving ligand is different: in one case³⁴ this is methoxide, an excellent electron donor, while in the other case, in the vitamin B₁₂ replacement, the orienting ligand is cyanide, which can function as an electron-withdrawing ligand (Hammett's σ_m and σ_p are 0.56 and 0.66, respectively). The data reported in ref. 34 also show the importance of group factors: the replacement rates of pyridine derivatives are higher than those of imidazole derivatives. Just an opposite observation was made by the previously mentioned authors⁷² in the replacement of coordinated water in iron(III) porphyrin microperoxidase-8. Furthermore, the replacements in vitamin B₁₂ show a linear free energy relationship, *i.e.*, $\log K = a(pK_a) + b$, while in the replacements of coordinated MeOH, generally speaking, the dominant trend is: the smaller the pK_a , the larger the k_{obs} at pK_a smaller than 6. It appears that, besides all the mentioned factors that direct metal $\rightarrow$ ligand bonding, such as group-specific factors, basicity of L, and π bonding, there can be a dominant influence of the orienting ligand *trans* to the leaving ligand, like in the case of the methoxo complex.³⁴

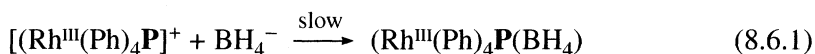
Finally, it should be mentioned that the replacement rates of coordinated methanol,³⁴ supposedly related to the metal $\rightarrow$ ligand π bonding, are associated with negative entropies of activation, as one would expect because of the increased order in the reaction transition state due to π bonding (and solvent association).

Regarding the basicity of the methoxide orienting ligand, it should be stressed that alkoxides are excellent electron donors. The following sequence is observed: methoxide < isopropoxide < *sec*-butoxide. One should bear in mind that methoxide in methanol is a stronger base than hydroxide is in water,^{75,76} and obviously an excellent electron donor, much better than hydroxide in aqueous solution. Higher energy is required to separate methoxide from its proton (or from the positive metal center) in methanol than for analogous separation of hydroxide in aqueous solution.

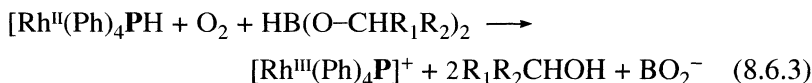
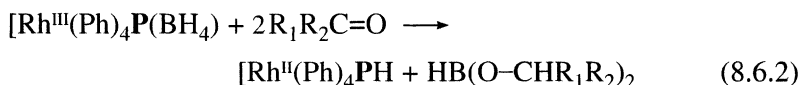
M. L. Tobe and co-workers studied the influence of L on the rate of acid hydrolysis of $[\text{Co}^{\text{III}}(\text{en})_2\text{LCl}]^+$ yielding $[\text{Co}^{\text{III}}(\text{en})_2\text{LH}_2\text{O}]^{2+}$. They arranged the L groups in order of decreasing tendency to donate electrons to cobalt and increasing tendency to accept electrons.⁷⁷ The hydroxide ion is considered to be the strongest electron donor among the 21 ligands listed. The electron donating ability of CN^- is placed much below that of OH^- . On the other hand, there are reports that CN^- is a better donor than OH^- . Besides, it is difficult to discern the modes of bonding of ligands which can form σ bonds as well as ligand to metal and metal to ligand π bonds.^{78,79}

8.6. CATALYTIC ACTION OF METALLOPORPHYRINS

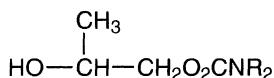
Molecular oxygen and a metalloporphyrin represent a potential catalytic system. Thus, it has been shown⁸⁰ that $[\text{Rh}^{\text{III}}(\text{tetraphenylporphyrinato})\text{Cl}]$ is a very efficient catalyst for the reduction of a ketone to alcohol in the presence of oxygen and NaBH_4 in tetrahydrofuran. The rate-determining step is reaction (8.6.1), in which the metalloporphyrin catalyst is formed, serving as a generator of borane (BH_3), which can be then transferred to ketone (P = porphyrinato):



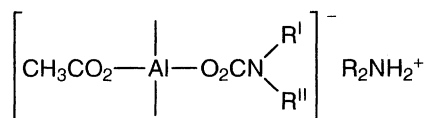
If borane were not bonded to rhodium, it would undergo oxidation with molecular oxygen and subsequent hydrolysis, yielding boric acid and hydrogen. The overall reduction of ketone to alcohol proceeds through steps (8.6.2) and (8.6.3), involving dialkylborane:



An interesting example of the catalytic action of a metalloporphyrin is the fixation and activation of CO_2 on Al porphyrin where, in the presence of the secondary amine and an epoxide, 2-hydroxypropyldiethylcarbamate



is formed in a 47% yield, under mild conditions⁸¹ (atmospheric pressure, room temperature). Carbon dioxide first binds to $[\text{Al}^{\text{III}}(5,10,15,20\text{-tetraphenylporphyrinato})\text{acetate}]$ in the *trans* position relative to the acetate; in the presence of a secondary amine an intermediate,



is formed. The intermediate reacts with the epoxide, so the final product is the mentioned carbamate, while the catalyst is regenerated.

The metalloporphyrin system can also mediate in the oxidation of mercury to Hg^{2+} ion.

The mediator is the catalase enzyme with the prosthetic group of the iron-(III) protoporphyrin IX core.⁸² It is considered that this oxidation takes place in the blood, thus preventing, or at least reducing, the migration of mercury into the brain, where the consequences would be disastrous.

The peroxidase enzyme, which has the same prosthetic group as catalase, can oxidize mercury only in the presence of hydrogen peroxide whereas catalase can do it even in the absence of hydrogen peroxide.⁸³ Thus, peroxidase from horse-radish root oxidizes mercury into its divalent ion by a simple two electron shift from mercury to the iron heme of the peroxidase system, the enzyme being the oxidizing agent, which permanently regenerates in the reaction with hydrogen peroxide.⁸³

Several papers have emphasized the special catalytic ability of various cofacial porphyrins to reduce molecular oxygen into water⁸⁴, the metalloporphyrin catalyst being adsorbed on the graphite electrode. The cofacial phthalocyanine dimer with a 4-atom bridge, adsorbed on the electrode, proved to be a good catalyst for electroreduction, enabling a four-electron reduction of the molecular oxygen⁸⁵ (phthalocyanines are tetraazatetrabenzo derivatives of porphyrin). Unfortunately, the dimer is not stable and loses its activity with time. Later, a more stable phthalocyanine dimer, with a bridge of five covalently bonded atoms, was prepared.⁸⁶⁻⁸⁸ These dimers are soluble in organic solvents, and are thus easily purified and characterized. Figure 8.6.1 depicts a phthalocyanine

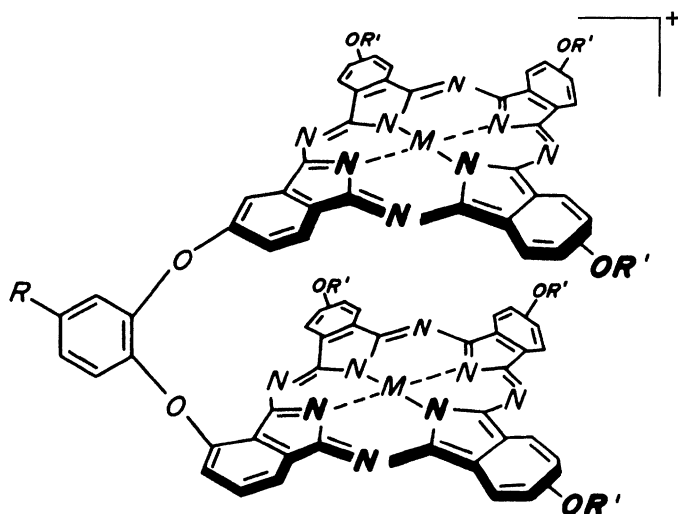


Figure 8.6.1. Cofacial phthalocyanine dimer with a 4-atom bridge,⁸⁷ adsorbed on an electrode, is a catalyst for electroreductions. The central metal atom is cobalt. (Reproduced by permission from C. C. Leznoff and the National Research Council of Canada).

dimer with a 4-atom bridge, derived from catechol, in a cofacial conformation.

The electrochemical properties of such μ -dimers (involving two bridged metals) depend very much on the length and the nature of the bridge. This research is still in progress.

8.7. WHY ONLY PORPHYRINS, BUT NOT THEIR ISOMERS, IN NATURE

In 1929, Hans Fischer completed the synthesis of hemin (also spelled haemin). He was awarded the Nobel Prize for chemistry for 1930.*

In 1986, Emanuel Vogel, professor of organic chemistry at the Institute of Organic Chemistry in Cologne, synthesized porphycene, the first artificial porphyrin isomer.⁸⁹ Until then nobody had succeeded in synthesizing a stable macrocyclic compound of four pyrroles and four sp^2 -hybridized carbon atoms, other than porphyrin. For some time it was thought that if people could not do it, probably even nature could not do it either.⁹⁰ In the meantime, the synthesis of porphycene was successfully completed, see Figure 8.7.1:

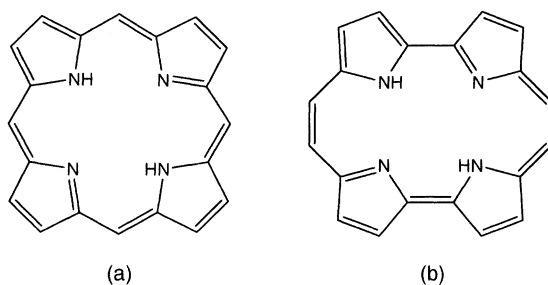


Figure 8.7.1. (a) porphin, and (b) porphycene.

* HANS FISCHER, 1881–1945, a German biochemist, was awarded the Nobel Prize for chemistry in 1930 for research into the constitution of hemin and chlorophyll. After receiving his Ph.D. in chemistry from the University of Marburg (1904) and his M.D. from the University of Munich (1908), Fischer worked as a physician and in medical research. He became a professor of medicinal chemistry at the University of Innsbruck, Austria. Five years later, in 1921, he returned to Munich as professor of organic chemistry. By splitting in half the molecule of bilirubin, a bile pigment related to hemin, Fisher obtained a new acid in which a part was still intact. He identified its structure and found it to be related to pyrrole. This made it possible to synthesize hemin from simpler organic compounds of known structure. He synthesized porphyrin in 1926 and hemin in 1929. He also established a close relationship between hemin and chlorophyll and showed that magnesium in chlorophyll is bonded in the same way as iron(II) is in hemin. This enabled him to establish the final structure of chlorophyll, and by the time of his death he had nearly completed the synthesis of chlorophyll. In 1945, almost at the end of the Second World War, his institute was bombed, and further research was made impossible, which probably led him to commit suicide.

It has been shown that the free space for metal coordination is smaller in porphycene than in porphyrin ($283 \times 263 \text{ pm}^2$ and $289 \times 289 \text{ pm}^2$, respectively), this being the reason for somewhat higher probability of metalloporphyrin formation.⁹¹ Thus, it was shown that the earlier claim that the porphyrin isomers cannot be prepared because they are unstable is not correct.

Very soon, other isomers of porphyrin and the analogous macrocycles were also synthesized: corrrhycene, hemiporphycene and *N*-confused porphyrin.

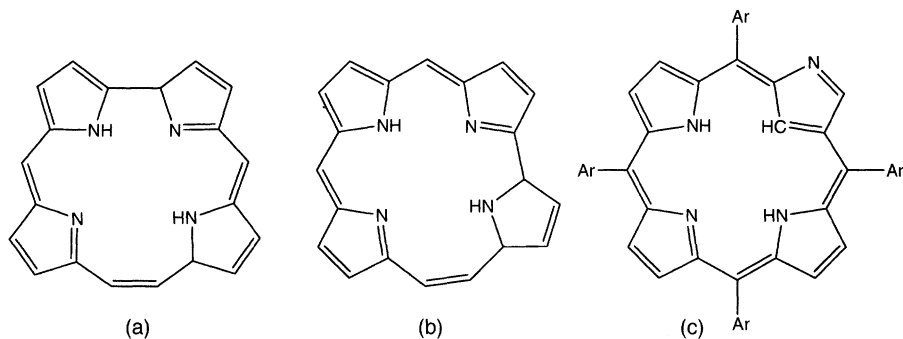


Figure 8.7.2. (a) corrrhycene, (b) hemiporphycene, (c) *N*-confused porphyrin; (Ar = aryl).

After preparation of various porphyrin isomers, a large number of papers were devoted to the study of the influence of geometry, the size of metal ion, steric interferences, and macrocycle deformations, with the purpose to offer the answer to the question: *why only porphyrins in nature*.

8.8. NITROSOAMINE COMPLEX OF METALLOPORPHYRIN, A PROBABLE INTERMEDIATE IN THE MECHANISM OF NITROSOAMINE ACTIVATION OF CANCER

Nitrosoamines ($\text{RNN}=\text{O}$) are generally considered to be carcinogenic. Nitrosoamines interact with heme-containing molecules, *e.g.* with cytochromes, or with hemoglobin, forming various adducts. Recently, George B. Richter-Addo and coworkers from the University of Oklahoma have been interested in determining how biologically active metal-NO compounds are involved in generating carcinogenic nitrosoamines *in vitro* and *in vivo*. They prepared a complex of the heme type containing nitrosoamine bonded to iron.⁹² It is presently known that nitrosoamine ligands are bonded by σ bonds over oxygen to the porphyrin iron(III) center. It appears that such bonds form more easily than previously thought, suggesting that this bonding might be responsible for nitrosoamine activation of cancer (see Figure 8.8.1). The mentioned

authors presented a high-yield synthesis and crystallographic characterization of such a nitrosoamine complex, the counter ion being ClO_4^- (TTP = tetraphenylporphyrinato). The axial ligands $-\text{O}=\text{N}-\text{N}(\text{C}_2\text{H}_5)_2$ (Figure 8.8.1) appear to cause carcinogenic activity.

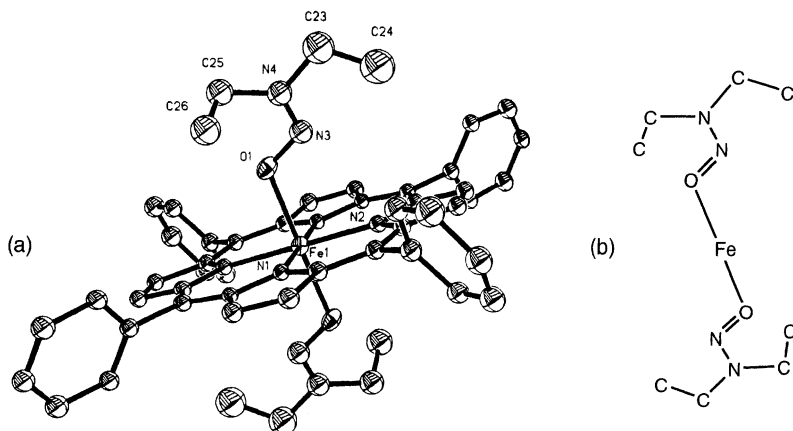


Figure 8.8.1. (a) Molecular structure of $[(\text{TTP})\text{Fe}(\text{Et}_2\text{NNO}_2)]^+$. Hydrogen atoms are omitted for clarity. Reproduced by permission from the principal author G. B. Richter-Addo,⁹² and the American Chemical Society; (b) The axial ligands (schematic).

8.9. THE SEQUENCE OF BONDED METALLOPORPHYRINS - A MOLECULAR PHOTONIC WIRE

J. S. Lindsey and R. W. Wagner⁹³ prepared a “wire” of interconnected metalloporphyrin complexes, which acts as a photonic molecular wire. Allegedly, Lindsey was inspired by chlorophyll complexes, which in principle act as a photonic wire at the molecular level.⁹⁴ These complexes absorb sunlight and in the reaction centers transform the light energy into chemical energy. Lindsey wanted to imitate this process and conceived a linear sequence of five pigments based on porphyrin macrocycles with the task to absorb and emit light in a solution. At one end of such a photonic wire was a boron-dipyromethylene dye (a porphyrin fragment), which absorbed the blue-green light. An excited state resulted and was transferred through the “wire”, assembled of three zinc-porphyrin complexes, to a porphyrin macrocycle containing no metal but with the ability to emit red light fluorescence. The efficiency of the transmission was about 76%. The molecular photonic wire bears some similarity to optical fibres. The authors hope that such a photonic wire will find application in the information technology. Figure 8.9.1 shows the structure of a photonic wire composed of metalloporphyrin complexes.⁹³

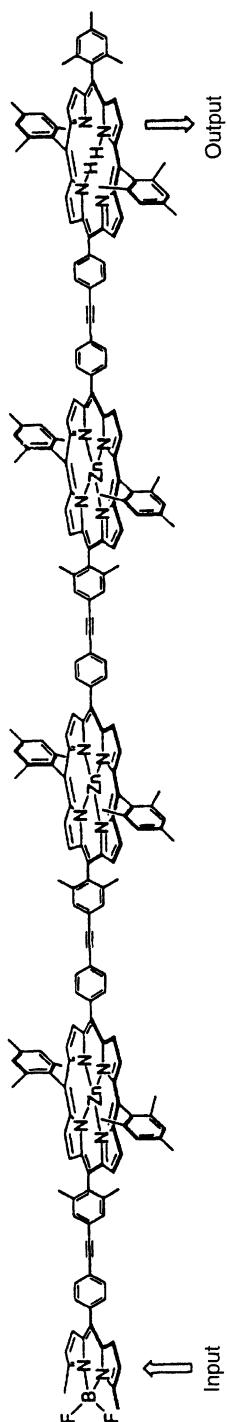


Figure 8.9.1. Molecular photonic wire composed of metalloporphyrin complexes (reproduced by permission from the senior author, J. S. Lindsey,⁹³ and the American Chemical Society).

8.10. METALLOPORPHYRINS, METALLOPHTHALOCYANINES AND ANALOGOUS COMPLEXES IN PHOTODYNAMIC THERAPY OF CANCER

8.10.1. Introduction

Phototherapy is the use of light (near the visible spectral region) in medical therapy.

Light can be applied:

(a) Directly, without using light-sensitive chemicals, the so-called photosensitizers;

(b) Indirectly, where the light effect is achieved by a photosensitizer, introduced into the organism. Such compounds, sensitive to light, are, in principle, metalloporphyrins, metallophthalocyanines (Figure 8.10.1), and similar compounds.

It is generally considered that phototherapy was introduced into medicine by N. R. Finsen,⁹⁵ a Danish physician.* The use of light-sensitive metal com-

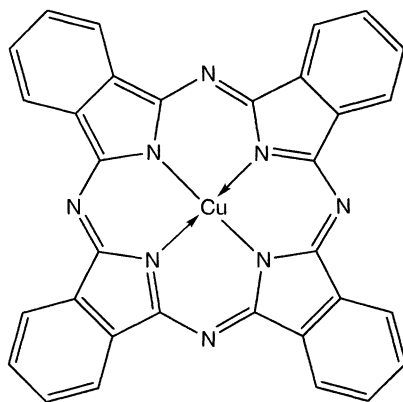


Figure 8.10.1. Copper(II) phthalocyanine.

* NIELS RYBERG FINSEN, 1860–1904, Danish physician, founder of modern phototherapy, received the 1903 Nobel Prize for medicine for the application of light in the treatment of skin diseases. While a student at the University of Copenhagen, Finsen became interested in the effect of light on living organisms and found that lengthy exposure of smallpox patients to the red light, obtained by filtering off the violet part of the spectrum, prevents suppuration of the pustules. Aware of the bacteria-destroying effects of sunlight, he developed an ultraviolet treatment for *lupus vulgaris*, a form of skin tuberculosis. His treatment was a great success. Finsen's work led to the use of ultraviolet sterilization techniques. His original apparatus for radiation using the light spark obtained by carbon electrodes is kept at the *Science Museum* in London.

plexes has become a very active field in tumor therapy, and is known under the name photodynamic therapy (PDT).⁹⁶ The term was coined according to the German expression *photodynamische Wirkung* to describe the damage of the living tissue by a combination of photosensitizer, visible light and oxygen. The idea underlying tumor phototherapy is to find a good sensitizer that shows some selectivity for photodamage to tumor tissue. In principle, the compounds sensitive to light are metalloporphyrins, metallophthalocyanines and similar complexes.

PDT destroys tumors by exposing them to light. A light-activated drug is injected into the patient's blood stream or tumor and the tumor is then exposed to light in a controlled manner, thus destroying the tumor cells while having little or no effect on healthy tissue. In comparison with conventional chemotherapy, the great advantage of this treatment is that the drug action is confined to the illuminated tumor site. Thus, the damage to healthy tissue is minimized and side effects are significantly reduced.^{97,98} Red laser light is commonly used. A tetrapyrrolic macrocycle such as the porphyrin can be employed as the photosensitizing agent.

The photosensitizer is administered intravenously. Time allowed for equilibration within the body is 3–96 hours, depending on the sensitizer. The photosensitizer selectivity for tumor cells, as compared to normal cells, is 3:1 for extracranial tumors, but up to 50:1 for brain tumors.⁹⁷

Tumor tissue fluoresces more strongly than the surrounding tissue because of the present porphyrin. The real photodynamic agent is singlet oxygen, $O_2(^1\Delta_g)$, high in energy, as shown in Table 8.10.1:

Table 8.10.1. Electronic configurations of O_2 molecule

State	π_a^*	π_b^*	Energy/kJ mol ⁻¹
$^1\Sigma_g^+$	↑	↓	155 ($\hat{=}$ 13 000 cm ⁻¹)
$^1\Delta_g$	↑↓	—	92 ($\hat{=}$ 8 000 cm ⁻¹)
$^3\Sigma_g^-$	↑	↑	0 (ground state)

The lowest energy is that of $^3\Sigma_g^-$ with two electrons in π^* orbitals; in the excited singlet state ($^1\Delta_g$) oxygen has an appreciable energy, and a much longer life-time than in the $^1\Sigma_g^+$ state, which enables reactions with various unsaturated organic compounds.

In principle, the cytotoxic agent is generated without chemically transforming the sensitizer, which is thus available to absorb another photon and repeat the cycle. Therefore, if there is enough oxygen, a single photosensitizer molecule is capable of repeatedly sustaining its own concentration.

If we consider the energy levels of an He atom with its two electrons, we know that the ground configuration is $1s^2$. It can be expected that in the excited configuration $1s^1 2s^1$ one electron is promoted into a $2s$ orbital. The two electrons need not be paired since they occupy different orbitals. The arrangement with parallel spins ($\uparrow\uparrow$) lies lower in energy than that with paired spins ($\uparrow\downarrow$). According to Hund's rule, both states are allowed and can contribute to the spectrum of the atom.

Parallel and antiparallel (paired) spins differ in their overall spin angular momentum. In the paired case, the two spin momenta cancel, yielding a zero net spin. The paired-spin arrangement is called a singlet. The angular momenta of two parallel spins add up and the result is a total spin of one, yielding a triplet state.

The parallel spin arrangement, *e.g.*, of helium, in configuration $1s^1 2s^1$ is lower in energy than the antiparallel arrangement of the triplet in the arrangement $1s^1 2s^1$. The conclusion can be drawn that the triplet state generally lies lower than the singlet state, this being due to the effect of spin correlation on the Coulombic interactions between electrons. The difference in energies between singlet and triplet states can be very large. Singlet and triplet states of helium differ by 77 kJ mol^{-1} .⁹⁹

8.10.2. Red light for photodynamic therapy: metallotexaphyrins of lutetium and gadolinium as photosensitizers in cancer therapy

*Chemistry in Britain*⁹⁸ tells a story about Jonathan Sessler, a PhD student of chemistry at Stanford University, California, who was diagnosed with Hodgkin's lymphoma. During one of his distressing chemotherapy sessions the young doctor who treated him said – You are a chemist, you ought to find a better anticancer drug. Twenty years later this student became a professor at the University of Texas, and two anticancer drugs, the “texaphyrins” of lutetium and of gadolinium, designed by Sessler's team, exhibited clear activity. Since the compounds were designed in Texas, their name appeared logical.

The texaphyrins are, in principle, based on porphyrins. They contain five nitrogen atoms around the metal, not four like porphyrins (Figure 8.10.2). This allows them to form complexes with large trivalent lanthanides, which exhibit useful cancer therapy properties. The lutetium(III) texaphyrin has a coded name PCI-0123, also known as “Lutex”. It absorbs light in the far red of the visible spectral region, penetrating very deep, showing a 10:1 preference for malignant cells as compared to normal cells. When “Lutex” is irradiated with red light, it yields singlet oxygen (see Table 8.10.1), which is, because of its high energy, able to destroy cancerous cells.

