ON THE STEREOCHEMICAL COURSE OF THE CHLORINE-38 FOR CHLORINE SUBSTITUTION IN DIASTEREOMERIC AND ENANTIOMERIC COMPOUNDS

by

Jiann-long Wu

Dissertation submitted to the Graduate Faculty of the
Virginia Polytechnic Institute and State University
in partial fulfillment of the requirements for the degree of
DOCTOR OF PHILOSOPHY
in
Chemistry

APPROVED:

Hans J. Ache, Chairman

Harold M. Bell

Luther K. Brice

George Sanzone

James F. Wolfe

May, 1977

Blacksburg, Virginia

ACKNOWLEDGMENTS

The author wishes to express sincere appreciation to Dr. Hans J. Ache, his research advisor, for his guidence, help, and encouragement throughout his graduate education.

Gratitude is also extended to the other members of the committee, Dr. Harold M. Bell, Dr. Luther K. Brice, Dr. George Sanzone, and Dr. James F. Wolfe for reviewing the manuscripts and offering helpful comments and valuable suggestions.

He also likes to express his gratitude to the Chemistry Department's glassblowing and electronic shops for their assistance.

Finally, the author is greatly indebted to his parents, , for their support and encouragement and to his wife, , for her devotion and understanding which have made this thesis possible.

TABLE OF CONTENTS

CHAPTER IV. DISCUSSION

LIST OF FIGURES

Figure Page

LIST OF TABLES

INTRODUCTION

The reactions of recoil halogen generated by nuclear processes, such as the radiative neutron capture (n,γ) or the isomeric transition activation process, have been subject to a large number of investigations.[1-11] In gaseous systems it has been found that primary products are predominantly formed by abstraction and replacement occuring by direct mechanisms, whereas in condensed systems direct replacement and caging mechanisms have been considered. The cage effect has been postulated as the result of the increase in product yields with increasing density in the gas to liquid to solid transition in recoil halogen reactions.

The studies on the substitution of recoil halogen for halogen at asymmetric carbon atoms[12-16] have shown that in the gas phase, the exchange occurs predominantly with retention of configuration, while in the condensed phase the stereospecificity decreases. The lesser degree of stereospecificity observed in going from the gas to liquid to the solid phase has been generally ascribed in the past to the radical-radical cage combination reactions, allowing racemization of the intermediate radical. However, recently Stöcklin et al.[17] observed a pronounced effect of the nature of the solvent on the stereochemistry of ^{38}Cl for Cl substitution in diastereomeric 2,3-dichlorobutanes. This result leads these authors to suggest a conformational effect including a hot one-step substitution which occurs via a collision complex that can be collisionally stabilized and has a life time sufficiently long to allow inversion of configuration.

Since it appears that this solvent effect which has so far been observed only in one system with a very limited number of solvents present could also be explained by other mechanisms, such as caging, in which case the course of the reaction is influenced by the interaction between the intermediates with the surrounding solvent molecules, we have focused our attention on the solvent effects on the stereochemical course of hot halogen substitution in diastereomers and optical isomers of haloalkanes in an effort to obtain a better understanding of the mechanism of this substitution process.

CHAPTER I

BASIC PRINCIPLE OF HOT ATOM CHEMISTRY

A. Introduction

Atoms which possess high translational energies are called "hot" atoms. The study of their chemical reactions is described as hot atom chemistry. The reactions of hot atoms are different from ordinary reactions where the system is at or near thermal equilibrium. In a thermal reaction a minimum amount of energy known as activation energy is generally required. In many cases, at this energy level only a very limited number of reaction paths are available. However, in the hot atom reaction, in most cases, sufficient energy is available to open many more pathways. This leads to a variety of products which are not formed in systems at thermal equilibrium. The field of hot-atom chemistry is therefore concerned with the study of reactions of atoms over the entire kinetic energy range in which chemical reactions occur.

Hot atoms can be generated by nuclear transformation, radiolysis, photolysis, arc, and beam acceleration. The technique used in this research is the method of nuclear transformation. There are three chief advantages of nuclear recoil as a source of hot atoms: (1) the product atom is radioactive; it allows subsequent tracer detection of the labeled products produced by the reactions of these atoms, (2) the detection techniques for radioactive species are extremely sensitive so that a very small amount of radioactive species is sufficient for analysis, (3) in a typical nuclear reaction, only about 10^8 hot atoms will be produced in the presence of 10^{20} molecules of substrate so that the chances of two hot atoms reacting with the same molecule to form a doubly substituted product are very unlikely, nor will there be any interaction between two hot atoms or their respective reaction products.