Even more important is the gadolinium texaphyrin (coded PCI-0120). The central metal atom is gadolinium(III). It is a very effective radiation sensitiz-

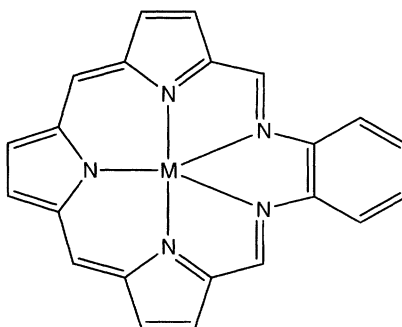


Figure 8.10.2. Basic structure of metallotexaphyrin (M = metal).

er; when it is preferentially absorbed by tumor cells, red light radiation can be applied. Gadolinium absorbs the X-ray energy, causing production of an electron and a hydroxy radical. Since the electron is well stabilized by the macrocycle, the hydroxy radical lives long enough to destroy the tumor cells.¹⁰⁰ *Chemistry in Britain* reports that the U.S. National Cancer Institute has included texaphyrins into its Decision Network for further trials.⁹⁸ The great advantage of the photodynamic treatment is that the drug action is limited to the illuminated tumor section, thus the damage to healthy tissue is very small. The disadvantage is that the PDT therapy is based on hem type complexes which are activated by visible light and in the presence of oxygen. But, deep in the tissue there is not enough oxygen, so the PDT is applicable to such tumors as those of the skin or possibly the bladder.

The texaphyrin action can be followed with an MRI scanner (Magnetic Resonance Imaging).

The MRI technique (*zeugmatography*) is a method of looking inside the body by applying magnetic field and radio waves. It is based on nuclear magnetic resonance in which magnetic field and radio waves cause atoms to give off tiny radio signal outputs from the body's tissue. The method was described in 1972 by Paul Lauterbur, an American scientist. His first MR image was published in 1973. Practically simultaneously, Raymond V. Damadian, also an American scientist, observed that different kinds of animal tissue emit proton response signals that vary in length, and that cancerous tissue emits response signals that last much longer than those of healthy tissue. He patented his observation in 1974.

The MRI technique is very difficult to apply to the lungs because they mostly contain air and water. In order to obtain an MRI image, the organ must contain atoms with polarized nuclei. An inert highly polarized gas can, in principle, be used, where the high concentration of polarized nuclei provides a sharp contrast in MRI. The US FDA (Food and Drug Administration), however, has not yet approved the commercial distribution of inert gas imaging equipment, because of the still undergoing trials.⁹⁸⁻¹⁰¹

It is generally accepted that singlet oxygen is involved in the photodynamic therapy, but this is very difficult to prove.⁹⁶ The observation that singlet oxygen can be detected from porphyrin, adsorbed on the cell surface, supports this assumption.¹⁰²

8.11. SOME MODELS OF METALLOENZYMES

Lately, extensive research has been devoted to metalloenzymes.^{103–105} Thus, carbonic anhydrase is a very effective catalyst for conversion of CO_2 to carbonic acid (H_2CO_3), and *vice versa*.¹⁰⁶ This enzyme is found in red blood cells, gastric mucosa, pancreatic cells, and renal tubules. Carbonic anhydrase plays an important role in respiration by influencing CO_2 transport in the blood. The enzyme also functions in the formation of hydrochloric acid by the stomach.

In carbonic anhydrase, zinc is coordinated to a water molecule and to three imidazole groups belonging to histidine residues (Figure 8.11.1). The classi-

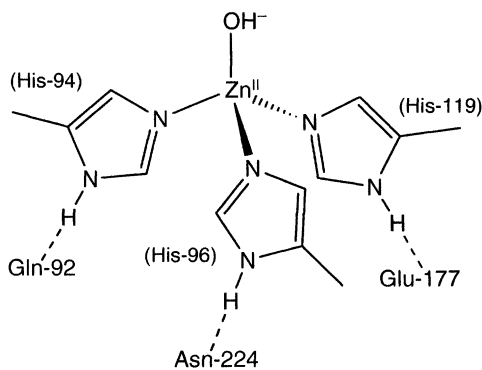
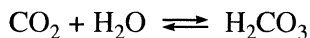


Figure 8.11.1. Carbonic anhydrase.

cal work of Riepe and Wang¹⁰⁷ explained the catalytic action of this enzyme. At physiological pH, CO_2 is in the form of the HCO_3^- ion, because the OH^- , being bonded to zinc, attacks CO_2 . The water molecule bonded to zinc is more acidic than water in an aqueous solution of fully hydrated Zn^{II} ions.¹⁰⁵ This is so because the oxygen electrons of the coordinative bond toward zinc are more engaged than in the hydrated zinc ion. Thus, the oxygen electron density directed towards hydrogens is reduced, and the protonic character of hydrogen is increased. As a consequence, $\text{p}K_a$ decreases from about 9 in aqueous solution to about 7 in carbonic anhydrase. Deprotonation of the water molecule coordinated to zinc yields bonded OH^- as an extraordinary nucle-

ophile, which then attacks CO_2 , transforming it to HCO_3^- . A reaction as simple as the conversion of CO_2 to H_2CO_3 , *i.e.*,



requires enzymatic catalysis in biological systems, which makes this reaction one of the fastest enzymatic reactions known. Each enzyme molecule can transform 10^5 molecules of CO_2 into HCO_3^- in a second. This enables a very effective transfer of CO_2 from tissue to blood.

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Chapter 9

METALLOCENES, STRONG ELECTRON DONORS

9.1. INTRODUCTION

For many years it was puzzling that metal atoms, which were not considered good Lewis acids, could form adducts with CO, considered to be a poor donor toward most Lewis acids. An example is the hexacarbonylchromium, $\text{Cr}(\text{CO})_6$. On the other hand, it was stressed that chromium, having 24 electrons, by accepting 6×2 electrons from 6 CO molecules, will fill its orbitals to a total of 36 electrons, which is the electron configuration of krypton. The LCAO approximation method (linear combination of atomic orbitals) helped to explain the stability of these adducts as being due to a two-way acid-base interaction between the metal and CO: the metal synergically interacts with CO, acting as an acid and a base, while CO simultaneously behaves as a donor and acceptor. In 1955 Ernst Otto Fischer, University of Munich, showed that an increase of the number of chromium electrons to 36 can be achieved by three π -electron pairs of benzene, like, *e.g.*, in benzenetricarbonylchromium, $(\text{C}_6\text{H}_6)\text{Cr}(\text{CO})_3$. Cyclopentadienyl, C_5H_5^- , has also been known to form compounds with metal atoms.

Ferrocene was discovered in 1951,¹ and an extensive exploration of metallocene chemistry followed.²⁻⁴ X-ray studies, as well as a variety of other physical and chemical evidence, showed that ferrocene has a “sandwich” structure. For their pioneering work on the chemistry of metallocenes, Ernst Otto Fischer, Technische Universität München, and Geoffrey Wilkinson (Imperial College London) shared the Nobel Prize in 1973. Ferrocene was shown to be the bis(pentahaptocyclopentadienyl)iron, $(\eta^5\text{-C}_5\text{H}_5)_2\text{Fe}$.

There are basically three types of complexes formed by $\eta^5\text{-C}_5\text{H}_5^-$, $\eta^6\text{-C}_6\text{H}_6$, and related molecules⁵ (Figure 9.1.1):

A. $(\pi\text{-R})_2\text{M}$ are symmetrical “sandwich” type complexes represented by ferrocenes **1a** and **1b** (staggered and eclipsed conformations, respectively); by dibenzenechromium (**2**), and by $(\eta^5\text{-cyclopentadienyl})(\eta^6\text{-benzene})$ manganese (**3**);

B. $(\eta^5\text{-C}_5\text{H}_5)_2\text{ML}_x$ are bent metallocenes where L represents some other ligands, such as H^- , R^- , halide, olefin, or NO. An example is **4**.

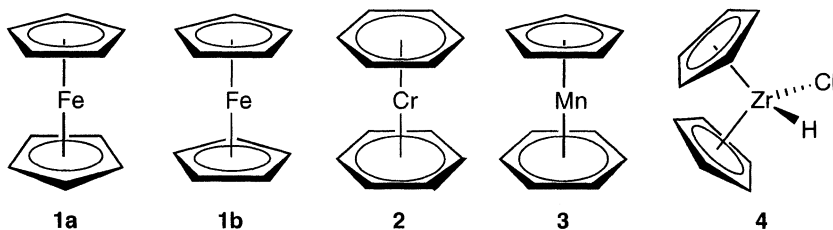


Figure 9.1.1. Some basic types of metallocenes.

The “sandwich” structure of ferrocene and its extraordinary thermal stability (up to 500 °C) have contributed to the extensive and still lively research in the field.

As already mentioned, stable organometallic compounds of transition metals have a total of 18 valence electrons around the metal, *i.e.*, they have the “effective atomic number” (EAN) of the next higher inert gas.⁶ There are exceptions. Molecules having only 16 valence electrons can be just as stable as the 18-electron molecules of the same metal.

9.2. BONDING IN THE $[\eta^5\text{-(C}_5\text{H}_5)_2\text{Fe}]$ COMPLEXES

Cyclopentadiene is a weak acid ($\text{p}K_{\text{a}} \approx 20$) and reacts with various bases to give salts. Owing to the stability of the C_5H_5^- anion, the cyclopentadienyl-metal compounds were treated as if containing C_5H_5^- anion and metal cation. Thus, ferrocene is commonly regarded as being composed of Fe^{2+} cation and 2 C_5H_5^- anions. The Fe^{2+} in ferrocene has 3 d-electron pairs (3d^6 configuration), and pentadienyls have 3 π pairs per one ($\eta^5\text{-C}_5\text{H}_5^-$), which makes a total of $(3 + 2 \times 3) = 9$ pairs, or 18 valence electrons. This is also the EAN of the next higher inert gas, krypton, and explains the extremely high stability of ferrocene (melting point 174 °C; boiling point 249 °C).

The nature of bonding between a transition metal and an unsaturated ring is well understood, but the picture can still be improved in quantitative sense.⁷⁻⁹ It appears that bonding does not depend critically on whether the rotational

orientation of the pentadienyl rings in $(\eta^5\text{-C}_5\text{H}_5)_2\text{M}$ is staggered (Figure 9.1.1, conformation **1a**), or eclipsed (Figure 9.1.1, conformation **1b**).^{10–13} In any case, the rotation barrier is low (about 8–20 kJ mol⁻¹). In condensed phases, especially crystals, where there are intermolecular energies of the same or greater magnitude than the barrier, either configuration may be found.¹⁰

The overlap of metal d orbitals (d_{z^2} , d_{xz} and d_{yz}) and the cyclopentadienyl π molecular orbitals is excellent.¹⁰

9.3. STABILITY OF α -METALLOCENYL CARBOCATIONS*

Metallocenes undergo most of the typical aromatic reactions, *e.g.*, Friedel-Crafts acylation, sulfonation, *etc.* The Friedel-Crafts acylation occurs 3×10^6 times faster than that with benzene.¹⁴

The great stability of α -metallocenyl carbocations is well known.^{15–22} The best demonstration of the electron releasing effect of the ferrocenyl group is the isolation of its stable salts.²³ There is general agreement that electrons from the region between the two cyclopentadienyl rings are most effective in accounting for this stability. The observed rate enhancement due to the ferrocenyl group (Fc), as compared to that of the phenyl group,²⁴ and the stereospecificity of solvolysis, may be explained either by model A involving conjugation with the π system¹⁶ or by model B involving metal participation^{25–29} (Figure 9.3.1). The study of the secondary α -deuterium kinetic isotope effect (α -D KIE) can, under certain circumstances, help solve this problem.

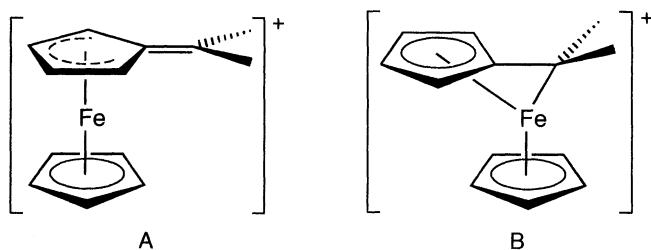


Figure 9.3.1. Possible structures of the ferrocenylmethyl carbocation, involving conjugation with the π system (A), and involving Fe–C_{exo} bond formation (B).

* The term carbonium ion has a long tradition in organic chemistry. This ion has an electron-deficient carbon with a sextet of electrons. The name has been challenged because comparable oxonium ions (*e.g.*, H_3O^+) and ammonium ions (NH_4^+) have electron octets, and the terms carbocation or carbenium ion have been suggested and are used in this book.

9.4. SECONDARY α -DEUTERIUM KINETIC ISOTOPE EFFECT AND THE STRUCTURE OF FERROCENYLMETHYL CARBOCATION TYPE TRANSITION STATE

The secondary α -D KIE (kinetic isotope effect) is a powerful tool for elucidation of the mechanism of nucleophilic substitutions. After the first observation of a sizeable α -D KIE in the presumed carbocation processes reported independently by four different groups,^{28–33} these effects were used to determine whether a mechanism is a dissociative or a synchronous displacement (the $k_H/k_{\alpha-D}$ ratio in the latter case being around 1.00).

The α -D KIE effect on a limiting solvolysis is thought to be principally due to the lowering of the H–C–H out-of-plane bending force constant, which is expected to accompany the breaking of the C–X bond. The smaller effect in nucleophilic reactions may arise from a partially compensating gain of a new bending force produced by the partial covalent attachment of the nucleophile to carbon. Several review articles on this subject have been published.^{34–36}

The S_N2 transition state model can be applied to reactions involving neighboring group participation. Participation, which involves bridging, may not occur simultaneously with the departure of the leaving group so that the transition state can still resemble the reactant. On the other hand, if bridging is pronounced in the transition state, a decrease in the magnitude of the α -D KIE is to be expected.^{35,37} It has been recently suggested that α effects are reduced by σ but not π bonds.^{38,39}

9.4.1. High secondary α -deuterium kinetic isotope effects for the primary carbon-oxygen cleavage in formolysis and acetolysis of dideuterioferrocenylmethyl benzoate

A few years ago, the secondary α -D KIE effect in acetolysis of ferrocenyl-1,1-dideuteriomethyl benzoate at 298 K was determined⁴⁰ as $k_H/k_D = 1.50$ (geometric mean = 22.5% per one D). This appears to be one of the largest α -D KIE observed for carbon-oxygen cleavage. The maximum α -D KIE for an oxygen leaving group was found by other investigators^{41–44} to be about 22%.

Primary alkyl derivatives do not normally solvolyze by the limiting dissociative mechanism, hence the maximum α -D KIE for the primary derivatives is not known, but calculations^{41,44} and experiments⁴⁵ suggest that the magnitude of this effect might be larger for the primary derivatives than for the secondary ones.⁴⁶ Kinetic and stereochemical evidence has led to the conclusion that the solvolyses of β -ferrocenylalkyl tosylates are dissociative in nature and almost “limiting”.^{24,27}

As previously pointed out, the rates of solvolysis in various media can be best summarized in terms of the ionizing power and nucleophilicity of the solvent, as suggested by Winstein *et al.*^{48,49} In a limiting solvolysis, the rate depends on the ionizing power rather than on the nucleophilicity of the solvent. Thus, the rates of limiting solvolysis are about the same in solvents of comparable ionizing power but of different nucleophilicity. On the other hand, the reactions that proceed by the solvent attack on carbon, with a nearly synchronous displacement of the leaving group, proceed faster in solvents of higher nucleophilicity, the criteria that have led to the conclusion that acetolyses of β -ferrocenylalkyl tosylate are dissociative processes.²⁴

The secondary α -D KIE effect in the acetolysis of dideuterioferrocenylmethyl benzoate exhibited a special salt effect, indicating the presence of solvent-separated ion pairs and the return to contact ion pairs. The high value of the α -D KIE (geometric mean = 22.5% per one D, as mentioned above) strongly suggests that acetolysis is a limiting dissociation process with a carbenium ion-like transition state stabilized mainly by conjugation with the π system of the pentadienyl rings. This result was compared with the previously-determined α -D KIE of only 11.4% per D in ethanolyses of dideuterioferrocenylmethyl acetate and benzoate, respectively,⁴⁶ where the stabilization of the transition state probably involves some Fe-C_{exo} bond formation. On the other hand, the α -D KIE in the solvolysis of ferrocenyl-1,1-dideuteriomethyltrimethylammonium iodide in aqueous solution was found to be about 3% per one D.²² The small isotope effect supports the transition state model involving participation of electrons localized on the iron atom. The calculated H/D fractionation factors, from valence force fields, are similar for the carbon, fluorine and nitrogen leaving atoms.⁵¹ It is therefore reasonable to assume that the limiting α -deuterium isotope effect for a nitrogen leaving group should be similar to that for oxygen, fluorine, or carbon, *i.e.*, about 20% per deuterium atom, calculated for a temperature of 80 °C. It should be pointed out that 1,1-dideuterio-2-ferrocenylethyl tosylate solvolyzes²⁴ in acetone-water, at 30 °C, with $k_H/k_D = 1.27$ (*i.e.*, k_H/k_D , calculated per one deuterium atom ≈ 1.14). This isotope effect is compatible with the presence of some neighboring group participation, as evidenced by comparison with situations in which such participation is known to exist (formolysis of 1,1-dideuterio-2-anisylethyl tosylate²⁴ gives k_H/k_D of 1.11 per D at 30 °C). A larger iron participation and a smaller isotope effect should be expected for FcCD₂N(CH₃)₃I (Fc = ferrocenyl) than for Fc-CH₂CD₂OTs, because it is known that the stabilizing effect of the ferrocenyl group is larger on α than on β carbon. Of course, one should have in mind that the reaction involving a relatively poor leaving group, such as N(CH₃)₃, might involve some nucleophilic attack by solvent molecules, with consequent lessening of the α -D KIE. But, if so, it would remain unclear

why the rate of formation of the ferrocenylcarbinol, from the ferrocenyl-methyltrimethylammonium salt, is practically independent of the hydroxide ion concentration,⁵² the rate being the same in water and in aqueous sodium hydroxide (0.2 mol dm⁻³).

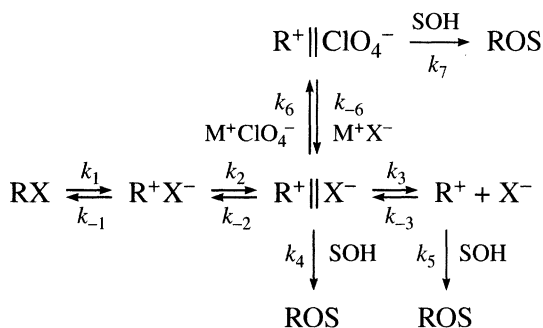
9.4.2. Possible contribution of tunneling to the high secondary α -deuterium kinetic isotope effect

The high α -D KIE, both in acetolysis and formolysis, prompted a study of the temperature dependence of the solvolysis rates, and of the α -D KIE, in order to see if tunneling might be operative.⁵⁰ That tunneling can contribute to secondary isotope effects is supported by model calculations, which predict appreciable tunnel corrections when the bending motions of the non-transferred proton are coupled with the stretching motion of the transferred proton.⁵³ Calculations also predict that tunneling can lead to the same sort of abnormal temperature dependence as observed for primary isotope effects, the ratio of Arrhenius pre-exponential factors A_H/A_D (or A_H/A_T) being significantly less than unity. An experimental example of this behavior is the reaction of $\text{PhCHTCH}_2\text{N}(\text{Me})_3^+$ with EtO^- , which gives $A_H/A_T = 0.705 \pm 0.024$.⁵⁴ Tunneling is expected to be diminished when an atom heavier than the proton is transferred, and $(k_H/k_T)_{\text{sec}}$ is in fact less when deuterium is transferred than when protium is transferred.⁵⁴ One might not expect tunneling to be important in solvolyses of ferrocenylmethyl esters because oxygen (mass 16) is now the transferred atom. The system appeared ideal for a critical test because the isotope effect is large, and it is easier to measure the temperature dependence of a large isotope effect than of a small one.

As already pointed out, the acetolysis and formolysis of dideuterioferrocenylmethyl benzoate exhibit large secondary α -D KIEs, and an abnormal temperature dependence has also been observed.⁵⁰ In the presence of LiClO_4 (ca. 0.1 mol dm⁻³), which prevents reversion from solvent-separated to contact ion pairs, k_H/k_D at 25 °C amounted to 1.53 ± 0.02 (acetolysis) and 1.48 ± 0.03 (formolysis).⁵⁰ In the presence of LiClO_4 , the ratios of Arrhenius pre-exponential factors A_H/A_D are significantly less than unity and amount to 0.49 ± 0.01 (acetolysis) and 0.38 ± 0.04 (formolysis). It has been suggested⁵⁰ that these surprisingly low values result from a change in the rate-determining step over the temperature range of about 25 °C from the formation of the solvent-separated ion pair at a low temperature to the reaction of the dissociated carbocation with solvent at highest temperatures. Values of A_H/A_D for primary deuterium isotope effects considerably lower than unity have been known for some time, and have usually been explained as a consequence of tunneling.⁵⁵

Values below unity have also been found for secondary deuterium isotope effects and have been given a similar explanation.⁵⁴

The mechanism of ferrocenylmethyl benzoate solvolysis can be best understood in terms of the Winstein mechanism for solvolysis (Scheme 9.4.1).⁵⁶ It can be assumed that, in the presence of lithium perchlorate, the solvent-separated ion pair reacts rapidly by the k_6 and k_7 route to give solvolysis products. This appears to be the major pathway. In this interpretation, the dissociation of the intimate ion pair (the k_2 step) is mainly or entirely rate determining.



Scheme 9.4.1.

Finally, one might ask if it is reasonable to ascribe the abnormal temperature dependence in the presence of LiClO_4 to tunneling. The postulated rate-determining step in this case is the conversion of the contact ion pair to the solvent-separated ion pair, so the answer depends on whether the motion of α hydrogens contributes to the motion along the reaction coordinate.⁵⁴ If the α carbon is already planar in the contact ion pair, it is difficult to see how such motion could contribute. If it is still non-planar in the contact ion pair and becomes planar as the solvent-separated ion pair forms, then the α hydrogen motion will contribute to the motion along the reaction coordinate, and a contribution of tunneling is a possibility. In any event, the low $A_{\text{H}}/A_{\text{D}}$ values can not be taken as a proof of tunneling because of mechanistic complexity.

9.5. FERROCENE ABILITY TO STABILIZE A CARBENIUM ION

The ability of ferrocene to stabilize positive charge has been recognized by several authors.⁵⁷⁻⁶⁰ Ferrocenylmethylium ions have been isolated as stable salts, *e.g.*, as tetrafluoroborates.⁶¹ Several research groups have studied the kinetics of their reactions with different nucleophiles.^{57,61-65} Crystal structure and mechanistic investigations on these ions have been published.^{25,66-68}

X-ray analysis of ferrocenyldiphenylcarbenium tetrafluoroborate⁶⁹ enabled determination of the Fe–C_{exo} distance of 271.5 pm, and showed that C_{exo} is bent to iron, the angle being 20.7°. It was calculated that the direct interaction of iron electrons with the cationic C_{exo} stabilizes the ferrocenylmethylcarbenium ion. It was concluded that the cation can be described as (η^6 -fulvene)iron with a small charge on C_{exo}. ¹³C NMR chemical shifts of the *para*-carbons in phenyl-substituted carbenium ions have been used as a probe for determining the positive charge at the carbenium center.⁷⁰ Other authors⁶⁵ also came to the conclusion that the positive charge in ferrocenylmethyl carbenium ions is only to a small extent located on C_{exo}.

A computational study of the stabilization of 2-ferrocenylmethyl cation was recently performed⁷¹ using the density functional theory (Becke3LYP). Within designated symmetry constraints, geometries were optimized with a *quasi*-relativistic effective core potential for iron and standard double zeta set 6-31G(d,p) with a set of d polarization functions for carbon and p polarization functions for hydrogen atoms. The resulting structure was found to be a hybrid of the previously proposed structures where the α -carbon is bent out of the cyclopentadienyl plane towards the iron center with no ring slippage. The formation of the ferrocenyl *vs.* benzyl cation is favored by over 100 kJ mol⁻¹. This stabilization is claimed to be due to the sharing of the positive charge by cyclopentadienyl rings, effectively spreading the charge through the ferrocenyl moiety.⁷¹

9.5.1. Solvent variations and the rates of ferrocenylmethyl ester solvolyses

More than forty years ago it was shown that triphenylmethyl (trityl) acetate solvolyzes in either aqueous dioxane or methanol almost entirely by alkyl-oxygen bond fission.⁷² In addition, a general tendency has been observed towards faster solvolyses of this type in solvents of higher ionizing power, consistent with a dissociative (S_N1) mechanism, with a carboxylate leaving group.

Recently, the solvolysis of ferrocenylmethyl acetate has been studied in 2,2,2-trifluoroethanol (TFE)-ethanol mixtures and in aqueous ethanol, acetone, and TFE.⁷⁴ For 19 solvents, a fair correlation with Y_{OTs} values has been obtained. This correlation was much improved when Y_{OTs} values were replaced with the derived solvent ionizing power (Y_{OAc}) values. The latter correlation, with a slope close to unity, supported the S_N1 assignment for ferrocenylmethyl acetate solvolyses.⁷⁴ The same authors obtained an excellent correlation against their Y_{OAc} values for α -ferrocenylethyl acetate solvolysis, as well. Since it had previously been shown⁵⁸ that the introduction of an α -methyl group into fer-

rocenylmethyl acetate leads to only a 10-fold increase in the rate of solvolysis (in 80% acetone), it was concluded⁷⁴ that most of the positive charge dispersion must be into the ferrocenyl system, and introduction of the α -methyl group provides only a minor route for further charge dispersion, which is in agreement with the already mentioned recent computations based on the density functional theory.⁷¹

9.5.2. Relative rates of ferrocenylmethyl benzoate solvolyses in formic and acetic acid

A kinetic study of the acetolysis of trityl acetate was carried out earlier.⁷³ The measured specific rates were about 300 times higher than the predicted values.⁷⁴ A possible explanation, consistent with the powerful catalysis by mineral acids of solvolyses in aqueous-organic solvents,⁷² is that the actual reactant in acetic acid is not the neutral acetate but an equilibrium concentration of the faster reacting protonated species,⁷⁴ a general idea suggested previously.⁷⁵

As already pointed out, the stabilization of the ferrocenylmethyl carbenium ion can be explained either by involving conjugation with the π system of pentadienyl rings (model A), or by involving metal participation (model B), Figure 9.3.1. The extremely high α -D KIEs for both formolysis and acetolysis of 21.7 and 23.8%, respectively (geometric means calculated per one α -D, at 298.16 K) strongly suggest that both solvolyses are S_N1 processes and that the direct participation of iron electrons to α -carbon can be neglected.

However, the most unusual feature is the observation of lower solvolysis rates in formic acid than in acetic acid.⁵⁰ Table 9.5.1 contains Y (ionizing power) and N (nucleophilicity) values for formic acid, acetic acid, and 100 and 96%

Table 9.5.1. Characterization of some solvents in terms of their ionization power Y , and nucleophilicity N

Solvent	<i>t</i> -Butyl chloride scale ⁷⁶		2-Adamantyl tosylate scale ⁷⁷	
	Y	N	Y	N
HCOOH	2.05	-2.05	3.04	-2.35
CH ₃ COOH	-1.64	-2.05	-0.61	-2.35
100% EtOH	-2.03	0.09	-1.75	0.00
96% EtOH	-1.40 ^(a)	0.07 ^(b)		

^(a) Interpolated from the data: -2.03 (100%), -1.68 (98%), -1.29 (95%), 0.00 (80%), 0.60 (70%), EtOH (from ref. 76).

^(b) Because water and ethanol are of comparable nucleophilicity, its change in EtOH-H₂O mixtures is small (ref. 78); interpolated from the data for 100, 90, and 80% EtOH (from ref. 76).

(vol. fraction) ethanol. We can see that both acids are equally poorly nucleophilic, but the difference in their ionizing powers is large.

The mentioned results of Kevill *et al.*,⁷⁴ who found that the rates of ferrocenylmethyl acetate solvolyses increase with increasing the solvent ionizing power, and the observation of close similarity in reaction rates of formolysis and acetolysis of ferrocenylmethyl benzoate,⁵⁰ despite the large difference in ionization power of these two acids,⁵⁰ prompted a reinvestigation of the mentioned kinetic data.⁵⁰ The new measurements⁷⁹ fully support the earlier results.

The close similarity in reaction rates of formolysis and acetolysis could be explained by the reaction involving the protonated ester, as discussed by Kevill *et al.*⁷⁴ They pointed out that the rates of S_N1 solvolyses with a neutral leaving group are virtually insensitive to changes in the solvent ionizing power.⁸⁰ If so, the new problem was discussed by the same authors,⁷⁴ why formolysis rates are actually lower than one would expect based on other available Y_x values for this solvent, and in addition why the protonated species would react in S_N1 reactions at a lower rate than the original substrate. A partial answer might be found in the supposition that the protonation takes place on the contact ion pair, as well, (Scheme 9.4.1), the rate-determining step being a combination of both k_1 and k_2 . On the other hand, the cationic charge is obviously effectively spread throughout the ferrocenyl moiety,⁷¹ possibly involving a partial oxidation of iron(II) in certain solvents. That metallocenes represent a solvent-dependent electron transfer system has been pointed out recently.⁸¹ Unfortunately, the question remains why the rates in formic acid, at 20 °C, are somewhat lower than in acetic acid.⁵⁰ At that temperature, the rate depression effect upon addition of sodium benzoate is negligible. On the other hand, the rate decrease is very large at 313.6 K, suggesting a change in the mechanism: at that temperature, the concentration of the contact ion pair (Scheme 9.4.1) seems to be very much reduced and the formation of the final reaction product appears to take place over the free ion, R^+ , the rate determining step being mainly the k_5 step. This step should be partly dependent on the solvent bimolecular contribution. The bimolecular solvent contribution appears to be somewhat larger with acetic acid than with formic acid. If so, one should expect this contribution to increase at higher temperatures, when, in the absence of $LiClO_4$, the solvolysis mechanism presented by the Scheme 9.4.1 is practically reduced to the reactions:



Indeed, at 313.16 K, the ratio of k_{obs} for acetolysis and formolysis is 1.69, while at 293.16 K the same ratio is 1.40.⁵⁰ The α -D KIE gets substantially

reduced with increased temperature, as it should be expected for reactions with increased bimolecular solvent contribution: at 293.16 K, KIE for α -D (geometric mean) for acetolysis and formolysis (in the absence of LiClO_4) amounted to $(23.3 \pm 0.1)\%$, and $(26.6 \pm 3.0)\%$, respectively, while at 313.16 K, KIE was reduced to $(9.1 \pm 1.9)\%$ (acetolysis), and $(10.1 \pm 2.8)\%$ (formolysis).⁵⁰ In the presence of LiClO_4 , at lower temperatures (293.16 K), when the reaction product ROS is considered to be formed exclusively over routes k_1 , k_2 , k_6 , and k_7 , the acetolysis and formolysis specific rates amounted to $(49.44 \pm 0.49) \times 10^{-4}$ and $(11.66 \pm 0.31) \times 10^{-4} \text{ s}^{-1}$, respectively.⁵⁰ Under these conditions, the solvolyses clearly follow the $\text{S}_{\text{N}}1$ mechanism, as manifested by very high α -D KIE of $(25.0 \pm 1.3)\%$ (acetolysis), and $(22.5 \pm 1.6)\%$ (formolysis). Since, under these conditions, bimolecular interference of the solvents is excluded, the slower rates in formic acid are puzzling. As already mentioned, the ionization constants for formic, benzoic, and acetic acids are 1.8×10^{-4} , 6.0×10^{-5} , and 1.8×10^{-5} , respectively, and the corresponding pK_{a} values are 3.74, 4.19, and 4.76. If protonation of the contact ion pair (Scheme 9.4.1) does take place, one might argue that the protonation is better in the stronger formic acid than in acetic acid, though protons are extensively available in both acids.

Other physical properties of the two solvents might also play an important role, *e.g.*, solvent friction. Recently, the solvent dependence of the electron transfer in metallocenes was analyzed in terms of the mentioned property.^{81–84}

9.6. ANTITUMOR ACTIVITY OF METALLOCENES

Transition metal compounds showing tumor inhibiting action are mainly represented by metallocene complexes of the type shown in Figure 9.6.1 (a) ($\text{M} = \text{Ti}, \text{V}, \text{Nb}, \text{Mo}$; $\text{X} = \text{e.g., Cl}$).^{85–89}

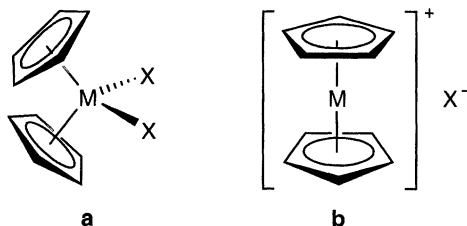


Figure 9.6.1. Metallocenes with potential antitumor activity.

These complexes have shown anti-proliferative activity against various experimental tumors, *e.g.*, Erlich ascites tumor, sarcoma 180, B16 melanoma, colon 38 carcinoma, Lewis lung carcinoma, as well as against xenografted human carcinoma.⁹⁰ Whereas the antitumor metallocene dihalides (**a**, Figure 9.6.1.)

are neutral compounds, the metallocenium cations ($M = \text{Fe}, \text{Co}$; *e.g.*, $X = \text{FeCl}_4^-$ (**b**, Figure 9.6.1.) are cytostatically active. The antitumor activity of these compounds against Erlich ascites tumor has been detected.⁹⁰ A review article on non-platinum group metal antitumor agents, including history, current status and perspectives appeared some years ago.⁹¹ The antitumor activity of metallocenes is expected to be due to their electron-donating ability.

Titanium dichloride exhibited excellent antitumor activity, especially against Lewis lung carcinoma and colon carcinoma. Unfortunately, therapeutic doses of this metallocene have an unwanted effect on the liver. The detailed mechanism is unknown. Substitution of chloride by other ligands has an insignificant therapeutic effect. On the other hand, changes on the cyclopentadienyl ring yield totally inactive compounds. Of special interest in this field is the review article by I. Haiduc and C. Silvestru,⁹² *Metal Complexes in Cancer Chemotherapy*, containing 400 references.

9.7. FERROCENES AS NUCLEOPHILIC CATALYSTS CAN MEDIATE KINETIC RESOLUTION

Chiral π complexes of heterocycles with transition metals can serve as effective catalysts for an array of useful organic reactions.^{93,94} The most efficient nucleophilic catalysts previously used had planar structures,⁹⁵ *e.g.*, 4-(dimethylamino)pyridine, and therefore required an asymmetric environment in the vicinity of an sp^2 -hybridized nucleophilic atom. In a recent paper, G. C. Fu *et al.*⁹⁶ describe a procedure, which they call a second-generation system for kinetic resolution, that employs an iron complex at a mole fraction of 2% as the chiral catalyst, and acetic anhydride as the acylating agent (Figure 9.7.1). The authors attached the 4-(dimethylamino)pyridine moiety to a chiral ferrocene analog. The lower portion of the ferrocene, coordinated to the iron atom is pentaphenylcyclopentadiene, as shown in Figure 9.7.1.

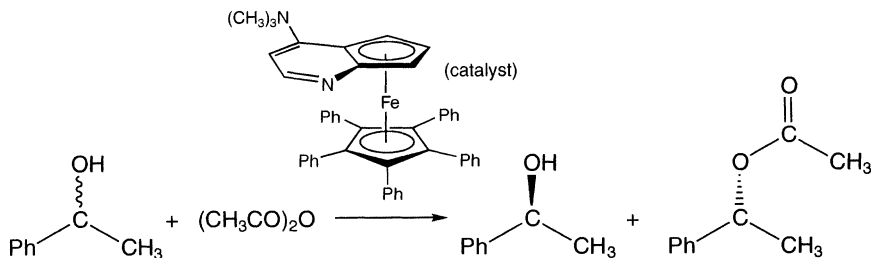


Figure 9.7.1. The nucleophilic ferrocene type catalyst enables kinetic resolution of chiral secondary alcohols with 95% enantiomeric excess at 62% conversion (according to G. C. Fu *et al.*⁹⁶). Reproduced by permission from the American Chemical Society.

Since one enantiomer of the alcohol reacts faster than the other, the result is a kinetic resolution that leaves the unreacted alcohol in 95% enantiomeric excess at 62% conversion. As it has been pointed out,^{97,98} the method can be applied to a number of interesting products including α -hydrogen acids, psychoactive arylethanolamines, pyrethrin insecticides, phenol-type antibiotics, *etc.* It is important to note that the stereoactivity displayed by the described catalysts is attributed largely to the η^5 -C₅Ph₅ group. Although the ferrocene framework is a common component of a chiral catalyst,⁹⁹ a significant improvement has been made by demonstrating that an increase in the steric bulk of a remote cyclopentadienyl ring can lead to a significant improvement in enantioselectivity. Decreased enantioselectivity upon substitution of an η^5 -C₅H₅ group with a more bulky η^5 -C₅Me₅ group has been reported.¹⁰⁰ The use of "supracyclopentadienyl" ligands in organometallic chemistry has been discussed previously.¹⁰¹

9.8. FERROCENES AND MOLECULAR RECOGNITION

Crown ethers afforded the opportunity to prepare a variety of synthetic cation transport agents. Anion recognition is a relatively recent topic although the first published anion receptor appeared in 1968, only one year after the discovery of crown ethers.¹⁰² Recently, great interest has been shown in the syntheses of redox-active microcyclic receptors that contain a redox center in close proximity to a cation or anion binding site. Gokel *et al.*¹⁰³ first considered the consequences of oxidation of the iron(II) center of ferrocene,¹⁰³ and in their following paper¹⁰⁴ they utilized the fact that the two coplanar cyclopentadienyl rings of ferrocene can rotate around the iron center. Thus, in the case of functionalized ferrocenes, a wide range of relative orientations of the substituents on pentadienyl may be achieved. Since rotational barriers in substituted ferrocenes are low, as already mentioned in the Introduction, it is possible to design a system which has all the correct functionality for binding a particular molecule, but not yet the functionality in the correct spatial position.¹⁰⁵ Correct spatial arrangement is induced by the substrate, which organizes the functional groups of the receptor in an optimal manner by selective rotation of the cyclopentadienyl rings, as it was recently pointed out.¹⁰⁵ The principle of bonding of a difunctional molecule to the ferrocene receptor is shown in Figure 9.8.1.

These systems can be designed to recognize electrochemically the binding of a charged "guest" either through space interaction and/or through bond linkages between the receptor site or redox center.¹⁰⁶ It is specific to the ferrocene redox couple that neutral ferrocene can be converted easily into the ferrocenium cation. Ferrocene d electrons may or may not serve as donors for

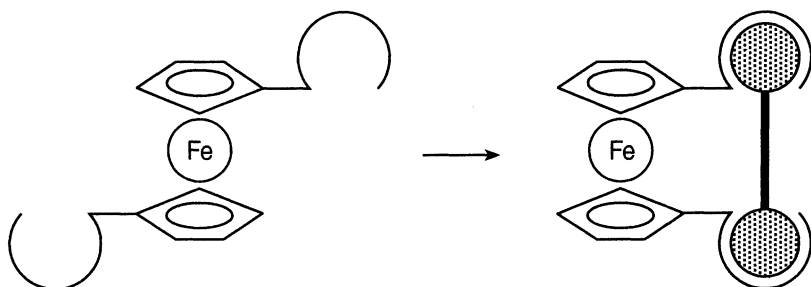


Figure 9.8.1. The principle of bonding of a difunctional molecule to the ferrocene receptor. The active conformation of the receptor is induced by the substrate¹⁰⁵ (reproduced by permission from the Wiley-VCH, STM-Copyright & Licenses).

a bound cation, but when iron(II) is oxidized to iron(III), a repulsive positive charge is placed in the proximity to the bound cation.¹⁰⁶ This change diminishes the cation binding capacity of the ligand. It is claimed that the complexation occurs within the cavity, rather than on the periphery.¹⁰⁶ Most of the reported redox-responsive ligand systems gave examples of “guest”- redox couple perturbations in organic solvents such as acetonitrile and dichloromethane. Using new water-soluble polyaza and polyammonium ferrocene macrocyclic ligands, the electrochemical recognition of a variety of transition metal cations (Ni^{2+} , Cu^{2+} , Zn^{2+}) and phosphate anions (HPO_4^{2-} , ATP) in the aqueous environment has been made possible.¹⁰⁷

Anion recognition continues to attract considerable research interest.^{108,109} This interest may be attributed to the biological role played by anions. For example, enzymatic binding and reactions with ATP are the basis of the free energy in metabolism and the majority of enzymes act on anionic substrates.¹⁰⁸ Several classes of artificial anion receptors have been reported, capable of not only binding but also of electrochemically recognizing anions.¹¹⁰ Such receptors have a potential application in the production of electrochemical anion sensors.

9.9. METAL-METAL INTERACTIONS IN LINKED METALLOCENES

Studies of linked metallocenes enabled the construction of a range of molecules comprising more than one metallocene unit. In particular, the interactions between metal centers have been studied. Several potential applications of such metallocene systems can be envisaged. For example, metallocene polymers can lead to interesting low-dimensional conductors.¹¹¹ Distinct Fe^{II} and Fe^{III} sites in various monooxidized biferrocenes, between which electron transfer can take place, can lead to semiconductivity. Several studies have cen-

tered on the use of the third-order nonlinear optical properties of binuclear metallocenes. An excellent paper by S. Barlow and D. O'Hare¹¹¹ reviews various classes of linked metallocenes, covering the literature up to the early 1996.

9.9.1. Metallocene derivatives

Ziegler-Natta catalysts have long remained the only organometallic catalysts in macromolecular chemistry. The area was revolutionized by the discovery that zirconocene derivatives catalyze the polymerization of propene.¹¹² At the same time, strong industrial interest has prompted a worldwide development in the field. The first polymers based on metallocene-type catalysts have recently appeared on the market¹¹³ under the names: Hostacen (Hoechst AG), Exact (Exxon), and Affinity (Dow). The metals zirconium and hafnium appear to be the most important metals in synthetic preparations.

The transition-metal-catalyzed ring-opening polymerization of silicon-bridged, strained, ring-tilted ferrocenophans yields polyferrocenylsilanes with intriguing properties.¹¹⁴

9.9.2. Concluding remarks

The problems discussed in this Chapter are primarily mechanistic and cover only partly the chemistry of ferrocene and related compounds. The remarkable structural and bonding forms displayed by these compounds provided the initial impetus to the immense and continuing research.

The most important chemical characteristic of ferrocene remains its ability to act as an electron releasing substituent, and the metallocenyl group is one of the strongest inductive electron-releasing agents known. This electron donor ability is further exemplified by its great propensity to undergo electrophilic substitutions. The result is the actual and potential practical use of ferrocenes and related compounds in industry. The theoretical and practical aspects of ferrocene chemistry guarantee that this subject will remain for some time one of the most active areas of inorganic chemistry.

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Chapter 10

METAL COMPLEXES IN TUMOR THERAPY

10.1. INTRODUCTION

The history of medicine shows that metal compounds have been extensively used in medical therapy. For example, antimony compounds were used as emetics and in tropical disease treatment, whereas bismuth compounds were widely applied as astringents and dermatological antiseptics. Arsenic derivatives were used in asthma, tuberculosis, leprosy and dermatoses (arsenic occurs in nature as a non-metal in anionic form and also as a metal in cationic form). By spreading of syphilis in Europe towards the end of the fifteenth century, the application of arsenic widened considerably. The greatest sensation was the discovery of salvarsan, Figure 10.1.1, which was prepared in 1909 by Paul Ehrlich,* a German chemist and bacteriologist, in collaboration with A. Bertheim, also a German chemist. They ascribed the formula shown in Figure 10.1.1 to salvarsan, 4,4'-arsenobis(2-aminophenol)dihydrochloride, but later on the X-ray structure analysis showed that the active compound was a cyclic trimer with six arsenic atoms in the ring, the two aminophenol molecules bound to every arsenic atom. In 1910, with his colleague Sahachiro Hata, Ehrlich conducted tests in combating syphilis. His preparation 606, later called salvarsan, was very effective and harmless despite a high arsenic content. Ehrlich called salvarsan a "magic bullet" because a single injection was sufficient. In fact, Ehrlich prepared 914 compounds similar to salvarsan, of which salvarsan was the most promising in the chemotherapy of syphilis.¹

* PAUL EHRLICH, 1854–1915, was born in Silesia (Strehlen), now Strzelin, Poland, into a Jewish family. He studied medicine at the University of Leipzig. Later on he did research at the famous Charité Hospital in Berlin and also at the Robert Koch Institute for Infectious Diseases in Berlin. Ehrlich shared the 1908 Nobel Prize for medicine with the Russian biologist Ilya Iljich Mechnikov (1845–1916). The greatest distinctions bestowed by the Prussian state were the title "Wirklicher Geheimer Rat" (Privy Councillor with the predicate of "Exzellenz") and an honorary citizenship by Frankfurt am Main, where the institute he founded still bears his name.

Ehrlich's success inaugurated the chemotherapeutic era. Salvarsan, or some of its modifications, remained the standard treatment for syphilis, until the discovery of penicillin. There are also some other arsenic compounds of the As_nAr_n ($\text{Ar} = \text{aryl}$) type with antibacterial activity.² Salvarsan is no longer in use.

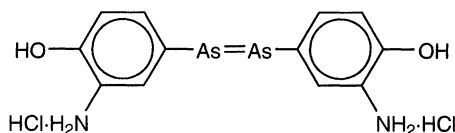


Figure 10.1.1. Salvarsan, 4,4'-arsenobis(2-aminophenol)dihydrochloride.

10.1.1. Chemotherapy of cancer

At first, most antitumor drugs were of organic origin. Metal complexes were not much investigated, since most of them were considered to be potential carcinogens.

The discovery of platinum complexes exhibiting antitumor activity (1969) was the turning point.³ Soon, intensive research was carried out. The compound *cis*-diaminodichloroplatinum(II), $\{cis\text{-}[\text{Pt}^{\text{II}}(\text{NH}_3)_2\text{Cl}_2]\}$ (Figure 10.1.2), later called cisplatin, proved to be most effective in fighting various types of human cancer.

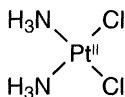


Figure 10.1.2. Cisplatin.

Consequently, many inorganic compounds were intensively investigated and systematically screened for antitumor activity. Various inorganic and complex compounds were tested, including the main-group metal complexes, transition metal complexes and organometallic complexes. Some organometallic complexes exhibited an antitumor activity even more pronounced than that of cisplatin.⁴⁻⁷ An excellent review by Haiduc and Silvestru⁸ covers the field thoroughly, quoting 400 references, as already mentioned in Chapter 9.

10.2. COMPLEXES OF THE *cis*-PtL₂X₂ TYPE AS ANTITUMOR AGENTS

Most of the investigated *cis*-PtL₂X₂ complexes (L = amine ligand, X = a labile ligand) were the starting material for the preparation of many other platinum(II) complexes. The observation of B. Rosenberg that *cis*-[Pt^{II}(NH₃)₂Cl₂] and *cis*-[Pt^{II}(en)₂Cl₂], (en = ethylenediamine) were very effective antitumor agents was followed by a number of papers dealing with these complexes.⁹⁻¹⁴ Soon, it was realized that the *cis*- rather than *trans*-isomer exhibits biological activity, probably because [PtL₂X₂] must lose both of its X ligands to form a particular biochemically important polymer with DNA, forming a bridge over *cis*- rather than *trans*-position, for steric reasons. Which bonding positions are in question is generally unknown. In spite of this limitation, investigations of platinum(II) complexes were extensively pursued.¹²

It has been shown that biochemical activity can be controlled by small changes in the chemical composition of these complexes. Therefore, many different new platinum(II) complexes were prepared and tested for their anti-tumor activity. It is expected that the *cis*-compound of the (L₂)Pt(X₂) type has two “*trans*-labilizing” ligands that promote the dissociation of the two X-ligands. Thus, two bonding coordination positions are free for bonding toward two nitrogen atoms of a DNA molecule. It is important that the two L-ligands are strongly bonded to the platinum central atom. The “*trans*-labilizing” effects on nitrogen bonding of the DNA molecule should be as small as possible, so that the bond Pt–DNA remains kinetically stable. Thus, a platinum complex with an optimum of desired properties should be found.