The chemical reaction initiated by a nuclear recoil was first studied by L. Szilard and T. A. Chalmers[19] in 1934. They observed that after the neutron irradiation of liquid ethyl iodide, part of the radioactive ^{128}I could be extracted from the ethyl iodide with an aqueous solution containing a trace of free iodine as a carrier. This result indicated the fact that the bond between carbon and iodine was broken when an ^{127}I nucleus was transformed by neutron capture to ^{128}I. In 1936 Glueckauf and Fay[20] found that recoil halogens which formed in the neutron irradiation of alkyl halide could enter into organic combination to form a new carbon halogen bond, some of the products appeared in the same chemical form as the parent compound, and some in a variety of new forms. This was the first evidence for the high chemical reactivity of the newly formed atoms. Since then, a great deal of work has been done in the field of hot atom chemistry.

B. Formation of Hot Atoms by Nuclear Recoil Methods

If, for example, a neutron is impinged on an atomic nucleus, the neutron may be captured with the resulting formation of an excited compound nucleus. The energy increase arises from the binding energy of the extra neutron and the kinetic energy of the neutron. Within a very short time ($\sim 10^{-15}$ sec.), the compound nucleus may be de-excited by emission of either neutron, proton, α-particle, or photon. The type of capture reaction depends upon the energy of the incident neutron and on the mass of the target nucleus. The capture of neutron with high kinetic energies will provide the nucleus with sufficient energy to eject a neutral or charged particle. But the probability of particle emission decreases with the increasing atomic number of the struck nucleus. As the result of the emission of the charged particle, the newly formed nucleus undergoes recoil with considerable kinetic energy. Thus, these nuclear reactions lead to the formation of energetic recoil species.

According to the law of energy and momentum conservation the average kinetic energy of the recoil atom, $\bar{E}_B$, formed in a A(X,Y)B nuclear reaction can be calculated by the following equation:

$$\bar{E}_B = \frac{E_X}{(M_Y + M_B)^2} \left\{ M_B M_X + M_Y (M_Y + M_B - M_X) \left[1 + \frac{Q}{E_X} \cdot \frac{M_Y + M_B}{(M_Y + M_B - M_X)} \right] \right\} \qquad (1)$$

Where E_X = energy of the incident particle, M_X, M_Y = the mass of the incident particle and emitted particle, respectively, M_B = the mass of the recoil atom, and Q = the energy change in the nuclear reaction,which can be calculated from the mass difference between the reaction products and that of the reactants.

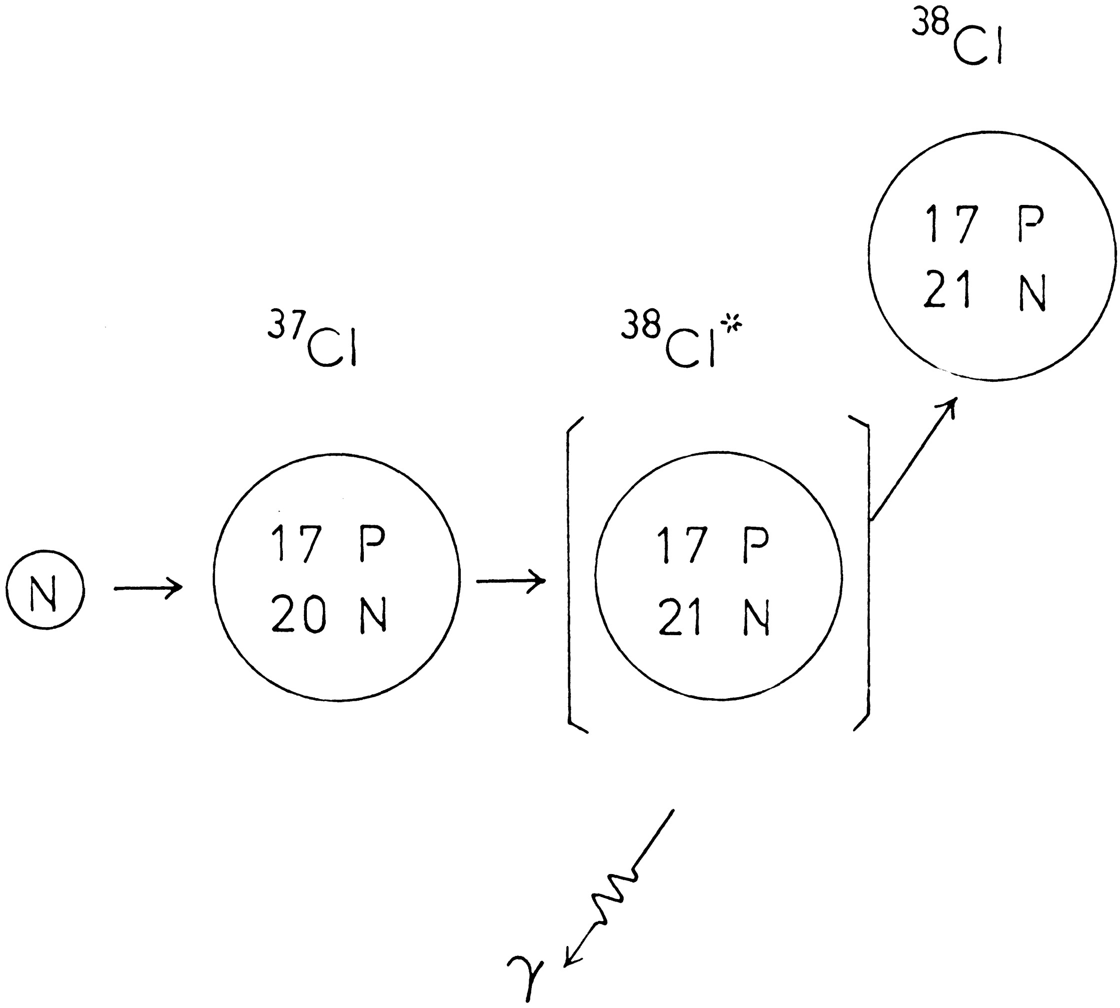
In the case where E_X is small compared to the Q value, the equation (1) can be simplified to:

$$\bar{E}_B = Q \cdot \frac{M_Y}{M_B + M_Y}$$

The recoil energy imparted to the particles formed in a nuclear reaction usually ranges from KeV to a few MeV. Thus, if the target atom has been incorporated into a molecule, the newly formed recoil atom will break the chemical bonds and leave the molecule in which it was bound.

In a thermal neutron reaction, the energy increase of the nucleus is about 6-8 MeV. This amount of energy generally is insufficient to eject a particle and the excitation energy is dissipated by the emmision of one or more γ-rays. Hence, the reactions are generally of the (n,γ) type. A γ-ray of energy E_γ has a momentum of $P_\gamma = E_\gamma/C$. Due to the conservation of momentum, the recoil atom must have an equal momentum. Therefore, the recoil energy is $E_R = P_\gamma^2/2M = E_\gamma^2/2MC^2$. Where M is the mass of the atom and C is the speed of light. For M in atomic mass units and E in MeV we have $E_R = 537\ E_\gamma^2/M$ eV. This is under the assumption that the excess energy is emitted as a single γ-ray. Since γ-rays are emitted in cascade and in different directions, some cancellation of recoil momenta may occur. As a result, the effective recoil energy available is considerably smaller, but usually still large enough to break chemical bonds. In most (n,γ) processes, the recoil energy is in the range of 100 to 1000 eV. As an example, the nuclear reaction $^{37}Cl(n,\gamma)^{38}Cl$ is described in detail in Figure I.

The yield of a nuclear reaction, R, can be calculated by the following equation:



$$E_\gamma = 6.11 \text{ MeV}$$

$$\text{Recoil Energy} \quad E_R = \frac{537\ E_\gamma^2}{M} = 528 \text{ eV (max)}$$

Figure 1. $^{37}\mathrm{Cl}(n,\gamma)^{38}\mathrm{Cl}$ Nuclear Reaction.

$$R = \sigma \phi N(1 - e^{-\lambda t})$$

Where σ = the cross section of the reaction, ϕ = flux of particles, N = the number of target atoms, λ = decay constant of the nuclear species produced, and t = the irradiation time.

Table I outlines the properties of some recoil halogen induced by neutron capture which is an interesting aspect of the study of hot atom chemistry.

C. The Principle of Isomeric Transition

The radioactive decay of radionuclide by α-particles, β-particles, electron capture, etc. may result in the formation of a metastable nucleus. This metastable nucleus will subsquently stabilize itself by de-excitation to a more stable state or to its ground state. The excess energy in each step is released by the emission of γ-rays.

If such a metastable state has a half-life long enough to allow chemical handling, then it is commonly called a nuclear isomer. Its transition to a lower energetic state is known as isomeric transition (I.T.). For example, when bromine is irradiated with neutrons both ^{80m}Br and ^{82m}Br are produced. The small letter m following the mass number is used to indicate the metastable state. The decay of ^{80m}Br to ^{80}Br is illustrated in Figure 2. The transition of ^{80m}Br to a lower excited state occurs by

Table I. Properities of Recoil Halogens Induced by Neutron Capture.