Since the following sequence of the metal-ligand bond strengths has been established: CN[−] > OH[−] > NH₃ > SCN[−] > I[−] > Br[−] > Cl[−] > F[−] ≥ H₂O and RS[−] > R₂S ≥ NH₃, thermodynamically possible replacements have been determined as well.

It has been established that, besides cisplatin, the platinum complex of the type depicted in Figure 10.2.1 also shows a very high antitumor activity.

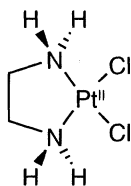


Figure 10.2.1. *cis*-Pt^{II}(ethylenediamine)dichloro complex.

In these complexes, the bond between platinum(II) and Cl[−] ligands has a low thermodynamic and kinetic stability. The *trans* effects of NH₃ groups and

of the ethylenediamine group are relatively small. Therefore, the bond between platinum and protein is only slightly weakened. In addition, ethylenediamine, a bidentate ligand, is strongly bonded to the platinum central atom with two coordinative bonds.

Among the large number of platinum complexes^{15–20} tested *in vivo*, and partly in clinical procedures, cisplatin exhibited by far the best results. However, cisplatin, as well as many other similar complexes, cause side effects, *e.g.*, kidney trouble, digestion disturbances and vomiting. This appears to be due to the inhibition of enzymatic activity caused by platinum coordination to –SH groups in proteins. Sulfur compounds, *e.g.*, diethylthiocarbamate and thiourea, can suppress these symptoms.²¹ Besides, cisplatin causes small, fortunately reversible, damage to the spinal tract.

10.3. SECOND GENERATION OF CISPLATIN ANALOGS

In smaller doses, the complexes of this class have equivalent therapeutic activity. Consequently, they exhibit smaller negative side effects. Such compounds are carboplatin, spiroplatin, oxoplatin and iproplatin (Figure 10.3.1).

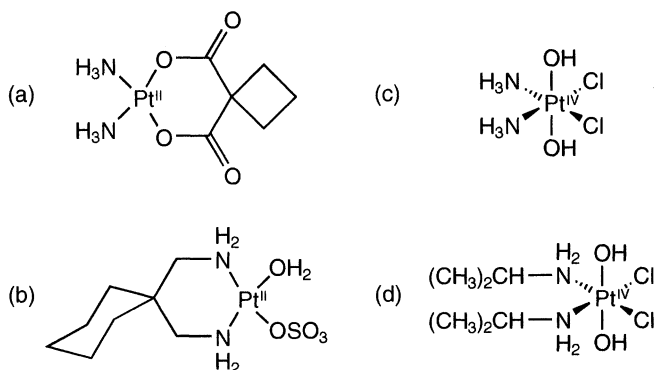


Figure 10.3.1. Second generation of cisplatin analogues: (a) carboplatin (CBDCA, JM 8); (b) spiroplatin (TNO 6); (c) oxoplatin; (d) iproplatin (CHIP, JM 9).

All these platinum complexes exhibit very strong antitumor activity, suggesting that the platinum oxidation state of either Pt^{II} or Pt^{IV} does not determine the quality of antitumor activity. In general, the activity of platinum(IV) complexes is somewhat smaller than that of platinum(II) complexes. It might well be that the activity of platinum(IV) is, in fact, that of platinum(II), in which case the reduction occurs *in vivo*, probably by the action of cysteine.²¹

As already mentioned, the antitumor activity was first ascribed to the *cis*-complexes of platinum(II), but later on it was found that in some cases *trans*-configuration can produce an even more pronounced antitumor activity than *cis*-configuration.²²

It has been established that amine ligands are the most convenient “non-leaving” ligands. Leaving ligands (X) are usually anions of medium stability, and their replacements can take place on a physiologically and therapeutically useful scale. The best leaving ligands are halogenides, carboxylates, sulphates, water and hydroxo ligand. Hydroxo ligand is often very important, since it can increase the low solubility of platinum complexes in aqueous solution (*e.g.*, the solubility of cisplatin is only 0.25 g per 100 ml).

The leaving ligand (X) should not be too labile in the kinetic sense because the complex might become toxic. On the other hand, if the X ligand is kinetically too inert, it will become therapeutically inactive.

The third generation of platinum antitumor agents connects the platinum complex with an adequate molecular carrier. Such a carrier can increase the antitumor activity synergically, and also increase the selectivity toward tumor tissue.²¹

Recently, an improved version of the photodynamic therapy, which uses a fiber optic cable and specifically triggers the reaction on the desired location, has been published.²³ This is very important because cisplatin is not restricted to cancer cells only. It also attacks healthy cells, which can be minimized by the use of a fiber optic cable.

10.3.1. The mechanism of antitumor activity of cisplatin

It has been generally considered that the antitumor activity of cisplatin is primarily due to its coordination to DNA in the cell nucleus, whereas the reactions in other fields, *e.g.*, the reaction with serum, cause undesirable side effects. The antitumor activity of cisplatin is a very complex process depending on the nature of a Pt complex. It is due to the inhibition of DNA and RNA, or of protein synthesis.

Cisplatin cannot be administered orally because stomach acid would cause its hydrolysis. It bonds to plasma protein. The kidneys eliminate about 30–70% of the original complex. The rest is transported by the blood stream through cell membranes of different organs and tumor cells. The complex hydrolysis is rather fast because of the low chloride concentration in the intracellular region. Therefore, the platinum complex in the cell is partly in aqua form (about 40% as $[cis-Pt^{II}(NH_3)_2Cl(H_2O)]^+$). The aqua complex is kinetically labile since the coordinated water is weakly bonded, compared to Cl^- . In addition, when the Cl^- leaves the complex, its increased positive charge is likely to promote

the reaction with the negatively charged DNA. The net result is the special antitumor activity of the cisplatin aqua form.^{8,21}

Interactions of metal ions and their complexes with nucleic acids are of primary importance. The details are not known yet. However, the experimental data suggest that after dissociation of Cl^- , the cisplatin cationic species forms coordinate bonds with the nitrogen atoms of nucleic bases; *in vitro*, this includes bonds with 7-N guanine, 1-N and 7-N adenine, and 3-N cytosine.^{21,24} It is known that 1-N adenine and 3-N cytosine are hydrogen-bonded inside the DNA structure. The strongest hydrogen bond is formed between 7-N guanine and platinum.

After coordination to $[\text{Pt}^{\text{II}}(\text{NH}_3)_2]^{2+}$, the structural changes of DNA can be estimated by measuring the thermal stability. Thus, the bonding of the *cis*-complex to DNA leads to destabilization of the species formed, resulting in a lowering of the melting point. On the other hand, the bonding of *trans*- $[\text{Pt}^{\text{II}}(\text{NH}_3)_2]^{2+}$ to DNA raises the melting point, suggesting that the stability of the product is increased.²⁵ Electronic spectroscopy has provided additional structural information.

10.4. GOLD COMPLEXES AS ANTITUMOR AGENTS

Gold has been used therapeutically since the ancient times. There are Chinese recipes from the 6th century B.C. where gold solutions were considered to be the elixir of life. From these documents, one may conclude that gold was dissolved by an oxidation procedure which included KNO_3 and IO_3^- .²⁶ Reduction of IO_3^- with organic material, or with FeSO_4 , yielded I^- , a lowering of the gold oxidation potential by 1 V, so that gold was dissolved as $[\text{AuI}_2]^-$ anion. For example, gold was used as a remedy for leprosy.

In 1890, Robert Koch* noticed that AuCN suppressed the growth of tuberculosis bacteria. This observation was not of practical use due to the very high

* ROBERT KOCH, 1843–1910, a German bacteriologist, won the Nobel Prize for physiology and medicine in 1905. Koch discovered the bacilli of tuberculosis and cholera. He is one of the founders of the science of bacteriology. Koch attended the University of Göttingen, where he studied medicine. He became district surgeon in Wollstein (which was then Germany). In his small laboratory, equipped only with a microscope, a microtome and a home-made incubator, he began a study of algae, and later of pathogenic organisms. He cultivated anthrax organisms. Koch found that the dried spores could remain viable for years, even under exposed conditions. The dormant spores could, under favorable conditions, develop into the rod-shaped bacilli that cause anthrax. Thus, Koch demonstrated with ingenious experiments the complete life cycle of an important organism. He was soon recognized as a great investigator and was given excellent research possibilities in Berlin's German Health Office. Working in Egypt and India, he discovered the cholera bacterium and its transmission *via* drinking water, food and clothing. In 1882, Koch announced in Berlin that he had isolated and grown the tubercle bacillus.

toxicity of gold salts. Later on, it was established that thioglucose-gold(I) helps in the therapy of rheumatic fever.²⁷⁻²⁹

It has been shown that only univalent gold exhibits therapeutic activity. The most important antirheumatics with gold are: trisodium bis(thiosulphato)aurate(I) (sanocrysin), disodium thiomalato-S-aurate(I) (myochrisin), (thioglucose-S)gold(I) (solganol) and 2,3,4,6-tetrakis-*O*-acetyl-1-thio- β -D-glucopyranosato-S(triethylphosphine)gold(I) (auranofin),³⁰ (see Figure 10.4.1).

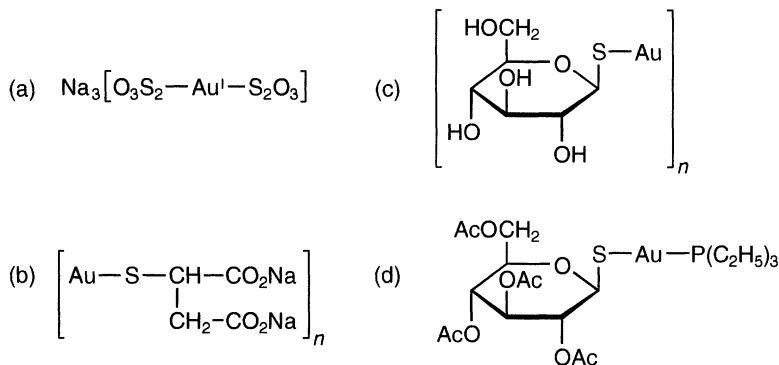


Figure 10.4.1. Antirheumatic agents with gold: (a) sanocrysin, (b) myochrisin, (c) solganol, (d) auranofin.

There are different hypotheses on the antirheumatic activity of gold(I). All these hypotheses can be reduced to the inhibition of formation of unwanted antibodies in the collagen region or to the action of superoxide ion, $\text{O}_2^{\cdot-}$, leading to protein degradation. It has been shown that different oxidizing agents can relatively easily transform $\text{O}_2^{\cdot-}$ radical into the very reactive singlet oxygen, $\text{O}_2 (^1\Delta_g)$, the energy of which is 92 kJ mol^{-1} higher than the energy of O_2 in the ground state, as already discussed (see Chapter 8, Table 8.10.1). It appears that gold(I) deactivates the singlet oxygen.³¹

10.5. ANTITUMOR ACTIVITY OF ORGANOGERMANIUM COMPOUNDS

The most investigated organogermanium compound is spirogermanium (spiro compounds are bicyclic compounds with one carbon atom common to two rings), Figure 10.5.1.

Spirogermanium inhibited the *in vitro* growth of tumor cells of a wide spectrum.³²⁻³⁴ There have been extensive investigations *in vivo*,³⁵ and the results are promising.³⁶ Great attention has been paid to carboxygermanium sesquioxide [*sesqui* (Lat.) = one and a half]: $(\text{HOOCCH}_2\text{CH}_2\text{GeO}_{1.5})_n$, known as Ge-132.

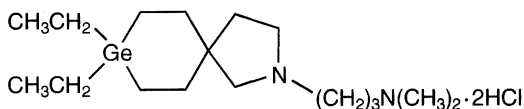


Figure 10.5.1. Spirogermanium.

The compound has a layered structure, being composed of Ge_6O_6 rings, similar to crown ether, with $-\text{CH}_2\text{CH}_2\text{COOH}$ groups that form hydrogen bonds between layers.³⁷ Both germanium compounds mentioned (spirogermanium and Ge-132) are applied in clinical practice.³⁸

The antitumor activity of metallocenes is described in section 9.6.

As we have noticed, metal complexes are widely used in cancer therapy. However, the non-metal boron recently appears to be a promising agent in the so-called boron neutron capture therapy (BNCT). This is the reason why we want to point out the importance of this newly developing field, despite the fact that boron is a non-metal.

This therapy involves the capture of neutrons by boron-10 (^{10}B) nuclei that have been selectively introduced into tumor cells. Neutron capture leads to excited ^{11}B nuclei, followed by fission, yielding highly energetic $^4\text{He}^{2+}$ (α -particles) and $^7\text{Li}^{3+}$ ions. The energy released by fission of the ^{10}B nuclei propels these high-energy particles, only by a distance of about one-cell diameter, damaging whatever they run into. About 10^8 – 10^9 ^{10}B nuclei, which are uniformly distributed within a cell, provide an adequate number of targets for destroying cancer cells. In the fifties, this technique was proposed for inoperable brain tumor treatments to destroy tiny clusters of malignant cells left behind after the bulk of the most dangerous tumor (glioblastoma) was removed. Unfortunately, the tests were not successful because the boron-containing agents did not deliver enough boron to kill the cells.

Recently, new clinical trials are carried out in the U.S.A., Japan, Sweden, the Netherlands, and Finland. The results are promising.³⁹

In clinical therapy, the patients are first given a non-toxic compound containing ^{10}B , which will be picked up selectively by cancer cells. After radiation, the beam of neutrons of adequate energy will pass harmlessly through most tissues. However, when the neutrons hit ^{10}B nuclei, the high energy of the mentioned particles ($^4\text{He}^{2+}$ and $^7\text{Li}^{3+}$) causes destruction of tumor cells. The large number of boron atoms needed in the treatment are recently provided by a protoporphyrin scaffold to which carboranyl cages are attached.³⁹ In specific experiments, the two glycosyl groups were attached to 10 carboranyl cages, or 100 boron atoms. Liposomes developed in Hawthorne's laboratory at UCLA have the potential to carry massive amounts of boron-containing compounds into cells. Carborane phosphate oligomers, with as many as 20 carboranyl cages each, can be incorporated into the liposome bilayer.⁴⁰

In a decade of studying, the Hawthorne group learned how to pack molecules containing B₂₀ ion cages into the liposome aqueous core. Even more effective than to get boron compounds into tumor cells is to place them within the cell nucleus. Hawthorne pointed out that DNA is the best target for the boron neutron capture damage.³⁹ For additional information, specific literature should be consulted.⁴⁰⁻⁴³

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Chapter 11

HETEROGENEOUS AND HOMOGENEOUS CATALYSIS BY METALS AND TRANSITION METAL COMPLEXES

11.1. INTRODUCTION

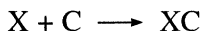
The term catalysis was coined by Berzelius* in 1835, and catalysts are defined as substances which by their mere presence evoke chemical reactions that would not otherwise take place. Ostwald** was the first to emphasize that a catalyst influences the rate of a chemical reaction but has no effect on the position of equilibrium because it accelerates the forward and the reverse reactions with equal intensity. Ostwald's famous definition was: "A catalyst is a substance that changes the rate of a chemical reaction without itself appearing in the end products". A catalyst is adequately compared to a coin that activates a slot machine to yield a valuable product, along with the coin.

For example, an uncatalyzed reaction occurs through collision of X and Y

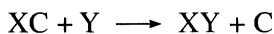
* JÖNS JACOB BERZELIUS, 1779–1848, Swedish chemist, professor of chemistry at the Royal Caroline Medico-Chirurgical Institute in Stockholm, from 1818 permanent secretary of the Stockholm Royal Academy of Sciences. He is especially noted for his determination of atomic weights with a remarkable degree of accuracy, for the development of modern chemical symbols, and for the development of classical analytical techniques (*e.g.*, he introduced the use of the water bath, desiccators, wash bottle, filter paper and rubber tubing). He is also famous for his investigations of isomerism and catalysis, which were both given their names by him. Berzelius discovered the elements cerium, selenium, and thorium. He also isolated silicon, zirconium, and titanium. His work on electrolysis led him to his dualistic electrochemical theory about positively and negatively charged species.

** FRIEDRICH WILHELM OSTWALD, 1853–1932, was born in Riga, Latvia, in a German family. He was professor of chemistry in Riga and at the University of Leipzig. Ostwald was primarily responsible for the founding of the *Zeitschrift für physikalische Chemie* (1887), the first journal in the field of physical chemistry. His process for the conversion of ammonia to nitric acid became of great industrial importance. Ostwald won the Nobel Prize for chemistry in 1909 for his work on catalysis, chemical equilibria, and reaction rates.

molecules ($X + Y \longrightarrow XY$), while a catalyzed reaction might follow a two-step mechanism consisting of reactions:



and



where C is a catalyst. We notice that the catalyst is used in the first step and regenerated in the second. It is, therefore, used over and over again; consequently, only a small amount of a catalyst is actually needed. A catalyst thus works by opening a new reaction path, which has a lower overall free energy of activation ($\Delta^\ddagger G$) than the uncatalyzed reaction. This is the reason for the increased reaction rate. On the other hand, the reaction enthalpy, $\Delta_r H$, for the catalyzed reaction remains the same as for the uncatalyzed reaction.

There are cases where the reaction rate increase is caused primarily by the entropy of activation increase. We recall:

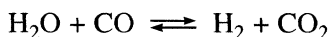
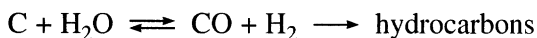
$$\Delta^\ddagger G^\circ = \Delta^\ddagger H^\circ - T\Delta^\ddagger S^\circ$$

One should make a distinction between homogeneous catalysis, in which the entire reaction occurs in a single phase, and heterogeneous catalysis, in which the reaction takes place at the interfaces between phases. In heterogeneous catalysis, the reactants and the catalyst are present in different phases. Reactant molecules are adsorbed on the surface of the catalyst, and the reaction takes place on that surface. In the so-called chemical adsorption (or chemisorption), the molecules are held to the surface by bonds that are of approximately equal strength as those in chemical compounds. The adsorbed molecules undergo changes so that some bonds may be stretched and thus weakened, or even broken.

The field of heterogeneous and homogeneous catalysis by metals and their complexes is enormous. It is partly presented in scientific journals, but mostly in patented literature.

11.2. HETEROGENEOUS CATALYSIS BY METALS AND METAL OXIDES

The well-known Fischer and Tropsch reaction involves the conversion of coal to hydrocarbons according to the equations:



The reaction is important because the cheap reactants, coal and water, are converted to very useful hydrocarbons. The so-called synthetic gas, composed mainly of carbon monoxide and hydrogen, is converted to hydrocarbons under the influence of elevated temperatures and normal or elevated pressure in the presence of a magnetic iron oxide catalyst. The process was first initiated in Germany in 1923 and mostly applied in the 1940s, as a method of producing liquid and gaseous hydrocarbon fuels, such as gasoline or gas oil, and was named after the German chemists Franz Fischer* and Hans Tropsch.** Attempts to improve the uneconomical procedure have continued ever since, with the intensity depending on the market oil prices. The reaction was catalyzed by various metals (Fe, Co, Ni, and Ru on Al_2O_3), and by cobalt and chromium oxides. By varying the catalysts, temperature and pressure, it is possible to obtain methane, liquid hydrocarbons, methanol, higher alcohols, olefins and other products. Thus, nickel is successfully applied in the production of methane; cobalt is used in the production of higher alkenes and rhodium in the production of ethanol, acetaldehyde and acetic acid.

Table 11.2.1 contains thermodynamic data for some reductions of CO with H_2 .

Table 11.2.1. Some thermodynamic data for the reduction of CO by H_2 (500 K)¹

Reaction	$\Delta_r G / \text{kJ mol}^{-1}$	$\log K$
$\text{CO} + 3\text{H}_2 \rightleftharpoons \text{CH}_4 + \text{H}_2\text{O}$	-96.22	10.065
$\text{CO} + \text{H}_2 \rightleftharpoons \text{HCHO}$	50.62	-5.293
$\text{CO} + 2\text{H}_2 \rightleftharpoons \text{CH}_3\text{OH}$	21.23	-2.222
$2\text{CO} + 3\text{H}_2 \rightleftharpoons \text{HOCH}_2\text{CH}_2\text{OH}$	65.92	-6.891

Under the given conditions, only the first reaction, in which methane is produced, is thermodynamically possible, because this reaction is the only one in which the Gibbs free energy is lowered. However, changing the temperature and pressure makes it possible to shift individual equilibria in the

* FRANZ FISCHER, 1877–1948, professor of chemistry at the University of Berlin, later Head of Carbon Research in Mülheim/Ruhr. He is primarily responsible for the development of the Fischer-Tropsch reaction (procedure).

** HANS TROPSCH, 1889–1935, worked in Mülheim/Ruhr on the Fischer-Tropsch reaction, which proved to be of significant industrial importance. In 1931 he emigrated to Chicago as scientific adviser.

direction of product formation, and by using an appropriate catalyst the adequate rate of the overall reaction can be obtained.

Among the above mentioned reactions, the third one is very important, in which methanol is produced using heterogeneous, copper-zinc oxide catalysts at 250 °C and 50 atm. Methanol can then be converted to acetic acid.

There have been many discussions and speculations about the reaction mechanism of CO reduction by hydrogen.²⁻⁶ The chemical industry mostly uses heterogeneous catalysts, metals and metal oxides. Such catalysts are stable and universal (can be applied to various reactions), and the products are easy to separate. But, also homogeneous catalysts have some advantages: lower temperatures and pressures are needed, and the catalysts are more selective in leading the reaction to a desired product. In addition, spectroscopic methods are easily applied, enabling studies of the reaction mechanisms and their desired corrections.^{7,8}

11.3. HOMOGENEOUS CATALYSIS BY TRANSITION METAL COMPLEXES

Homogeneous catalysis by transition metal complexes has been thoroughly presented in monographs and monographic articles.⁹⁻¹¹

Importance of homogeneous catalysis in industry can be seen from Table 11.3.1.

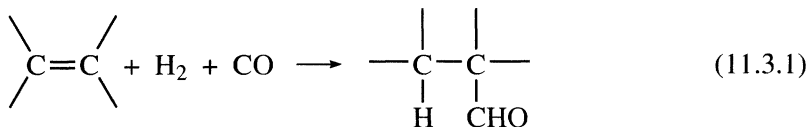
Table 11.3.1. Some important industrial processes catalyzed in the homogeneous phase⁹

Reaction	Production in 1990/10 ⁶ tons
Hydroformylation	1.818
Hydrocyanation	0.420
(production of nylon)	6.6
Polymerization of alkenes	10.0
Methanol carbonylation	1.16
($\text{CH}_3\text{OH} + \text{CO} \longrightarrow \text{CH}_3\text{COOH}$)	

11.3.1. Hydroformylation of unsaturated compounds

Hydroformylation reaction is the addition of molecular hydrogen and carbon monoxide to an alkene, usually terminal, or 1-alkene. This is a very important reaction, which is catalyzed homogeneously in industry. Otto Roelen, a German chemist in the Ruhr chemical area, discovered the reaction in 1938.

The mechanism of this reaction is now known with reasonable certainty. The name "hydroformylation" reminds us that the reaction involves addition of H and the formyl group, CHO (derived from H_2 and CO) to an olefin:

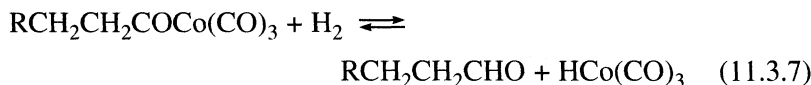
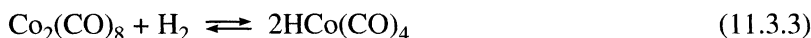


The reaction enables conversion of an alkene into an aldehyde with the increase in the number of carbon atoms by one carbon atom. Generally, we can write:



The industrial importance of this reaction has been thoroughly described.^{12,13} The commonly accepted catalyst was $HCo(CO)_4$, derived from $Co_2(CO)_8$ and H_2 , which is formed at 150 to 180 °C, and at pressures above 200 atm.

Hydroformylation is of the first order regarding the cobalt concentration, and of the first order in alkene. The reaction rate is increased by increasing the hydrogen pressure, and reduced by increasing the CO pressure. Based on these observations, Heck and Breslow,¹⁴ proposed the following reaction steps:



Reaction (11.3.5) involves transfer of β -H to the coordinated olefin. Spectroscopic investigations suggest splitting of molecular hydrogen, as proposed by equation (11.3.7).

Later on, it was shown that $HRh(PPh_3)_3CO$ was a better catalyst.¹⁵ It was introduced by the Shell corporation.¹⁶ The reaction conditions are much milder: the temperature is below 100 °C, and the pressure is only a few atmospheres. Besides, there is practically no loss of alkenes.¹⁷ Details of the reaction mechanism have been mainly solved.^{18,19} The essential reaction steps are depicted in Figure 11.3.1. They are:

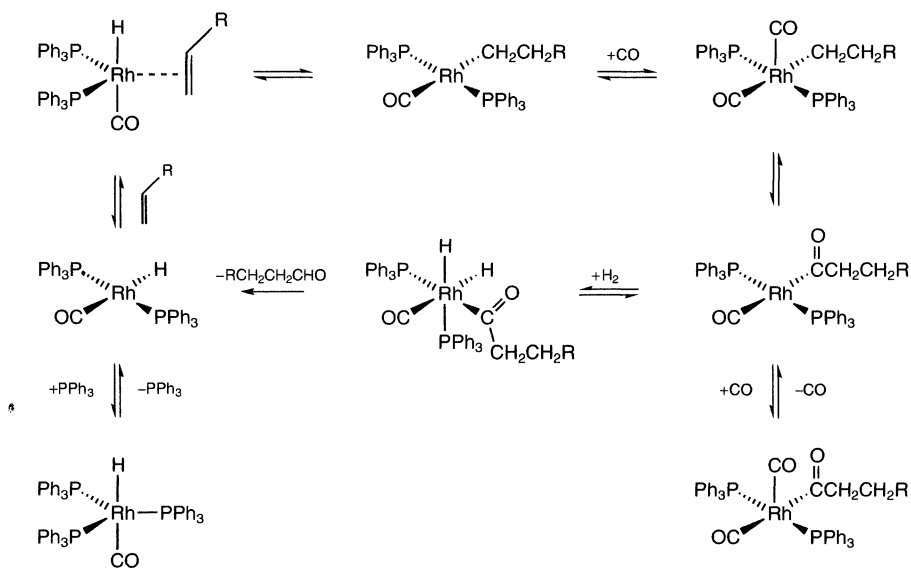


Figure 11.3.1. Simplified catalytic cycle for hydroformylation using rhodium complexes. The five coordinated species are fluxional. The solvent is C₂H₄ or CH₃CH=CH₂, see F. A. Cotton and G. Wilkinson, ref. 6. Reproduced by permission of John Wiley & Sons, Inc. Copyright © 1999.

(a) Formation of the square intermediate by alkene coordination and the H-atom transfer, followed by CO addition and insertion.

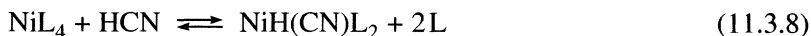
(b) The obtained product undergoes oxidative addition of H₂ and the change in the oxidation state of rhodium. This step is thought to be the rate-determining step. The last step is the transfer of the H atom to the C atom of the acyl group. This step is actually a reductive elimination of the aldehyde, leading to regeneration of the rhodium catalyst. The process is carried out at high PPh₃ concentrations so that the catalyst is in a relatively high concentration. The binding of alkene is sterically hindered because of PPh₃ groups. It is thought that penta-coordinate species are fluxional; on the other hand, calculations show that this intermediate is relatively stable. The square intermediates appeared to be strongly stabilized by solvation. All the mentioned intermediates are too unstable for isolation.⁶

11.3.2. Hydrocyanation of alkenes

In the 1930s, W. H. Carothers,* an American chemist, and his associates at E. I. DuPont de Nemours & Company in Wilmington, Del., developed nylon, the first synthetic polymer fiber to be produced commercially in 1938. These findings laid the foundations of the synthetic-fiber industry.

Condensation polymerization occurs between molecules of monomers by the elimination of, commonly, water but also of other small molecules.

Thus HCN, although a weak acid, adds oxidatively to nickel phosphite compounds (NiL_4), as in equation:



Further reactions might include addition of the alkene:

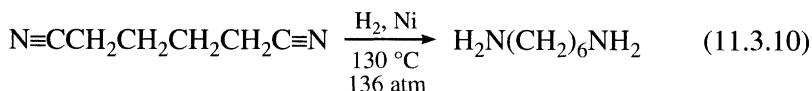


Oxidative additions and reductive eliminations can also take place.

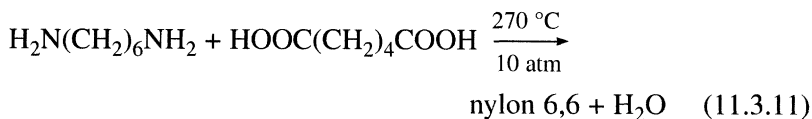
Polyamides are an important class of commercial polymers. The best known is nylon 6,6, which is a polymer formed from 1,6-diaminohexane and adipic acid ($\text{HOOC(CH}_2)_4\text{COOH}$):



Nylon 6,6 is so named because it is synthesized from two different organic compounds, each containing six carbon atoms. The 1,6-diaminohexane can be effectively obtained by hydrogenation of adiponitrile using a heterogeneous catalyst:²⁰



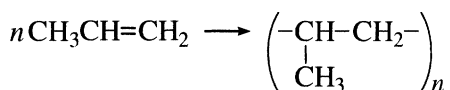
The polymer is manufactured by heating an equimolar mixture of the two monomers:



Polymerization occurs through elimination of water molecules. The production of a small section of the chain can be illustrated in a simplified manner:

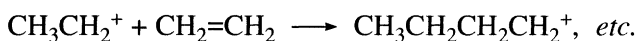
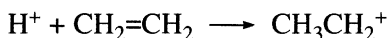
* WALLACE HUME CAROTHERS, 1896-1937, worked in organic chemistry at the University of Illinois and later at Harvard University. In 1928, he was appointed director of research in organic chemistry at the mentioned company, where he investigated the structure and formation of polymers. This fundamental research led to the development of the well-known nylon, an artificial fiber, in many ways superior to such natural fibers as wool, cotton, and silk.

of propylene (propene) is an exothermic process ($\Delta_r H/n = -83.68 \text{ kJ mol}^{-1}$):

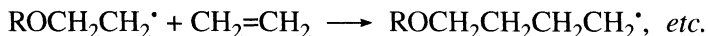
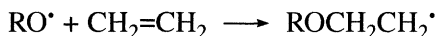


Polymerization can take place by an ionic or by a free radical mechanism.

Anionic polymerization is rare because nucleophiles do not usually react with the olefinic bond, but cationic polymerization is more frequent:



Polymerization induced by free radicals is the most important polymerization. It involves the following steps:



The growing radical will finally meet another radical and the polymerization chain will be broken.

Ziegler-Natta catalysts* are an important class of mixtures of chemical compounds, remarkable for their ability to effect the polymerization of olefins to polymers of high molecular weights and highly ordered, that is, with stereoregular structures.

These catalysts were introduced in 1954 by Karl Ziegler, for the polymerization of ethylene at atmospheric pressure. Ziegler employed a catalyst consisting of a mixture of titanium tetrachloride and an alkyl derivative of aluminium. Ziegler noted that polymerization of ethylene yields 1-butylene, but

* KARL ZIEGLER, 1898–1973, German chemist, professor at the Universities of Heidelberg and Halle and director of the Institute for Research of Carbon Compounds in Mülheim/Ruhr. He worked on the synthesis of polyethylenes at low pressures. In 1975, The Society of German Chemists established a prestigious award, “Karl-Ziegler-Preis” in his honor; the first winner was Georg Wittig, 1897–1927 (Wittig reaction). Herbert C. Brown and Georg Wittig shared the 1979 Nobel Prize for chemistry for the use of boron- and phosphorus-containing compounds in organic synthesis.

GIULIO NATTA, 1903–1979, Italian chemist, professor at the Polytechnic in Milan and director of the Milan Chemical Institute. He contributed to the development of high polymers, useful in the manufacture of films.

Ziegler and Natta shared the 1963 Nobel Prize for chemistry.

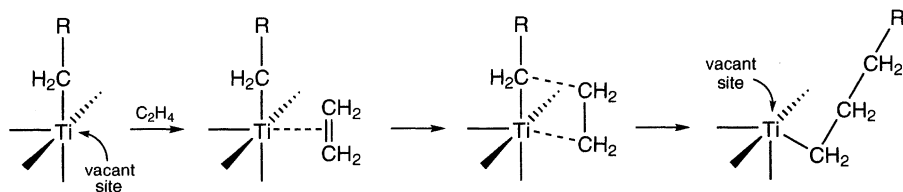
not the polymeric chain.²⁴ He supposed that another metal might catalyze extension of the chain to high molecular masses and found that ethylene, triethylaluminium, and tris(acetylacetonato)zirconium(III) yield a linear polyethylene. However, if titanium chloride is used instead of the zirconium compound, a stereoregular polypropylene is obtained.

Ziegler's discovery that TiCl_4 , dissolved in a hydrocarbon, in the presence of aluminium trialkyls (*e.g.*, AlEt_3 , electron-pair-acceptor catalysts – Lewis acids), reacts with ethylene to yield polymers in which only a few monomers are involved, led to the discovery of the so-called Ziegler-Natta catalysts. These catalysts polymerize the otherwise unreactive ethylene, and do it in a very regular and reproducible way. The catalyst is a heterogeneous suspension, which enables polymerization at a pressure of only 1 atm. Meanwhile, aluminium trialkyl generates transition-metal alkyl species. This opened a new and strange field of chemistry. While the reaction mechanism of these catalyses was discussed,^{25,26} the world polyethylene and polypropylene production rose to thousands of tons.^{27,28}

The products are: polyethylene (plastic bags), Teflon (pan coating), polyvinylchloride (phonograph records), orlon (rug fibers), polystyrene (combs, insulation materials), lucite (plexiglas), latex (dyes and lacquers), see organic chemistry textbooks.

At about the same time, the chromium-based catalysts were developed, which are highly selective for the polymerization of ethylene to a high linear polymer. These are now major industrial processes, with an annual polyolefin production of more than 50 million tons in 1993.

The Ziegler-Natta catalyst is heterogeneous, and the active species is a fibrous TiCl_3 , formed from TiCl_4 and AlEt_3 . The catalytic process begins with addition of ethylene to the vacant coordination site, as depicted in the following Scheme 11.3.1 (see F. A. Cotton and G. Wilkinson, ref. 29):



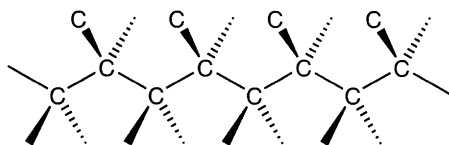
Scheme 11.3.1. Reproduced by permission of John Wiley & Sons, Inc. Copyright ©1988.

The olefin monomer is inserted into the growing polymer at the metal site of the catalyst. The most important catalytic step is the change in bonding from the π interaction to a metal-carbon σ bond, accompanied by migration of CH_2R from the metal (Ti) to the carbon atom. It is important for the metal-

olefin attraction to be strong enough to enable the bond formation; on the other hand, the metal-carbon σ bond must not be too strong, so as to enable a relatively easy ligand migration.

The titanium catalyst might yield:

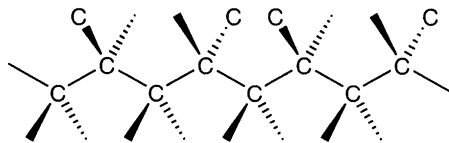
(a) a regular (isotactic) arrangement where all tertiary carbons have the same configuration:



Isotactic polymer chain

or

(b) an alternation configuration (syndiotactic), with a regular configuration alternation:



Syndiotactic polymer chain

If the orientation of the methyl groups is randomly distributed (no regularity of configuration), the polymer chain is called atactic.^{30,31}

Several mechanistic investigations, involving studies of deuterium isotope effects and deuterium incorporation into α -M-CH(D), support the mechanism of TiCl_3 -catalyzed polymerization of ethylene, as shown in the Scheme 11.3.1.³²⁻³⁴

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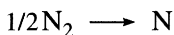
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Chapter 12

CHEMICAL AND BIOLOGICAL NITROGEN FIXATION

12.1. INTRODUCTION

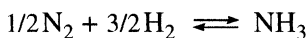
It is well known that nitrogen (N_2) is extremely chemically inert. This is because the dissociation of N_2 into atoms breaks a triple bond, which requires a very high energy:¹



$$\Delta_f H^\circ = 472.704 \text{ kJ mol}^{-1}; \Delta_f G^\circ = 455.563 \text{ kJ mol}^{-1}; T = 298 \text{ K}$$

(subscript f stands for formation)

The requirement for such a high energy will be, of course, partly compensated by newly formed bonds of the stable product.¹ Thus, the reaction of ammonia formation:



$$\Delta_f H^\circ = -46.1 \text{ kJ mol}^{-1}; \Delta_f G^\circ = -16.45 \text{ kJ mol}^{-1}; T = 298 \text{ K}$$

is both exothermic and exergonic and, at room temperature, the equilibrium lies well to the right. The Gibbs energy of the reaction is favorable, so that at room temperature the equilibrium is shifted well to the right, but the reaction is exceedingly slow under these conditions. Even at 700 °C, the yield of ammonia is far too small for practical use. Since no adequate catalyst was found (in the 1930s), the only solution remained to force the equilibrium to shift in the direction of the forward reaction by increasing the pressure to about 200 atm (Haber-Bosch procedure). In the presence of adequate catalysts, the energy of activation can be reduced to about 80 kJ mol⁻¹, or even less.² Adequate tempera-

tures are 400–550 °C, and the catalyst is, *e.g.*, finely powdered iron and Fe_3O_4 , containing small amounts of K_2O and Al_2O_3 ; there are also other catalysts.*

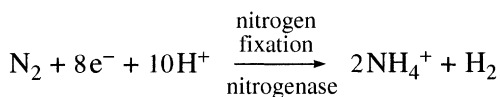
12.2. BIOLOGICAL NITROGEN FIXATION

Plants are amazingly successful in utilizing carbon from the relatively small amounts of carbon dioxide in the air, but they have never developed the ability to utilize atmospheric nitrogen, which is abundant in the air (78%). Only plants of the legumes group (bean family), which include lupines, peas, peanuts, *etc.*, can utilize atmospheric nitrogen. Nitrogen fixation to ammonia by adequate catalysts at room temperature is presently only a dream.

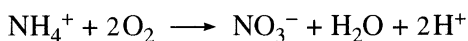
12.2.1. Nitrogen fixation in bacteria

An important property of many cyanobacteria is their ability to fix atmospheric (molecular) nitrogen. This process depends on the enzyme nitrogenase. This enzyme can function only under anaerobic conditions. It has been suggested that the metabolism of cyanobacteria functions best at low O_2 concentrations because these organisms are relics of nearly two billion years of evolution under conditions of the oxygen-poor earth's atmosphere.³

Biological systems that participate in nitrogen fixation contain a composite metal-requiring enzyme system which assures a source of electrons of high reductive efficiency, and another enzyme which makes use of these electrons to reduce N_2 to NH_4^+ :



Biological nitrogen fixation is then followed by nitrification:



* FRITZ HABER, 1868–1934, German physical chemist, winner of the Nobel Prize for chemistry in 1918 “for the synthesis of ammonia from its elements.” With Carl Bosch, he invented a process for the large scale production of ammonia for nitrogen fertilizers.

CARL BOSCH, 1874–1940, German industrial chemist, developed the Haber-Bosch process for high-pressure synthesis of ammonia. Bosch shared with Friedrich Bergius the 1931 Nobel Prize for chemistry for “their contribution to the invention and development of chemical high pressure methods.”

The resulting nitrate can be utilized by most plants. Both of these enzyme systems are proteins, containing iron and sulfur. The iron is bonded to sulfur of the cysteine residue and to inorganic sulfide.

Since 1930, it has been known that molybdenum is essential for bacterial nitrogen fixation because the removal of molybdenum turns off the process, and its restoring turns it on again. Magnesium and iron are essential elements, too. Nitrogenase can be separated into two proteins: one, Fe-protein, with a molecular mass of about 260 000, and the other, MoFe-protein, with a molecular mass of about 240 000. These proteins are active only if mixed together.

Adenosine triphosphate (ATP) is absolutely necessary for the conversion of N_2 to NH_4^+ by nitrogenase; a strong reducing agent is also necessary because $N_2 \rightarrow 2N^{3-}$ is a six-electron reduction. Most nitrogen fixing microorganisms use reduced ferredoxin for this reduction. Ferredoxin is a soluble component in the chloroplast ("fer" stands for iron and "redoxin" for redox-protein). In its reduced form, ferredoxin gives electrons directly to the system that reduces nitrate and sulfate *via* NADPH (nicotinamide adenine dinucleotide phosphate) and to the system that reduces carbon dioxide. A copper-containing protein called plastocyanin (PC) carries electrons from one place to another in the electron transport chain, since PC molecules are water-soluble.

Some ten years ago, an X-ray crystallographic study of the MoFe-protein showed that its structure has a metal cluster arrangement.

Metal clusters are compounds with metal-metal bonds. In the last few decades, the preparation and structural determination of such species has been a very active field of inorganic chemistry. Almost all transition metals form such compounds. There is also a tendency of transition metals to form bonds with themselves. An extensive overlap of d orbitals is required for the formation of such compounds, and the bonding is best accounted for in terms of the molecular orbital theory.⁴ The short distances between metal atoms and the low magnetic moments of metal clusters speak in favor of metal-metal bonding, but the X-ray structural determinations have provided an unambiguous evidence.

In a typical "nitrogenase C pasteurianum", both proteins, MoFe-protein and Fe-protein, share one [Fe-4S] cluster of the ferredoxin type. Later on, it was shown that all molybdenum, and partly sulfur, can be isolated as an insoluble substance of the relative molecular mass from 1000 to 1500. This substance was named the iron-molybdenum cofactor (FeMoco); it contains 2Mo, 6 to 8 Fe and 6 or more S atoms.

In 1992, an X-ray crystallographic study by J. Kim and D. C. Rees,⁵ (Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena) helped to understand the basic Fe₇Mo-sulfur cluster arrangement. They found that the FeMo-cofactor has 4Fe:3S and 1Mo:3Fe:3S clusters bridged by three non-protein ligands, and two 4Fe:4S clusters bridged by two

cysteine thiol ligands. Six of the seven Fe sites in the FeMo-cofactor seem to have trigonal coordination geometry; the remaining Fe site has tetrahedral geometry. The Mo site exhibits approximate octahedral geometry. It is interesting to note that six of the seven iron atoms are three-coordinated, and only one iron atom is coordinated to four sulfur atoms. It is presumed that this very unusual situation is connected with the coordination of N_2 as the first step of its fixation,⁴ but these are only speculations.

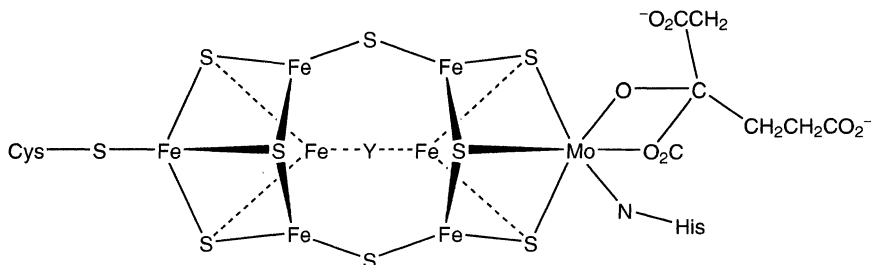
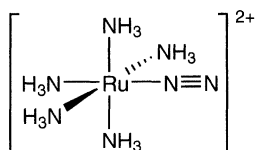


Figure 12.2.1. Simplified structure of the Fe_7Mo -sulfur cluster, found in the MoFe-protein of nitrogenase. The structure was solved by J. Kim and D. C. Rees.⁵ Reproduced by permission of the "American Association for the Advancement of Science" from *Science*, **1992**, 257, 1677, for the use in *Chemical Kinetics and Inorganic Reaction Mechanisms*.

12.3. REACTIONS OF N_2 WITH TRANSITION METAL COMPLEXES

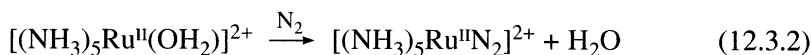
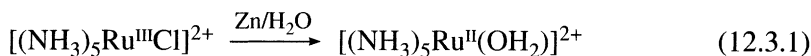
For many years it was thought that N_2 was inert to metal ions, in spite of the fact that N_2 is actually bonded to N^- (in azides, N_3^-), to O (in N_2O), and to organic cations (in N_2Ph^+).

In 1965, the Canadian researchers Allen and Senoff⁶ prepared an N_2 complex in which the N_2 is bonded at one end:

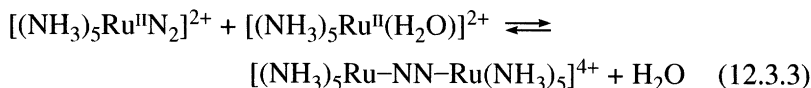


The complex was prepared by reduction of $RuCl_3$ with hydrazine (H_2N-NH_2) in aqueous solution; in hydrazine, N_2 is already reduced by accepting 2 electrons per one nitrogen atom. The importance of this discovery was fully understood three years later.⁷ However, the first example of direct bonding of N_2 was due to the Russian chemist Shilow.⁸⁻¹⁰ He prepared

the $[\text{Ru}^{\text{II}}\text{Cl}_2(\text{H}_2\text{O})_2(\text{THF})(\text{N}_2)]$ complex (THF = tetrahydrofuran). Only a year later, Harrison and Taube¹¹ prepared the $[(\text{NH}_3)_5\text{Ru}^{\text{II}}\text{N}_2]^{2+}$ complex ion by reducing $[(\text{NH}_3)_5\text{Ru}^{\text{III}}\text{Cl}]^{2+}$ with Zn in a nitrogen atmosphere:¹¹



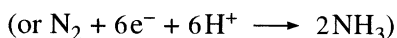
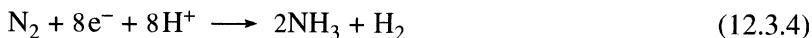
In this reaction, the water molecule of the Ru^{2+} ion is replaced by N_2 at room temperature. A further, most interesting observation is the existence of the following equilibrium:¹²



The formation of the linear Ru–NN–Ru bridge from $2[(\text{NH}_3)_5\text{Ru}^{\text{II}}(\text{H}_2\text{O})]^{2+}$ and N_2 is an exothermic process ($\Delta_r H = -92.05 \text{ kJ mol}^{-1}$).¹³ The stretching vibration wave number of NN is 2100 cm^{-1} , while the stretching vibration wavenumber in N_2 is 2331 cm^{-1} . On the other hand, the stretching vibration wavenumber of the NN bond in $[(\text{NH}_3)_5\text{Ru}^{\text{II}}\text{N}_2]^{2+}$ is 2140 cm^{-1} . We can see that the smallest stretching vibration wavenumber is that in the Ru–NN–Ru bridge. However, interpretation of these data is not easy since the –NN– bonding involves the $\text{N}_2 \rightarrow \text{metal}$ σ -donation as well as the $\text{metal} \rightarrow \text{N}_2$ back π bonding. Both of these donations influence and determine the force constant changes, and thereby the NN-stretching wavenumbers.^{13,14}

As already said, the problem of catalyzed N_2 fixation under mild conditions, similar to those of the biological fixation, is actually reduced to the problem of achieving the 6-electron reduction $\text{N}_2 \rightarrow 2\text{N}^{3-}$.

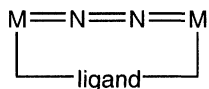
Obviously, the overall process



should involve several reaction steps and the catalysis. One should bear in mind that the $\text{N}\equiv\text{N}$ dissociation energy is not equally distributed to individual bonds. The first bond rupture requires more than half of the total dissociation energy need.¹⁵

It is generally considered that a successful nitrogen fixation should be found in reactions involving binuclear complex intermediates, and that the N_2 reduction involving an M–NN–M complex will have better chances than that

involving a mononuclear M–NN intermediate. It is further considered essential that a binuclear complex should have a common ligand, connecting both metal atoms:



Such an intermediate leads to a smaller entropy loss than the potential mononuclear M–NN complex intermediate, thus causing a relative rate increase by several orders of magnitude¹⁵ (we recall that the entropy of activation increase of $19.14 \text{ JK}^{-1} \text{ mol}^{-1}$ causes a tenfold rate increase).

In addition, it is important for both types of complexes to possess an additional electron source near the reaction center, which can increase the electron-donating capacity of the catalyst. This electron source can be a cluster of low-valence metal ions. In this way, the negative charge of nitrogen atoms will be increased, thereby increasing protonation and fostering further N_2 reduction. It is not clear, however, why this additional electron source should be more advantageous to a binuclear active center (M–NN–M), as compared to a mononuclear (M–NN) center.¹⁵

Some ten years ago, new types of N_2 complexes with further reduction possibilities appeared in the literature.¹⁵ Complexes are binuclear, and N_2 is the bridging ligand.^{16–20}

Table 12.3.1. Examples of binuclear complexes with N_2 bridging ligand

Complex	Ref.
$[\text{Zr}(\text{C}_5\text{Me}_5)_2(\text{N}_2)_2]_2(\mu\text{-N}_2)^{(a)}$	16
$[\text{V}(o\text{-Me}_2\text{NC}_6\text{H}_4)_2\text{py}]_2(\mu\text{-N}_2)$	17, 18
$[\text{Nb}(\text{S}_2\text{CNEt}_2)_3]_2(\mu\text{-N}_2)$	19
$[\text{Ta}(\text{S}_2\text{CNEt}_2)_3]_2(\mu\text{-N}_2)$	19
$[\text{Mo}(\text{C}_5\text{Me}_5)_2\text{Me}_3]_2(\mu\text{-N}_2)$	20
$[\text{Mo}(\text{C}_5\text{Me}_5)_2\text{Me}_3](\mu\text{-N}_2)-[\text{W}(\text{C}_5\text{Me}_4\text{Et})\text{Me}_3]$	20

^(a) $(\mu\text{-N}_2)$, bridging ligand.

Regardless of the intermediates involved in the reactions of these binuclear complexes, a high capacity of electron donation must be available, like in the case of enzymatic reactions. For further information, relevant literature^{21–23} can be consulted.

It is obvious that we are still a long way from solving nitrogen fixation under mild conditions such as in biological nitrogen fixation. Besides, such

a catalytic procedure has to be cheap to compete with the mighty industry producing ammonia by the Haber-Bosch procedure. But, there is no doubt the research will continue and we can expect many new preparations of organo-nitrogen compounds.

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Chapter 13

CASCADE MOLECULES (DENDRIMERS)

13.1. INTRODUCTION

Cascade molecules or dendrimers (from Greek: *dendron* = tree and *meros* = part) have been known for about two decades. Dendritic macromolecules are synthetic 3-dimensional macromolecules prepared in a stepwise way from simple branched monomer units, whose nature and functionality can be easily controlled and varied. Their structure results in previously unknown or improved physical and chemical properties as compared to the common linear polymers. Dendrimers are now one of the most important nanometer-scale building blocks for the construction of nanoscale systems, molecular devices, advanced drug-delivery systems, *etc.* These nanodevices are presently undergoing tests to determine their biological activity as anticancer drugs. Dendrimers are polymers, but very different from, *e.g.*, the well-known nylon polymer: nylon and all other plastics have very poorly defined chemical structures, which can be described as an average molecular structure with constant bulk properties. On the other hand, dendrimers are precisely defined chemical structures with precisely defined bonds between atoms. Thus, dendrimers are ideal building blocks for creating, *e.g.*, a biologically active nanomaterial.

Dendrimers consist of a series of chemical shells built on a relatively small core molecule. Each shell consists of two chemicals, always in the same order. Each shell is called a generation (G). For the first three generations, dendrimers are like ordinary organic molecules. By G4, dendrimers get more and more spherical. Beyond G5, dendrimers are highly structured spheres.

The first cascade molecule was described in 1978.¹ Since then, several thousands of papers have been published, including several books and review articles.^{2,3a-c} Some procedures of dendrimer preparation are patented.⁴ Ref. 3c by M. Fischer and F. Vögtle contains 76 citations covering thoroughly the field (F. Vögtle, Institute of Organic Chemistry, Bonn, Germany).

Various dendrimers with different cores and branching units have been synthesized lately. The best known are poly(anido-amine) dendrimers (PAMAM) and poly(propyleneimine) dendrimers;^{3c} they are produced in kilograms and are commercially available.

(a) The divergent method, in which one branching unit after another is attached to the core molecule, the branching multiplicity being usually 2 or 3. Thus, the dendrimer can be built up until steric effects prevent further reaction.

A higher generation of divergently built dendrimers always contains certain structural defects. On the other hand, in the convergent course, a segment growing with each reaction step is coupled with only one branching unit; this, in principle, enables the removal of undesired by-products,^{3c} which appears to be an advantage. Thus, the divergent method allows the formation of more generations, while in the convergent method steric problems are encountered in the reaction of the segment and the core molecule.

The image displays several chemical structures of dendrimers, which are branched, tree-like molecules. The structures include:

- A primary amine: $\text{R}-\text{N}$ with two arrows indicating branching.
- A bis-ether: A central carbon atom bonded to two phenyl rings, each with an oxygen atom at the para position, and two arrows indicating branching.
- A tertiary amine: A central nitrogen atom bonded to three phenyl rings, each with an oxygen atom at the para position, and two arrows indicating branching.
- A triphenylmethane: A central carbon atom bonded to three phenyl rings, each with a methyl group (CH_3) at the para position, and two arrows indicating branching.
- A triphenylmethylidene: A central carbon atom bonded to three phenyl rings, each with a methyl group (CH_3) at the para position, and two arrows indicating branching.
- A triphenylmethylidene dendron: A central carbon atom bonded to three phenyl rings, each with a methyl group (CH_3) at the para position, and two arrows indicating branching.
- A dendronized porphyrin: A central porphyrin core with four phenyl rings at the periphery, each with a methyl group (CH_3) at the para position, and two arrows indicating branching.

Figure 13.2.1. Examples of some di- to tetravalent core units (K) used in syntheses.^{3c}

The first dendritic molecule with a porphyrin core covalently encapsulated into a huge dendritic cage ("caged" porphyrin) was first reported by Ren-Hua Jin, Takuzo Aida and Shohel Inoue.^{7a} Later, Aida *et al.*^{7b} described the aggregation of negatively and positively charged porphyrin dendrimers in solution through electrostatic interaction.

Figure 13.2.2. depicts a porphyrin-type dendrimer with zinc as the central metal atom.^{3a}

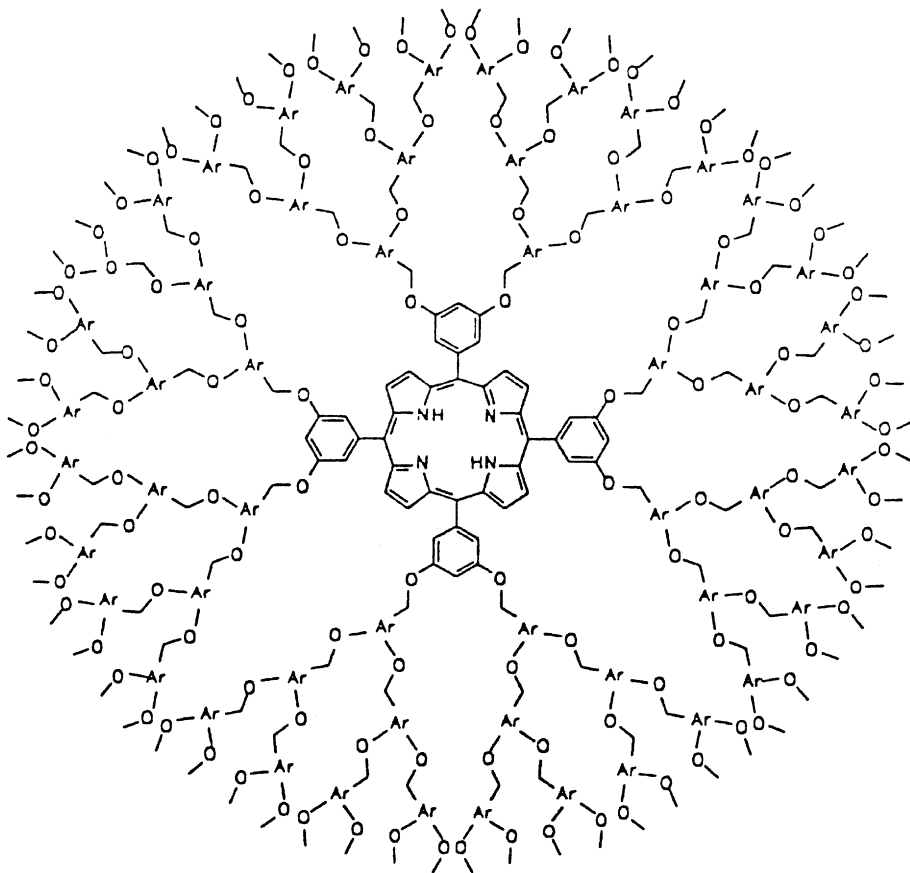


Figure 13.2.2. Schematic illustration of a porphyrin-type dendrimer prepared with zinc as the central metal atom (reproduced by permission from F. Vögtle and the *Chem. Soc. Rev.*^{3a}).

The dendrimeric molecule with a porphyrin core and coordinated zinc was first reported by Inoue *et al.*^{7a}

It has been shown that dendrimer branching yields a medium rich in electrons. Substituents prevent electron addition to the positive metal center, which enables a fine control of the redox potential.⁸ It has been shown that the reduc-

tion potential of the zinc-porphyrin dendrimer increases by increasing dendrimer branching of a certain generation. This is explained by the increase of electron density of the micromedium, which prevents electron transfer to the positive metal center.⁹

Dendrimers have already found application in medical diagnosis,⁹ and other practical applications are expected.¹⁰

Recently, Japanese chemists synthesized a dendric macromolecular rod that harvests light over a wide range of wavelengths and converts it to blue light.^{11,12} The rod consists of a rigid poly(phenyleneethylen) conjugated backbone wrapped in a flexible poly(benzyl ether) dendric envelope. Photons in the 220–450 nm region¹² were collected; the quantum yield (fraction of trapped photons converted into fluorescence) is very high, in some cases up to 100%.¹² It was shown that fluorescence is the strongest when the backbone is encapsulated in third-generation dendric wedges. The ability of poly(phenyleneethylen) to fluorescence at a blue wavelength is known. Unfortunately, the molecules tend to aggregate, spoiling their use as light emitters. Using this phenomenon, the authors hope to prepare photoconductive molecular wires.

The American Center for Biologic Nanotechnology has demonstrated several biologically active nanomaterials with an idea to create a catalog of nanocomponents that can be used as building blocks in the creation of larger, highly sophisticated nanodevices.

The question arises about the best way of connecting dendrimers – van der Waals, ionic, covalent or molecular linkers. Currently, efforts are being made to decide which is the best possible architecture.

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A

Chapter 14

METAL COMPLEXES WITH SHORT MEMORY EFFECT

14.1. INTRODUCTION

Transition metal complexes of the $3d^n$ type ($n = 4, 5, 6$, or 7), for which the spin state of the central metal atom changes from high-spin to low-spin when the temperature is lowered, constitute a phenomenon that has been much discussed lately.¹⁻¹⁵ A review article of Gütllich *et al.*¹⁶ citing 192 references covers the field thoroughly until 1993. The phenomenon is accompanied by changes of magnetic and optical properties, which enable the so-called spin crossover (or spin transition) to be easily followed.

Molecular bistability is caused by the presence of the states, the ground state and the metastable state, within which the system can be trapped. The phenomenon was discovered in 1931 by Cambi and Szegő.¹⁷ In due course, it was realized that the spin crossover systems could be used as memory devices.^{18,19} Later, it was found² that the green light switches the low-spin state to the high-spin state; it has practically infinitely long lifetimes below 50 K and the red light switches the system back from the high-spin to the low-spin state. These findings suggested that the spin-crossover compounds might be used as optical switches.

Let us briefly recall the bases for the spin crossover phenomenon on the example of a Fe^{2+} complex ion (Fe^{2+} surrounded by six ligands situated at the apices of an octahedron). Such ions can exist either as low-spin or high-spin ions. The alternative electronic structures are primarily due to the strength of the ligand field.²⁰ The examples often used are the complex ions $[Fe(CN)_6]^{4-}$ and $[Fe(H_2O)_6]^{2+}$. In $[Fe(CN)_6]^{4-}$ six CN^- ligands induce a “strong” field and the energy difference between e_g and t_{2g} energy levels is larger than the analogous energy difference in $[Fe(H_2O)_6]^{2+}$ ion, where the six H_2O ligands induce a weak field. The situation is depicted in Figure 14.1.1.

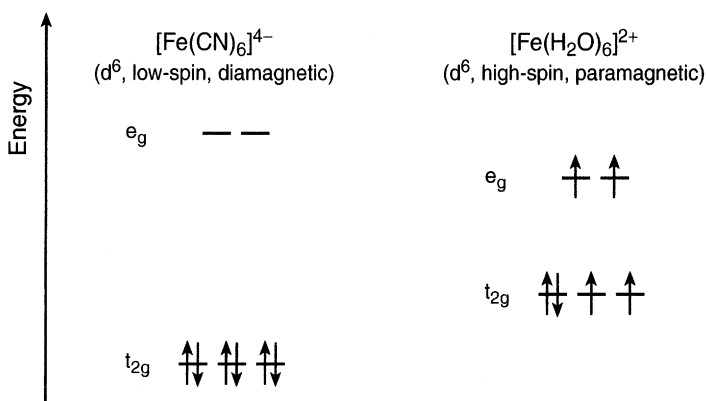


Figure 14.1.1. In the low-spin state, six d^6 electrons are paired at the t_{2g} level. In the high-spin state, only two electrons are paired at the t_{2g} level.

The low-spin state has all six electrons paired, whereas the high-spin state has two unpaired electrons at the e_g level. The state to be formed depends on the energy difference, ΔE , between the two states. If ΔE is large, the electron may be forced to pair with an electron in a t_{2g} orbital even though the pairing requires the so-called pairing energy, P . This energy is needed to overcome the interelectronic repulsion. Thus, the high-spin state is caused by $\Delta E < P$, and the low-spin state by $\Delta E > P$. According to Hund's rule, this results in two unpaired electrons at the e_g level of the $[\text{Fe}(\text{H}_2\text{O})_6]^{2+}$ ion, as shown in Figure 14.1.1.

The P value depends upon the metal ion. On the other hand, ΔE is different for each complex. Values of ΔE can be obtained from the studies of the absorption spectra of the respective complexes. If the complex is $[\text{Ti}(\text{H}_2\text{O})_6]^{3+}$, which is a $3d^1$ system, there is only one electron that can occupy either t_{2g} or e_g orbitals. The wavelength of light absorbed most strongly by this ion is 490 nm and the corresponding energy ΔE is about 243 kJ mol^{-1} .

Interpretation of the absorption spectra of complexes with more than one d electron is much more complicated, since more than two arrangements of d electrons are possible.

The spin crossover phenomenon, as pointed out by Kahn,¹ may be induced by the variation of temperature, pressure or by irradiation. The crossover occurs when the enthalpy of the low-spin state in its equilibrium geometry is slightly lower than that of the high-spin state, also in its equilibrium.² At low temperatures, the thermodynamically stable state is the low-spin state with the lowest enthalpy ΔH . Since the free Gibbs energy, ΔG , is given by the equation:

$$\Delta_r G = \Delta_r H - T\Delta_r S \quad (\text{at constant } T)$$

the decrease of the enthalpy, ΔH , results in a decrease of the free energy ΔG . On the other hand, when the temperature is increased, the high-spin state might become the thermodynamically stable state, because the entropy associated with the high-spin state is larger than the entropy of the low-spin state. This might lead to a larger decrease in the Gibbs free energy and, consequently, to the increase of the equilibrium constant of the low-spin $\rightleftharpoons$ high-spin crossover, because a decrease of the standard Gibbs free energy, ΔG° , determines the equilibrium constant:

$$-\Delta_r G^\circ = RT \ln K^\circ$$

The two-electron transfer between the t_{2g} and e_g orbitals causes a lengthening of the Fe-ligand bonds. In the high-spin state, the bonds are longer by about 0.015–0.020 nm, causing an abrupt transition along with hysteresis loops.²

Figure 14.1.2. shows the spin crossover behavior of a sample of *cis*-bis(thiocyanato)bis[*N*-(2'-pyridylmethylene)-4-(phenylethynyl)anilino]iron(II) (**I**) made of single crystals, accompanied by changes in the molar magnetic susceptibility (χ_M). At room temperature, $\chi_M T$ is equal to $3.5 \text{ cm}^3 \text{ K mol}^{-1}$; by lowering the temperature, it decreases smoothly to $3.0 \text{ cm}^3 \text{ K mol}^{-1}$, and then drops suddenly to about 194 K. At 80 K, $\chi_M T$ is close to zero. The warming and cooling modes reveal the thermal hysteresis loop.^{1,4} The thermal hys-

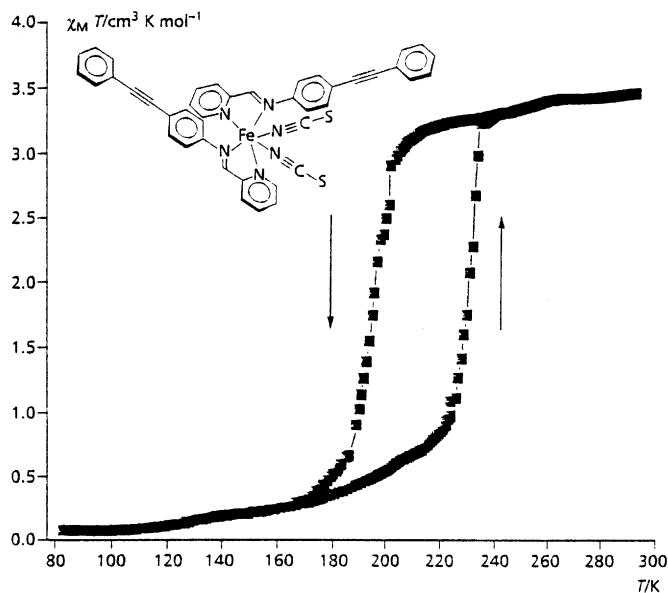


Figure 14.1.2. Spin crossover behavior of **I** showing the thermal hysteresis loop. Reproduced by permission of the authors (J. F. Létard *et al.*, ref. 4) and the American Chemical Society.

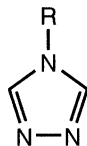
teresis width amounted to about 40 K, and it roughly ranged from 180 to 220 K, *i.e.*, a rather low temperature.

Figure 14.1.2 shows a thermal hysteresis width of about 37 K with $T_c \uparrow = 231$ K and $T_c \downarrow = 194$ K ($T_c \uparrow$ = critical temperature in low-spin $\rightarrow$ high-spin transition in the warming mode, while $T_c \downarrow$ = critical temperature in high-spin $\rightarrow$ low-spin transition in the cooling mode; $T_{1/2}$ is the temperature for which there is 50 percent of the low-spin complex).

In a memory device, we must be able to read easily the state of the system by measuring a physical property, *e.g.*, magnetic property in the described cases. The high-spin and the low-spin electronic states depend on their history and hence on the information that the system stores.

Most attractive spin transition materials are those for which room temperature falls in the middle of the thermal hysteresis loop, which is not the case with complex **I**, as can be seen in Figure 14.1.2. However, Kahn *et al.*⁴ succeeded in increasing the transition temperature by replacing the two NCS groups (bound to the Fe^{2+} ion) by NCSe groups. Thus, the compound became bistable at 293 K. Unfortunately, the spin crossing transitions of the mentioned compounds exhibited no color changes (thermochromism) and, therefore, proved to be unsuitable for display devices.¹

Triazole and pyrazole are excellent chelating ligands to form six-coordinate iron complexes with a chain structure. An iron(II)-triazole complex was first reported to exhibit a spin transition above room temperature by Haasnoot *et al.*²¹ Kahn and co-authors^{22,23} prepared also several polymeric compounds in which Fe^{2+} ions were bridged by the 4-R-1,2,4-triazole system:



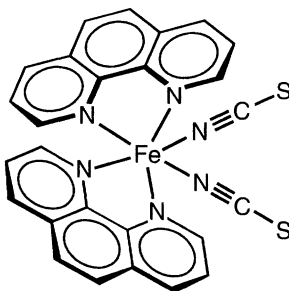
4-R-1,2,4-triazole (Rtrz)

Most of these compounds have a general formula: $[\text{Fe}(\text{Rtrz})_3\text{A}_2 \cdot n\text{H}_2\text{O}]$, where A is an anion and $n\text{H}_2\text{O}$ stands for non-coordinated water molecules.^{3,6} For all compounds, the authors investigated the structure in the low-spin state, consisting of linear chains in which the neighboring Fe atoms were triply bridged by Rtrz ligands through the N atoms in positions 1 and 2 of the Rtrz.^{18,19} The mentioned compounds exhibited a spin crossover accompanied by the color change from violet low-spin to colorless high-spin states. Some compounds showed a very abrupt transition, and a well defined thermal hysteresis loop that was highly reproducible, *e.g.* $[\text{Fe}(\text{NH}_2\text{trz})_3](\text{NO}_3)_2$ switched at $T_c \uparrow = 348$ K and $T_c \downarrow = 313$ K.^{1,2,4} Between $T_c \uparrow$ and $T_c \downarrow$, the system was bistable.

Transitions can be governed by the synergy between the spin transition and dehydration-rehydration processes, as pointed out by Kahn *et al.*²⁴ They observed that at room temperature, $[\text{Fe}(\text{NH}_2\text{trz})_3](\text{tosylate})_2 \cdot 2\text{H}_2\text{O}$ was low-spin and had a violet color. As the temperature increased, the non-coordinated water molecules were removed, followed by an abrupt transition at 361 K from the metastable low-spin state to the stable high-spin state. The $T_c \downarrow$ occurred at 279 K and $T_c \uparrow$ at 296 K. The dehydrated material was hygroscopic and spontaneously reverted to the starting material, $[\text{Fe}(\text{NH}_2\text{trz})_3](\text{tosylate})_2 \cdot 2\text{H}_2\text{O}$.

Some other Fe^{II} -1,2,4-triazole compounds were previously described.^{10,11,13,25}

A spin-crossover study on one of the most studied iron(II) complexes, the $[\text{Fe}(\text{phen})_2(\text{NCS})_2]$ (phen = 1,10-phenanthroline) was recently published:²⁶



Single crystals of the complex were irradiated with an He/Ne laser ($\lambda = 647 \text{ nm}$, $T = 30 \text{ K}$). The magnetic transition upon irradiation revealed that Fe–N bond lengths were much shorter (and the distortion parameters lower) in the low-spin state than in the high-spin state.

An important feature of the effect of light irradiation is the absence of any fatigue based on the spin-crossover phenomenon. The authors have concluded that the general modification of the intermolecular interaction topology mainly consists of variations of the sulfur-carbon distances during irradiation. They consider this observation as relevant information for a general study of photo-excited states in future attempts to design materials for electric molecular devices.

14.2. MAGNETIC MATERIALS AND INFORMATION STORAGE

It is well known that magnetic materials (used for information storage) are metallic alloys and oxides. On the other hand, molecular compounds exhibiting the spin crossover phenomenon can be also used for information

storage, especially if they exhibit thermochromic behavior. A temperature sensor can be provided not only by a color change, but also by a change of magnetic properties. It is even possible to design a material that would undergo spin transition at a desired temperature. In magnetic resonance imaging, it might prove important to know the temperature *in situ*, and to receive a signal when the upper limit temperature has been reached.^{1,2}

14.3. HYPERTHERMY TREATMENT OF SOME TUMORS

The procedure is based on the fact that the tumor affected cells are more sensitive to hyperthermy than healthy cells. In the treatment, it is important to reach the temperature not higher than that at which necrosis of both healthy and diseased cells would take place. The idea is to design the spin transition crossover compounds with transition temperatures of this upper limit. At the critical temperature, the electron crossover causes a change of the magnetic resonance image, since the low-spin diamagnetic complex becomes a high-spin paramagnetic compound.

A number of world-known research centers are engaged in these projects [*e.g.*: Laboratoire des Sciences Moléculaires, Institut de Chimie de la Matière Condensée de Bordeaux, Pessac, France (Professor Olivier Kahn[†], and now his previous coworkers); University of Mainz, Institut für Anorganische Chemie und Analytische Chemie (Professor Philipp Güthlich); Institut für Anorganische und Physikalische Chemie der Universität Bern (A. Hauser); and others].

It is expected that different new bistable molecules with memory effects will be prepared in the near future and will find various applications.

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Chapter 15

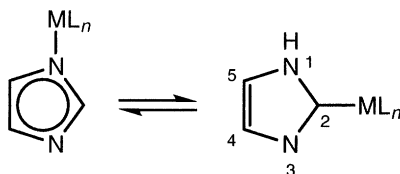
SOME RECENT PUBLICATIONS IN THE SCIENTIFIC SPOTLIGHT

15.1. INTRODUCTION

As already mentioned in the Preface, during the writing of the book several papers relevant to the book's subject have been published. Although a time distance is usually needed for a proper appreciation of recent papers, the author discusses a few of them in this Chapter. The selection is very arbitrary, and limited by the author's own interest and judgment, and the available space.

15.2. C-BINDING *vs.* N-BINDING OF IMIDAZOLES TO METAL FRAGMENTS

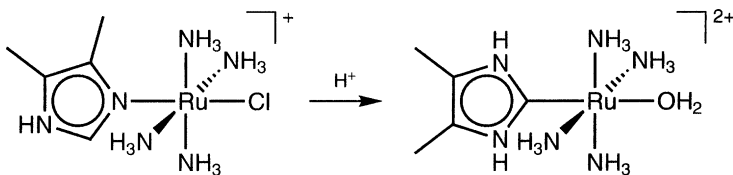
The nature of bonding of imidazole and pyridine to Co^{III} , Fe^{III} and Ru^{III} was discussed in section 8.4. It was mentioned that imidazole is a considerably poorer π acceptor than, *e.g.*, pyridine. In contrast to the good π -donor properties of imidazole, pyridine is a much weaker π donor, since pyridine does not have a high energy HOMO as does imidazole. In any case, it was always assumed that a metal is bound to one of the ring's nitrogen atoms. A recent paper by Sini *et al.*¹ shows that this is not necessarily the case and that the metal may be bonded to one of the imidazole carbons. The authors (G. Sini, University of Cergy-Pontoise, France; O. Eisenstein, University of Montpellier, France; R. H. Crabtree, Yale University, New Haven, Connecticut, U.S.A.) used the density functional method² to calculate the relative stabilities of the C- and N-bonded isomers:



In the above equilibrium, M denotes a metal and L_n denotes a variety of ligands. Imidazole-derived carbenes bonded at C-2 are known.³ The shift from the C-bonded isomer to the N-bonded isomer has been shown to have a high activation energy.¹

The rearrangement is actually not seen but, as the authors claim,¹ this does not prove that the C-bonded form is more stable, because these species were only formed by a direct attack of an amine on $M(CNR)$, giving the C-bound imidazole.

In fact, in just one case has a conversion of the mentioned type been seen, namely, H. Taube *et al.*⁴ have shown that acid catalyzed conversion from N- to C-binding occurs in the reaction:



Sini *et al.*¹ found that for several second- and third-row transition metals (*e.g.*, for palladium, osmium and platinum) the C-bound imidazoles are predicted to be thermodynamically more stable than the usual N-bound forms. On the other hand, CuCl prefers the N form, probably because the electropositive Cu prefers to bind to the electronegative N.¹

For the mentioned Taube complex, involving unsubstituted imidazole, calculations indicate¹ that the N form is more stable.

The observations reported are valid for imidazole itself but cannot be safely extended to N-substituted imidazoles.

The N-substituted imidazole isomer is by far the most likely tautomer for the first-row elements.

The C binding is expected to drastically change the properties of the metal. Nature might employ this change in certain metalloproteins, as the authors suggest.¹

References (section 15.2)

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15.3. HEXAPHYRIN, AN EXPANDED PORPHYRIN LIGAND FOR THE UO_2^{2+} AND NpO_2^+ COORDINATION

The unique properties of actinides have revolutionized the modern world with regard to the nuclear energy production. Isolation of the transuranic actinides from a matrix, including fission products and uranium, requires an efficient separation for actinide purification.

Porphyrin macrocycles have been recognized as excellent cation complexation agents for cations of the late transition series.¹

J. L. Sessler, University of Texas, Austin, (whom we have already met, see section 8.10 – gadolinium texaphyrin), and D. W. Keogh of the Seaborg Institute at Los Alamos National Laboratory, together with their coworkers,^{2–4} have shown that an expanded porphyrin, called hexaphyrin, is an excellent complexation agent for binding the late transition series cations of uranium, neptunium and plutonium. It was prepared from a linear precursor by oxidation with aqueous $\text{Na}_2\text{Cr}_2\text{O}_7$ and acid-catalyzed condensation in the trifluoroacetic acid solvent (TFA), as depicted in Figure 15.3.1:

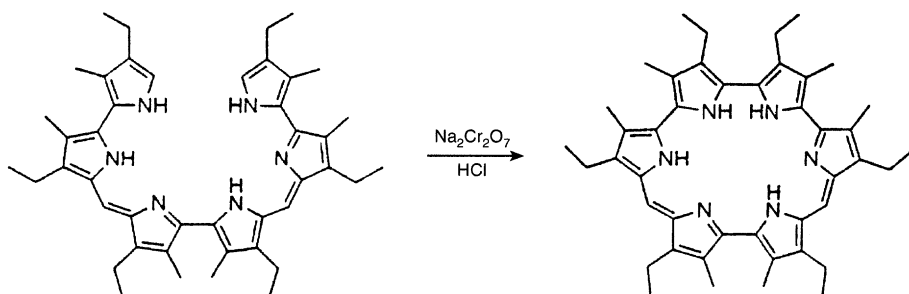


Figure 15.3.1. Hexaphyrin, prepared from a linear hexapyrrolic precursor² (reproduced by permission from J. L. Sessler and the Wiley-VCH, STM-Copyright & Licenses).

The resulting chelating macrocyclic ligand, hexaphyrin, rendered adequate space for coordination of the large late transition series cations of uranium, neptunium and plutonium. Subsequent addition of $\text{UO}_2(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ in the presence of a base gave the uranyl complex in 74% yield² (Figure 15.3.2).

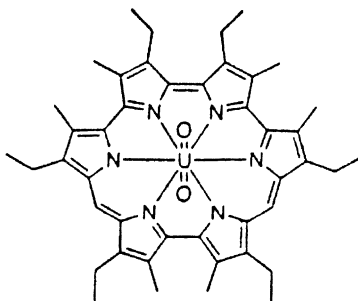


Figure 15.3.2. The uranyl complex² (reproduced by permission from J. L. Sessler and the Wiley-VCH, STM-Copyright & Licenses).

The authors have concluded that hexaphyrin in its oxidized, aromatic form is capable of complexing actinide ions, specifically uranyl (UO_2^{2+}) and neptunyl (NpO_2^+); neptunyl represents the first crystallographically characterized neptunium complex. The complex is very stable and the authors believe that the system could see application in remediation of radioactive waste.²

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15.4. ALKANE PICOSECOND CARBON-HYDROGEN BOND CLEAVAGE AT THE IRIIDIUM CARBONYL CENTER

The use of metals to activate the alkane C–H bond cleavage has been known for some time.^{1–4} First observations were made upon irradiation of the rhodium $\eta^5\text{-C}_5\text{H}_5\text{Rh}(\text{CO})_2$ complex. It has been well established that C–H bond activation involves the initial fragment $\text{CpRh}(\text{CO})$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) generated upon irradiation of the corresponding dicarbonyl complex. At room temperature, in cyclohexane, the $\text{CpRh}(\text{CO})(\text{cyclohexane})$ solvate is formed, which undergoes conversion to $\text{CpRhCO}(\text{cyclohexyl})(\text{H})$ on the nanosecond to microsecond time scale.

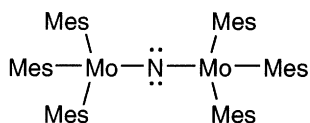
Using a new, very sensitive femtosecond infrared spectrometer, Asbury *et al.*⁵ have recently shown that iridium-mediated cleavage (instead of rhodium mediated) of alkane C–H bonds is exceptionally rapid, occurring in the 2 ps range, suggesting a negligible barrier for C–H activation. These authors have concluded that the rate of C–H activation at iridium is 3–5 orders of magnitude faster than that for C–H activation by the corresponding rhodium complex. Upon absorption of a 267 nm photon, the excited $\text{CpIr}(\text{CO})_2$ molecule reacts through two pathways:⁵ about 80% of the molecules relax to a nondissociative excited state $\text{CpIr}(\text{CO})_2^*$ with a 10 ps lifetime, while 20% undergo dissociation, losing a CO ligand and yielding CpIrCO , or a solvate of this species. The activation of a cyclohexane C–H bond in the CO-dissociation pathway was found to occur within 2 ps, *i.e.*, the conversion to $\text{CpIrCO}(\text{cyclohexyl})(\text{H})$ proceeds with a negligible energy barrier. The authors claim this to be the first report of a picosecond alkane C–H bond activation in solution at room temperature.

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15.5. PHOTOCHEMICAL ACTIVATION OF THE $\text{N}\equiv\text{N}$ BOND IN A DIMOLYBDENUM-DINITROGEN COMPLEX

Solari *et al.*¹ have cleaved the $\text{N}\equiv\text{N}$ bond using light and transition metal complexes. Only two research groups^{2,3} have given information on the pathways leading to the six-electron reduction of nitrogen. Professor Carlo Floriani of the University of Lausanne, Switzerland, with coworkers,¹ claims that such a reduction is a stepwise metal-assisted transformation, consisting of a four-electron reduction of N_2 , leading to a dimetallohydrazone, $\text{L}_n\text{M}=\text{N}=\text{N}=\text{ML}_n$, followed by a final cleavage of the $\text{N}-\text{N}$ bond. Their report is focused on the generation of the $[\text{Mo}(\text{Mes})_3]$ fragment (Mes = mesityl = 2,4,6- $(\text{CH}_3)_3\text{C}_6\text{H}_2$), as an active species for achieving the four-electron reduction of dinitrogen in $[(\text{Mes})_3\text{Mo}=\text{N}=\text{N}=\text{Mo}(\text{Mes})_3]$. This complex does not usually undergo further reduction to the corresponding metal nitrides, which makes its potential photolability of special interest with regard to nitrogen reduction.¹ When this compound is exposed to UV light, it undergoes a photoinduced cleavage of the residual $\text{N}-\text{N}$ bond to give the Mo_2N complex,



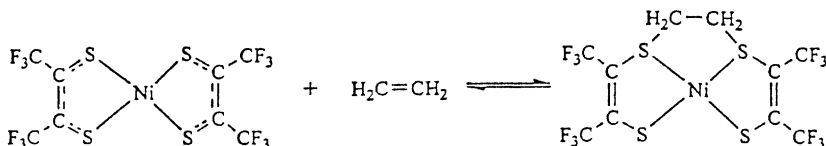
in 79% yield. Some details of the mechanism are still being discussed.

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15.6. SEPARATION AND PURIFICATION OF OLEFINS USING DITHIOLENE COMPLEXES

Nickel dithiolene complex reacts with light olefins, including ethylene and propylene, selectively and reversibly, report Kung Wang and Edward I. Stiefel¹ of Exxon Mobil Research & Engineering, Annandale, N. J. The olefin binding occurs through the bridging sulfurs rather than through the metal center:



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The authors found that, under mild conditions, the reaction proceeds with simple aliphatic olefins, selectively and reversibly, to form 1:1 adducts. Upon reaction with olefins, the deep purple solution turns light yellow. The 1:1 adducts are formed when an olefin is in the oxidized form, and the bound olefin is released when it is reduced. Fast on-off switching from the higher to lower oxidation state by electrochemical control allows binding and then release of the olefin, thus enabling olefin separation from other components and its purification. The purification makes use of the rapid binding of an olefin by the electrochemically generated neutral dithiole species and the subsequent release of the olefin upon electrochemical reduction of the adduct. In this way, reversible olefin complexation to dithiolene complexes offers a novel approach to olefin separation and purification.

The equilibrium constants for different olefin binding are roughly of the same magnitude, but bulkier olefins have somewhat smaller equilibrium constants.^{1a} The reaction rates are sensitive to the electronic states of the olefins. Thus, faster reactions of propylene *versus* ethylene may be attributed to the electron-rich double bond in propylene. Generally speaking, the initial rates exhibit a trend with electron-rich olefins reacting faster. The reaction can be viewed as electrophilic addition of the nickel complex to the olefin, with the olefin donating electron density into the LUMO of the nickel complex. The reaction with 1-hexene is mildly exothermic ($\Delta_r H = -33.9 \text{ kJ mol}^{-1}$, suggesting that olefin binding is not very strong).^{1b} The entropy of activation, $\Delta^\ddagger S$, amounts to $-150.6 \text{ J K}^{-1} \text{ mol}^{-1}$ in cyclohexane at 30–60 °C. The large negative entropy of activation is consistent with the bimolecular addition reaction, indicating a highly ordered transition state. The lightest olefin, ethylene, is an

organic chemical produced in the largest volume, thus its purification is of extreme importance to the chemical industry.

References (section 15.6)

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15.7. HIGHLY EFFICIENT RING-OPENING METATHESIS POLYMERIZATION (ROMP)

Ring-Opening Metathesis* Polymerization (ROMP) has become an efficient tool for the preparation of a variety of macromolecular structures.¹ The term ROMP was coined by the California Institute of Technology professor R. H. Grubbs. The reaction uses strained cyclic olefins to produce stereoregular and monodisperse polymers. Recently, a highly efficient initiator of olefin polymerization has been developed by professor Grubbs and C. W. Bielawski.² The importance of this achievement has been recently pointed out by M. Rouhi.³ The most widely used catalysts for ROMP and other metatheses are complexes based on molybdenum and ruthenium. The molybdenum ROMP catalyst² exhibits a much higher activity than the ruthenium one. However, the latter catalyst is much more stable; the newly developed ruthenium carbene catalyst of Bielawski and Grubbs, Figure 15.7.1(a), is more efficient than any of previous ROMP catalysts: it mediates ring-opening metathesis polymerization,

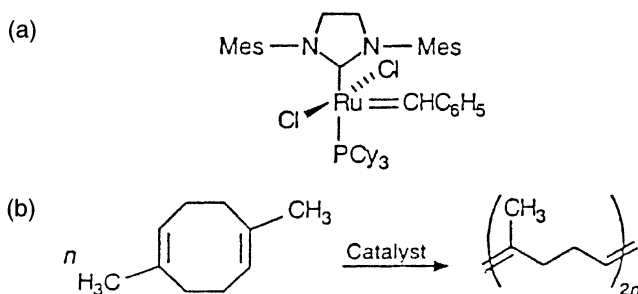


Figure 15.7.1. (a) Ruthenium ROMP carbene catalyst (Mes = mesityl = 2,4,6-trimethylphenyl; Cy = cyclohexyl); (b) Opening of the cyclic olefin monomer ring leaves a reactive end for further polymerization (reproduced by permission from R. H. Grubbs and the Wiley-VCH, STM-Copyright & Licenses).

* Metathesis (in chemistry): a chemical reaction in which different kinds of molecules exchange parts to form other kinds of molecules.

as shown in Figure 15.7.1(b), leaving a reactive end; the reactive end opens a second monomer ring, propagating the chain reaction.

Subsequent hydrogenation² using *p*-toluenesulfonylhydrazide as the hydrogen source afforded an ethylene-propylene copolymer in quantitative yield. This appears to be the first ROMP of this monomer. Previously, a six-step synthesis was necessary to obtain a similar copolymer.⁴

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15.8. SUPRAMOLECULAR CLUSTER CATALYSIS: BENZENE HYDROGENATION CATALYZED BY A CATIONIC TRIRUTHENIUM CLUSTER

Organometallic catalysis most often proceeds through a catalytic cycle that involves coordination of the substrate to the metal center of the catalyst. In all these reactions, the elementary steps of the catalytic action were believed to occur within the first coordination sphere of the organometallic catalyst, but the most recent work of professor Georg Süss-Fink, in collaboration with Matthieu Faure and professor Thomas R. Ward, Institute of Chemistry, University of Neuchâtel, Switzerland,¹ showed that it need not always be so. They supplied evidence that the ruthenium cluster cation (Figure 15.8.1) catalyzes

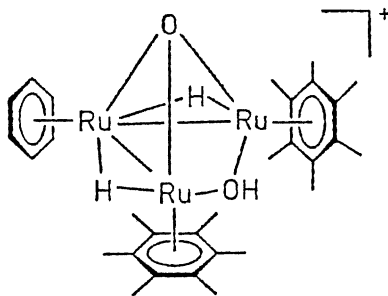


Figure 15.8.1. Organometallic cluster cation catalyst of G. Süss-Fink *et al.*¹ for hydrogenation of ethylbenzene to ethylcyclohexane (reproduced by permission from G. Süss-Fink and the Wiley-VCH, STM-Copyright & Licenses).

the hydrogenation of benzene to cyclohexane under mild conditions, the interactions between the catalyst and the substrate relying only on weak intermolecular contacts. Thus, they found that the catalytic hydrogenation of ethylbenzene to ethylcyclohexane proceeds at a catalyst/substrate ratio of 1 : 1000, under hydrogen pressure of 60 bar at 110 °C, with rigorous stirring of the aromatic substrate under aqueous biphasic conditions.

The cluster cation can be isolated from the reaction mixture as the BF_4^- salt. The authors suggest that the catalytic hydrogenation involves a stepwise mechanism, as depicted in Figure 15.8.2; they believe that the hydrogenation of the aromatic substrate occurs within the hydrophobic pocket of the catalyst,² *via* cyclohexadiene and cyclohexene intermediates. This implies that after the dihydride transfer, the partially reduced substrate leaves the hydrophobic pocket. The catalyst is finally regenerated by H_2 oxidative addition.

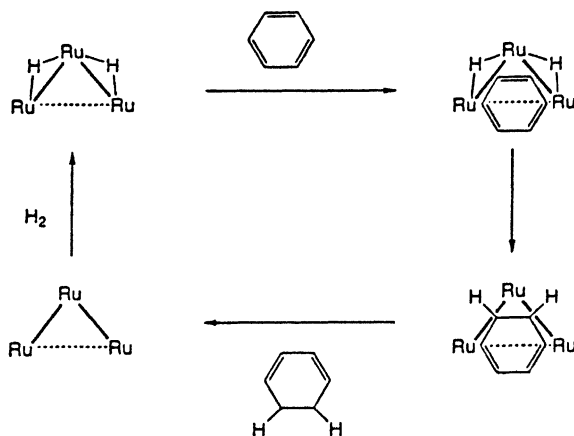


Figure 15.8.2. Mechanism proposed by G. Süß-Fink, M. Faure, and T. R. Ward¹ for the stepwise catalytic hydrogenation of benzene to cyclohexane *via* 1,3-cyclohexadiene (reproduced by permission from G. Süß-Fink and the Wiley-VCH, STM-Copyright & Licenses).

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15.9. A TRIMER OF ZINC(II), RUTHENIUM(II), AND TIN(IV) PORPHYRINS CALLED THE TRINITY OF METALS

Hee-Joon Kim, Nick Bampos, and Jeremy K. M. Sanders of the University of Cambridge, England, report what they claim to be the first association of heterometallic porphyrin oligomers designed to exhibit complementary geometries and cooperative binding properties.¹

The authors chose Zn^{II} , Ru^{II} , and Sn^{IV} porphyrins, making use of the contrast in their coordination chemistry, and assembled multiple components in a controlled manner. The authors were aware that Zn porphyrins prefer nitrogen donor ligands, adopting a 5-coordinate square pyramidal geometry, and are kinetically labile, while $\text{Ru}(\text{CO})$ porphyrins form stable and inert complexes with nitrogen donor ligands adopting a 6-coordinate geometry. On the other hand, Sn^{IV} porphyrins prefer oxygen donor ligands and the octahedral geometry and exchange carboxylate ligands slowly. The Sn^{IV} porphyrin rotates about the Sn^{IV} –carboxylate bond in pyridine, but the addition of the ruthenium

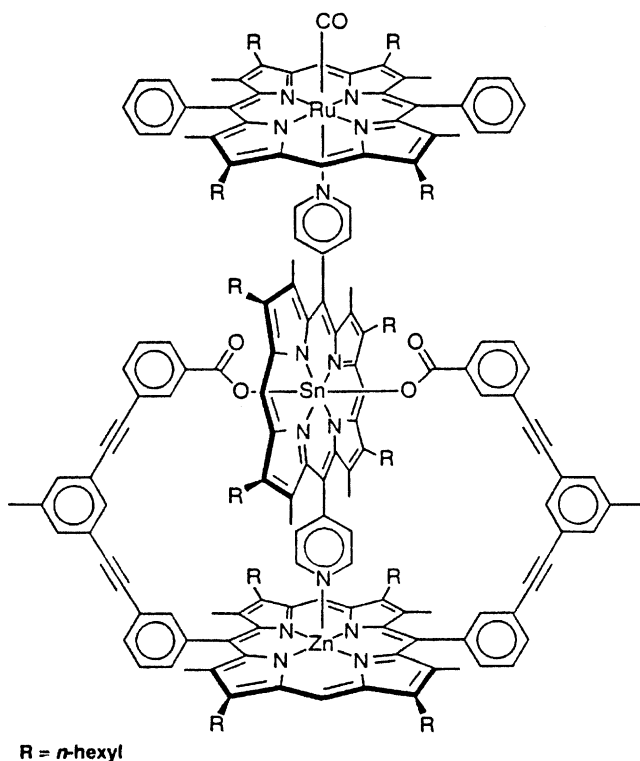


Figure 15.9.1. A porphyrin trimer assembled from zinc(II), ruthenium(II), and tin(IV),¹ (reproduced by permission from J. K. M. Sanders and the American Chemical Society).

porphyrin transforms the structure into a rigid one. Mairin Brennan,² the reviewer of *Chem. Eng. News*, informed us that the same heterotrimer assembled when the authors mixed the individual components in solution.

The trimer represents the first example of a thermodynamically constructed oligoporphyrin containing three different metals. Heteronuclear trimetallic complexes in nonporphyrin systems are known.³

The authors believe that the described work provides a new approach for the preparation of complex porphyrin assemblies, *e.g.*, catenanes.

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15.10. BIS(1,2,3,4- η^4 -ANTHRACENE)COBALTATE(1-)

W. W. Brennessel, V. G. Young, Jr., and J. E. Ellis of the University of Minnesota, Minneapolis, synthesized the homoleptic* bis(1,2,3,4- η^4 -anthracene)cobaltate(1-) salt by reducing CoBr_2 with potassium anthracene in tetrahydrofuran at -55 to -65 °C. A dark red solution resulted, from which deep red, nearly black microcrystals of the bis(anthracene)cobaltate(1-) were obtained in 82–87% yields.¹ Although the analogous naphthalene complex is highly reactive (*e.g.*, it readily reacts with carbon monoxide at normal pressure and at -60 °C to yield $[\text{Co}(\text{CO})_4]^-$), all attempts to isolate this interesting species have failed so far.^{1,2} Reduction of cobaltocene by three equivalents of potassium naphthalene yielded a similarly labile source of Co^{1-} . Isolation and characterization of the homoleptic Co^{1-} isonitrile complexes by other authors also encountered difficulties.³

The ^1H and ^{13}C NMR spectra of the bis(anthracene)cobaltate(1-) were found independent of the cation and it was shown¹ that the stoichiometry in solution is identical to that observed in the solid state. The NMR spectra also indicate that both η^4 -anthracenes, bound to cobalt through one peripheral ring each, are equivalent.¹ This is consistent with the previously observed patterns for the other η^4 -anthracene transition metal complexes^{1,4} (see Figure 15.10.1).

According to J. E. Ellis, the bis(1,2,3,4- η^4 -anthracene)cobaltate(1-) is the first anionic transition-metal complex with anthracene ligands only. The authors

* Homoleptic complexes are compounds in which all ligands bound to the metal center are identical.

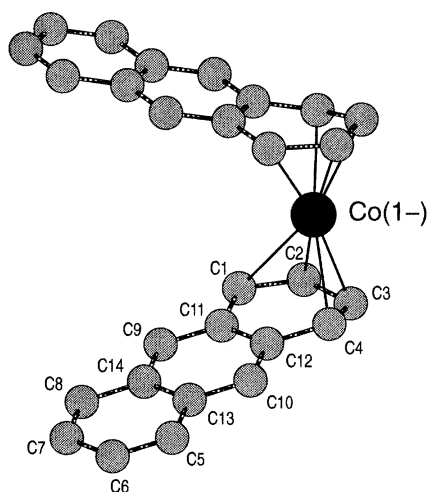


Figure 15.10.1. Simplified structure of the bis(1,2,3,4- η^4 -anthracene)cobaltate(1-), ref. 1; hydrogen atoms are omitted for clarity. Simplification was done by permission of the main author, J. E. Ellis; the copyright permission was issued by Wiley-VCH, STM-Copyright & Licenses.

emphasize that the complex is an effective and facile source of the “naked” cobalt anion, Co^{1-} . Such complexes are valuable because they often mimic free metal atoms in chemical synthesis, enabling a variety of reactions involving cobalt anions.

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1. W. W. Brennessel, V. G. Young, Jr., and J. E. Ellis, *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1211, and refs. therein.
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15.11. sp -CARBON CHAINS SURROUNDED BY sp^3 -CARBON DOUBLE HELICES: A CLASS OF MOLECULES ACCESSIBLE BY SELF-ASSEMBLY AND MODELS FOR “INSULATED” MOLECULAR-SCALE DEVICES

DNA was the first chemical substance to be recognized in 1953 as a double helix. For this discovery, James D. Watson, Francis H. C. Crick, and Maurice Hugh Frederick Wilkins shared the 1962 Nobel Prize for physiology and medicine. Recently, professor J. A. Gladysz, Institute of Organic Chemistry, the Friedrich-Alexander-University Erlangen-Nürnberg, synthesized, in collaboration with colleagues at the University of Utah, a double helical platinum complex.^{1a,b} The complex lacks the conventional binding between helix strands (*e.g.*, hydrogen bonds or covalent bonds to metal templates). The double helix complex consists of a diplatinum sp -carbon chain, $[\text{Pt}(\text{C}\equiv\text{C})_n\text{Pt}]$, with a double helical structure. The authors utilized the $[\text{Pt}(\text{C}\equiv\text{C})_4\text{Pt}]$ complex, involving an eight-carbon tetrayne bridge and square-planar end groups. The complex underwent a facile phosphane substitution.² Pentafluorophenyl (C_6F_5) ligands were introduced to increase the Lewis acidity of platinum in order to retard phosphane dissociation. The end groups could anchor two or more long flexible chains, *e.g.*, polymethylene $(\text{CH}_2)_n$. In a self-assembly process the diplatinum complex reacted with the $[\text{Ar}_2\text{P}(\text{CH}_2)_{14}\text{P}(\text{Ar})_2]$, where Ar = aryl. The reaction product was the double-helical complex in which the two methylene chains (two $(\text{CH}_2)_{14}$ chains) wound around the linear tetrayne bridge. Thus, there were only van der Waals attractions between the helix strands. The authors describe what they believe to be the first molecular analog of beanpoles (the tetrayne bridge functioning as a beanpole), while the sp^3 -carbon chains twist in a double-helical motif, see Figure 15.11.1.

The authors point out that these wire-like assemblies are insulated similarly to electrical cords. The assemblies can be considered to be a novel family of building blocks with potential applications in nanotechnology.

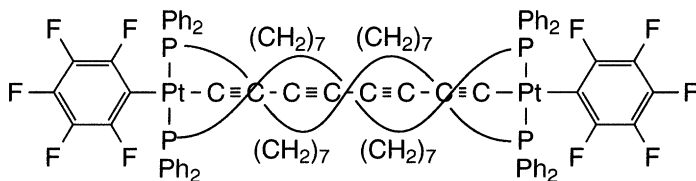


Figure 15.11.1. The double helical diplatinum complex is chiral;^{1a} both enantiomers are presented in the unit cell. (Reproduced by permission of the principal author, professor Gladysz, and the Wiley-VCH, STM-Copyright & Licenses).

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15.12. FERROCENE AND FULLERENE HYBRID

The idea of the fusion of a molecule of ferrocene with a molecule of fullerene is intriguing since such a “bucky ferrocene” would exhibit the properties of both parent molecules. Very recently professor Eiichi Nakamura, University of Tokyo, with his collaborators¹ synthesized such a ferrocene/fullerene hybrid molecule by a route as depicted in Figure 15.12.1¹. The route involved a suitably modified fullerene derivative that can act as a 6π -electron donor to the d^6 iron(II) atom.^{2,3} By heating $C_{60}Me_5H$ (**1**) and $[FeCp(CO)_2]_2$ (Cp = cyclopentadienyl) together in benzonitrile at 180 °C for 8 hours, the product (**2**) was obtained in 52% isolated yield.

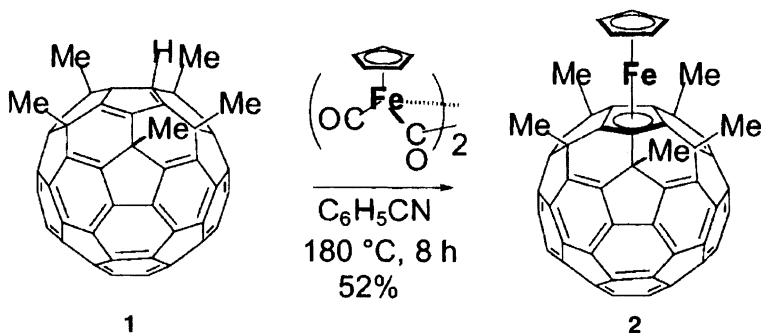


Figure 15.12.1. Synthesis of ferrocene/fullerene hybrid molecule (**2**). The single and double bonds in fullerene are only formal, as for fullerene itself.¹ (Reproduced by permission from the principal author E. Nakamura, and from the American Chemical Society.)

Compound **2** was found extremely stable (even after standing for many months in air, or after 24 h at 200 °C in *vacuo*, or after irradiation in benzene with a high-pressure mercury lamp under nitrogen for 15 h).¹

The cyclopentadienide ring can be a part of a C₆₀ or C₇₀ cage. The methyl groups provide an adequate electronic environment making the pentagon they surround a suitable 6π -electron ligand for the iron.

The hybrid molecule can not only be oxidized reversibly like ferrocene but it can be reduced reversibly like fullerene. This offers a very special com-

bination of redox properties of such hybrids, which might find application as building blocks in material science, and in construction of various nanostructures with promising electronic properties. Modifications of ferrocene moiety and the versatile chemistry of the fullerene core are promising in this respect.^{4,5}

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EPILOGUE

The majority of publications in the field of inorganic chemistry (about 2/3) are related to transition metal complexes. This includes organometallic chemistry, catalysis and bioinorganic chemistry. It may be expected that the future research in inorganic chemistry will be intensively pursued in these fields.

Electron-transfer reactions, especially long distance electron-transfer reactions in biological systems, will probably be of primary interest. The influence of the media on the rates of electron-transfer reactions is still poorly understood. It has been established that the electron-transfer reactions can occur at quite high rates when the reactants are separated far beyond the distances of collision. It has been observed that if reactants are linked by an aliphatic chain, the rates can be substantially enhanced. Such studies will be especially pursued in redox reactions involving proteins.

It appears that the electron transfer in some biological systems is temperature independent at temperatures close to absolute zero. It is therefore inferred that such reactions proceed through a quantum mechanical tunneling mechanism, sometimes involving distances up to 30 Å (3 nm). Such electron transfers seem to be involved in biological redox reactions of chloroplasts and mitochondria. It appears that the electron-transfer reactions will be one of the central subjects of inorganic reaction mechanism studies in the future.

Researchers are more and more concerned with the total free and bound metal content of a cell under the given growth conditions; the term "metal-lome" has been coined as a clear parallel to the genome. The experiments recently performed, focused predominantly on iron- and copper-containing enzymes, showed that biological processes undergo considerable isotope fractionation, which should enable studies of the heavy element uptake into cells. Researchers already talk of metal shuttling within cells. It can be expected that many proteins that mediate between metals and living organisms will be identified, which will broaden our knowledge of how these proteins actually function.

Metallocene chemistry is presently a very promising field of inorganic chemistry. *E.g.*, metallocene complexes of titanium and zirconium play an important role in the production of polymers. The role of ferrocene derivatives as effective nucleophilic catalysts in kinetic resolutions of many useful

organic reactions has been observed and this type of research will be certainly carried on. "Molecular recognition" has been widely employed in studying molecular systems that show specific interactions with particular molecules, a borderline field between organic chemistry, inorganic chemistry and biochemistry. Substituted ferrocenes have been used to prepare bisferrocenes containing a potential bonding cavity. A "correct" substrate can selectively organize the receptor to "correct" conformation, yielding an element of recognition. It should be expected that such template reactions will occupy the future attention of inorganic chemists.

Recently, some low-molecular-weight catalysts have been found that mimic enzymes and have potential practical applications. Reactions of limited complexity, mediated by metalloenzymes, have been reported. One such example is a mimic of the copper enzyme galactose oxidase, which catalyzes the oxidation of primary alcohols to aldehydes in the presence of air.

Nitrogen fixation, catalyzed by transition metal complexes, will most probably be achieved in the future, but it appears that there is still a long way to achieving catalyzed production of ammonia from nitrogen and hydrogen under mild conditions.

The understanding of organic reaction mechanisms has always been associated with the hope of achieving a synthetic path. Nowadays, chemists attempt to "tailor" a catalyst by introducing ligands into certain positions so as to selectively promote a planned reaction. Such attempts are often done in enzyme catalyses.

Certain optically active octahedral transition metal cations exhibit very effective antiviral or antibacterial activity. As described in the present book, platinum(II) complexes are used as effective antitumor agents. New discoveries should be expected in this field.

The thermally induced spin crossover phenomenon found in the solid state, as well as in solutions of the complexes of iron(II), iron(III) and cobalt(II), is a very promising, relatively new research field. In these complexes, the spin state of the central atom changes from high spin to low spin when the temperature is lowered. This phenomenon is expected to find application in the treatment of some tumors by hyperthermy. A transition metal complex is expected to be designed in such a way that its upper-limit transition temperature corresponds to the temperature desired for the treatment of some tumors by hyperthermy. It should be expected that the crossover phenomenon will attract a number of researchers.

The sequence of linked metalloporphyrins has been found to act as a photonic wire. The photonic wire has some properties analogous to optical fibers and is expected to serve in information sciences. Ferrocene oligophenylene-vinylene methyl thiol bridges could be useful for wiring molecular electron-

ic elements because they exhibit rapid electron tunneling.

Computational chemistry and modeling will become a way of guiding researchers in the right direction, enabling them to realize whether it would be promising to study a certain reaction or not.

Nanotechnology and molecular electronics are progressing rapidly. As semiconductor devices approach their physical limits, researchers are trying to find ways to decrease the size of microelectronic circuits. Thus, cylindrical micelles composed of a ferrocenylsilane-siloxane block copolymer assemble on a silicon surface to form linear features. The micelle lines can then be transformed into a pattern of ceramic nanolines and create conjugated polymer nanowires by controlled chain polymerization. The micelle nanostructures can be converted into magnetic ceramic nanopatterns. It is possible that these lines will display magnetic, conductive and semiconductive properties.

The American Center for Biologic Nanotechnology has demonstrated several biologically active nanomaterials with an idea to create a catalog of nanocomponents that can be used as building blocks in the creation of larger, highly sophisticated nanodevices. The Center expects that a warehouse of viral protein recognition dendrimers will be stocked. This might enable building a particular antiviral dendrimer by coupling the appropriate dendrimer from the warehouse to a standard dendrimer, and a metal cation. It is expected that, *e.g.*, a “smart” anticancer therapeutic agent will perform functions such as cancer cell recognition, cancer cause diagnosis, drug delivery, reporting tumor location and reporting cancer cell death.

From the title of the book, one might conclude that the book has been planned to deal exclusively with inorganic reaction mechanisms, but we can see that a substantial part of the book deals with the reactions of carbon. This reminds us that the division of chemistry into inorganic and organic belongs to the past.

APPENDIX

Physical and chemical constants

(the CODATA recommendation: [<http://physics.nist.gov/constants>])

P. J. Mohr & B. N. Taylor, *Rev. Mod. Phys.* **2000**, 72, 351–495.)

	Symbol	Value
Avogadro constant	N_A	$6.022\,141\,99 \times 10^{23} \text{ mol}^{-1}$
Boltzmann constant	$k = (k_B) = R/N_A$	$1.380\,650\,3 \times 10^{-23} \text{ J K}^{-1}$ $8.617\,342 \times 10^{-5} \text{ eV K}^{-1}$
Gas constant	R	$8.314\,472 \text{ J K}^{-1} \text{ mol}^{-1}$ $0.082\,057 \text{ L atm K}^{-1} \text{ mol}^{-1}$ $1.987\,19 \text{ cal K}^{-1} \text{ mol}^{-1}$
Molar volume of the ideal gas ($p = 1 \text{ bar}$, $t = 0 \text{ }^\circ\text{C}$)	V_m	$22.710\,981 \text{ L mol}^{-1}$
Planck constant	h	$6.626\,068\,76 \times 10^{-34} \text{ J s}$ $4.135\,667\,27 \times 10^{-15} \text{ eV s}$
	$\hbar = h/2\pi$	$1.054\,571\,596 \times 10^{-34} \text{ J s}$ $6.582\,118\,89 \times 10^{-16} \text{ eV s}$
Faraday constant	$F = N_A e$	$9.648\,534\,15 \times 10^4 \text{ C mol}^{-1}$
Speed of light in vacuum	c_0	$299\,792\,458 \text{ m s}^{-1}$
Elementary charge	e	$1.602\,176\,462 \times 10^{-19} \text{ C}$
Mass (in rest)		
electron	m_e	$9.109\,381\,88 \times 10^{-31} \text{ kg}$ $5.485\,799\,110 \times 10^{-4} \text{ u}$
energy equivalent	$m_e c^2$	$8.187\,104\,14 \times 10^{-14} \text{ J}$ $0.510\,998\,902 \text{ MeV}$
proton	m_p	$1.672\,623\,1 \times 10^{-27} \text{ kg}$ $1.007\,276\,466\,88 \text{ u}$
energy equivalent	$m_p c^2$	$1.503\,277\,31 \times 10^{-10} \text{ J}$ $938.271\,998 \text{ MeV}$
neutron	m_n	$1.674\,927\,16 \times 10^{-27} \text{ kg}$ $1.008\,664\,915\,78 \text{ u}$
energy equivalent	$m_n c^2$	$1.505\,349\,46 \times 10^{-10} \text{ J}$ $939.565\,330 \text{ MeV}$

Unified atomic mass unit (u)	$m_u = 1 \text{ u}$	$1.66053873 \times 10^{-27} \text{ kg}$
energy equivalent	$m_u c^2$	$1.49241778 \times 10^{-10} \text{ J}$
		931.494013 MeV
Zero of Celsius temperature		273.15 K
Permittivity of vacuum	ϵ_0	$8.854187816 \times 10^{-12} \text{ F m}^{-1}$ ($\text{J}^{-1} \text{C}^2 \text{m}^{-1}$)
Permeability of vacuum	μ_0	$4\pi \times 10^{-7} \text{ H m}^{-1}$ ($\text{J s}^2 \text{C}^{-2} \text{m}^{-1}$)
Standard acceleration of free fall	g_n	9.80665 m s^{-2}
Bohr radius	a_0	$5.291772083 \times 10^{-11} \text{ m}$
π		3.141593
e		2.718282
$\ln 10$		2.302585

Conversion factors

$$1 \text{ J} = 1 \text{ VC} = 0.239 \text{ cal} = 6.2415 \times 10^{18} \text{ eV} = 1.0364 \times 10^{-5} \text{ FV}$$

$$1 \text{ cal} = 4.184 \text{ J}$$

$$1 \text{ eV} = 1.602 \times 10^{-19} \text{ J}$$

$$1 \text{ cm}^{-1} \triangleq 1.9864 \times 10^{-23} \text{ J} (= 0.1240 \text{ meV})$$

$$1 \text{ cm}^{-1} \times N_A \triangleq 11.9625 \text{ J mol}^{-1} = 2.8591 \text{ cal mol}^{-1}$$

$$1 \text{ atm} = 1.01325 \times 10^5 \text{ Pa} = 1.01325 \text{ bar} = 760 \text{ Torr}$$

$$1 \text{ bar} = 10^5 \text{ Pa} = 0.986923 \text{ atm} = 750.062 \text{ Torr}$$

$$1 \text{ Pa} = 0.98692 \times 10^{-5} \text{ atm} = 10^{-5} \text{ bar} = 7.50062 \times 10^{-3} \text{ Torr}$$

$$1 \text{ Torr} = 1.333 \times 10^2 \text{ Pa} = 1.31579 \times 10^{-3} \text{ atm}$$

$$1 \text{ dyn} = 10^{-5} \text{ N}$$

$$1 \text{ C} = 6.2415 \times 10^{18} \text{ e}$$

$$1 \text{ debye} = 3.33564 \times 10^{-30} \text{ C m}$$

$$1 \text{ \AA} = 10^{-10} \text{ m}$$

$$T = t + 273.15 \text{ K}$$

Some often used abbreviations

Hacac	acetylacetone
bipy	2,2'-bipyridine
Cp	cyclopentadienyl
cyclam	1,4,8,11-tetraazacyclotetradecane
diars	<i>o</i> -phenylenebis(dimethylarsine) (or 1,2-phenylenebis(dimethylarsine))
dien	diethylenetriamine

H ₂ dmg	dimethylglyoxime
en	ethylenediamine (1,2-ethanediamine)
H ₄ edta	ethylenediaminetetraacetic acid
Hgly	glycine
Hhfa	hexafluoroacetylacetone
p	porphyrin
pc	phthalocyanine
phen	1,10-phenanthroline
Ph	phenyl
pn	1,2-propanediamine
py	pyridine
tap	1,2,3-triaminopropane
terpy	2,2',6',2''-terpyridyl
tren	tris(2-aminoethyl)amine
triars	bis(3-dimethylarsinylpropyl)methylarsine
trien	triethylenetetraamine
tu	thiourea

Prefix	Symbol	Factor
tera	T	10 ¹²
giga	G	10 ⁹
mega	M	10 ⁶
kilo	k	10 ³
hecto	h	10 ²
deca	da	10
deci	d	10 ⁻¹
centi	c	10 ⁻²
milli	m	10 ⁻³
micro	μ	10 ⁻⁶
nano	n	10 ⁻⁹
pico	p	10 ⁻¹²
femto	f	10 ⁻¹⁵
atto	a	10 ⁻¹⁸

Electronic configurations of the elements

Element	1s	2s	2p	3s	3p	3d	4s	4p	4d	4f	5s	5p	5d	5f	5g
1. H	1														
2. He	2														
3. Li	2	1													
4. Be	2	2													
5. B	2	2	1												
6. C	2	2	2												
7. N	2	2	3												
8. O	2	2	4												
9. F	2	2	5												
10. Ne	2	2	6												
11. Na	2	2	6	1											
12. Mg	2	2	6	2											
13. Al	2	2	6	2	1										
14. Si	2	2	6	2	2										
15. P	2	2	6	2	3										
16. S	2	2	6	2	4										
17. Cl	2	2	6	2	5										
18. Ar	2	2	6	2	6										
19. K	2	2	6	2	6		1								
20. Ca	2	2	6	2	6		2								
21. Sc	2	2	6	2	6	1	2								
22. Ti	2	2	6	2	6	2	2								
23. V	2	2	6	2	6	3	2								
24. Cr	2	2	6	2	6	5	1								
25. Mn	2	2	6	2	6	5	2								
26. Fe	2	2	6	2	6	6	2								
27. Co	2	2	6	2	6	7	2								
28. Ni	2	2	6	2	6	8	2								
29. Cu	2	2	6	2	6	10	1								
30. Zn	2	2	6	2	6	10	2								
31. Ga	2	2	6	2	6	10	2	1							
32. Ge	2	2	6	2	6	10	2	2							
33. As	2	2	6	2	6	10	2	3							
34. Se	2	2	6	2	6	10	2	4							
35. Br	2	2	6	2	6	10	2	5							
36. Kr	2	2	6	2	6	10	2	6							
37. Rb	2	2	6	2	6	10	2	6			1				
38. Sr	2	2	6	2	6	10	2	6			2				
39. Y	2	2	6	2	6	10	2	6	1		2				
40. Zr	2	2	6	2	6	10	2	6	2		2				
41. Nb	2	2	6	2	6	10	2	6	4		1				
42. Mo	2	2	6	2	6	10	2	6	5		1				
43. Tc	2	2	6	2	6	10	2	6	6		1				
44. Ru	2	2	6	2	6	10	2	6	7		1				
45. Rh	2	2	6	2	6	10	2	6	8		1				
46. Pd	2	2	6	2	6	10	2	6	10						
47. Ag	2	2	6	2	6	10	2	6	10		1				
48. Cd	2	2	6	2	6	10	2	6	10		2				
49. In	2	2	6	2	6	10	2	6	10		2	1			
50. Sn	2	2	6	2	6	10	2	6	10		2	2			
51. Sb	2	2	6	2	6	10	2	6	10		2	3			
52. Te	2	2	6	2	6	10	2	6	10		2	4			
53. I	2	2	6	2	6	10	2	6	10		2	5			
54. Xe	2	2	6	2	6	10	2	6	10		2	6			

Element	K	L	M	4s	4p	4d	4f	5s	5p	5d	5f	5g	6s	6p	6d	6f	6g	6h	7s
55. Cs	2	8	18	2	6	10		2	6				1						
56. Ba	2	8	18	2	6	10		2	6				2						
57. La	2	8	18	2	6	10		2	6	1			2						
58. Ce	2	8	18	2	6	10	2	2	6				2						
59. Pr	2	8	18	2	6	10	3	2	6				2						
60. Nd	2	8	18	2	6	10	4	2	6				2						
61. Pm	2	8	18	2	6	10	5	2	6				2						
62. Sm	2	8	18	2	6	10	6	2	6				2						
63. Eu	2	8	18	2	6	10	7	2	6				2						
64. Gd	2	8	18	2	6	10	7	2	6	1			2						
65. Tb	2	8	18	2	6	10	9	2	6				2						
66. Dy	2	8	18	2	6	10	10	2	6				2						
67. Ho	2	8	18	2	6	10	11	2	6				2						
68. Er	2	8	18	2	6	10	12	2	6				2						
69. Tm	2	8	18	2	6	10	13	2	6				2						
70. Yb	2	8	18	2	6	10	14	2	6				2						
71. Lu	2	8	18	2	6	10	14	2	6	1			2						
72. Hf	2	8	18	2	6	10	14	2	6	2			2						
73. Ta	2	8	18	2	6	10	14	2	6	3			2						
74. W	2	8	18	2	6	10	14	2	6	4			2						
75. Re	2	8	18	2	6	10	14	2	6	5			2						
76. Os	2	8	18	2	6	10	14	2	6	6			2						
77. Ir	2	8	18	2	6	10	14	2	6	7			2						
78. Pt	2	8	18	2	6	10	14	2	6	9			1						
79. Au	2	8	18	2	6	10	14	2	6	10			1						
80. Hg	2	8	18	2	6	10	14	2	6	10			2						
81. Tl	2	8	18	2	6	10	14	2	6	10			2	1					
82. Pb	2	8	18	2	6	10	14	2	6	10			2	2					
83. Bi	2	8	18	2	6	10	14	2	6	10			2	3					
84. Po	2	8	18	2	6	10	14	2	6	10			2	4					
85. At	2	8	18	2	6	10	14	2	6	10			2	5					
86. Rn	2	8	18	2	6	10	14	2	6	10			2	6					
87. Fr	2	8	18	2	6	10	14	2	6	10			2	6					1
88. Ra	2	8	18	2	6	10	14	2	6	10			2	6					2
89. Ac	2	8	18	2	6	10	14	2	6	10			2	6	1				2
90. Th	2	8	18	2	6	10	14	2	6	10			2	6	2				2
91. Pa	2	8	18	2	6	10	14	2	6	10	2		2	6	1				2
92. U	2	8	18	2	6	10	14	2	6	10	3		2	6	1				2
93. Np	2	8	18	2	6	10	14	2	6	10	5		2	6					2
94. Pu	2	8	18	2	6	10	14	2	6	10	6		2	6					2
95. Am	2	8	18	2	6	10	14	2	6	10	7		2	6					2
96. Cm	2	8	18	2	6	10	14	2	6	10	7		2	6	1				2
97. Bk	2	8	18	2	6	10	14	2	6	10	8		2	6	1				2
98. Cf	2	8	18	2	6	10	14	2	6	10	10		2	6					2
99. Es	2	8	18	2	6	10	14	2	6	10	11		2	6					2
100. Fm	2	8	18	2	6	10	14	2	6	10	12		2	6					2
101. Md	2	8	18	2	6	10	14	2	6	10	13		2	6					2
102. No	2	8	18	2	6	10	14	2	6	10	14		2	6					2
103. Lr	2	8	18	2	6	10	14	2	6	10	14		2	6	1				2

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