Isotope	Nuclear Reaction	Neutron Energy	Cross Section (Barn)	Half Life	Recoil Energy	Decay & Mode	Energy (MeV)
^{18}F	$^{19}F(n,2n)^{18}F$	15.0 MeV	0.061	110 min	700 KeV	β^+, EC	1.65
^{38}Cl	$^{37}Cl(n,\gamma)^{38}Cl$	thermal	0.43	37.3 min	max 530 eV	β^-	4.91
^{80m}Br	$^{79}Br(n,\gamma)^{80m}Br$	thermal	2.7	4.4 hr		IT	0.085
^{80}Br	$^{79}Br(n,\gamma)^{80}Br$	thermal	8.2	17.6 min	max 417 eV	β^- β^+, EC	 2.02
^{82m}Br	$^{81}Br(n,\gamma)^{82m}Br$	thermal	3.0	6.1 min		IT, β^-	0.046
^{82}Br	$^{81}Br(n,\gamma)^{82}Br$	thermal	0.26	35.5 hr	max 360 eV	β^-	3.092
^{128}I	$^{127}I(n,\gamma)^{128}I$	thermal	6.2	25.0 min	max 180 eV	β^+, EC β^-	1.27 2.14

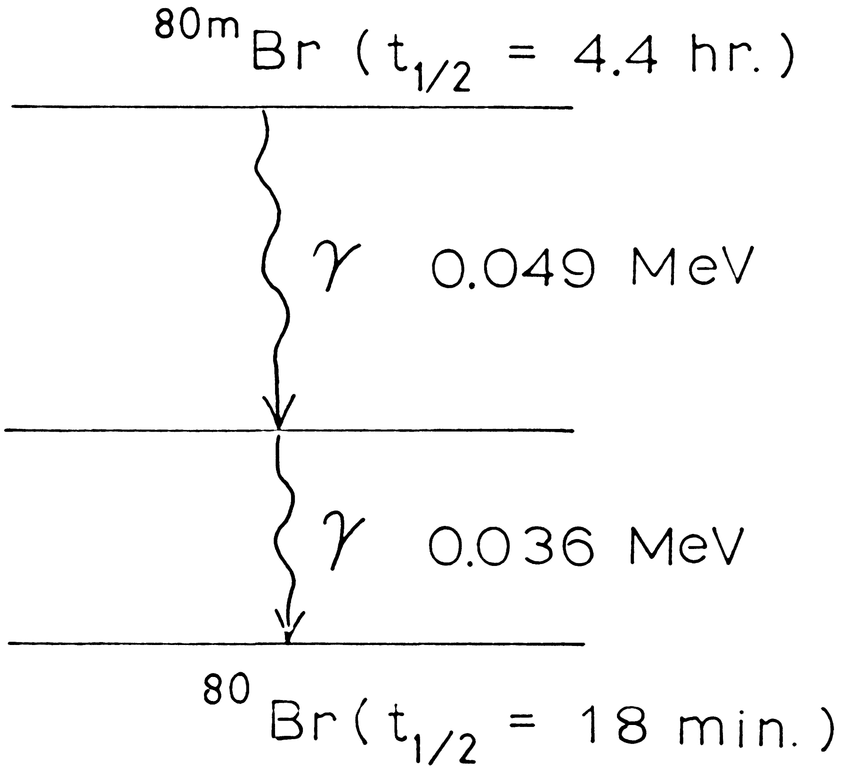


Figure 2. Schematic of ^{80m}Br to ^{80}Br Decay.

emitting a 49 KeV γ-rays with a half-life of about 4.4 hours.[21] A further de-excitation to ground state ^{80}Br follows with a half-life of 7.4 nanosecond. Usually the recoil energy associated with the nuclide formed as a result of isomeric transition is not enough to break the chemical bond involved. However, the γ-rays emitted in the transition are strongly internally converted, creating inner shell vacancies. The vacancies are subsequently occupied by electrons from outer shells. The energy created in this process may be emitted as x-rays or may be used in an internal photoelectric process in which additional electrons from outer shells are emitted. This process of repeated reshuffling and ejection of electrons is known as the Auger Effect. The time required to complete this process is very short, generally less than 10^{-15} second. As a result, the decaying nuclide accumulates a high positive charge. This high positive charge can be partially neutralized by intramolecular electron transfer creating another positive center within the molecule. Due to strong Coulombic repulsion between likewise charged ions, the molecule virtually explodes, producing highly charged ions with considerable kinetic energy.[22]

D. Charge State of Recoil Atoms

The species initially produced by nuclear transformation with very high kinetic energy ranged from several hundred eV to a few MeV are usually positively charged. These energies are well in excess of chemical bond energies and do not allow any chemical reaction to take place. After collision de-excitation with its chemical environment, the species reach a lower energy range (10-50 eV), in which chemical reactions become possible. However, during the energy degradation process the ionic character will usually change by charge exchange with the medium. Therefore, it is important to know what is the charge state of the hot species when it enters chemical combination, i.e. whether the recoil atom reacts as neutralized or ionic atom.

The adiabatic principle[23] or resonance rule has been used successfully for predicting the charge state of the recoil species. This principle states that the probability of an electronic transition on collision is maximum when the time of collision equals the period of the transition. The maximum probability of transition occurs when

$$a\ \Delta E/h\nu_{max} = 1$$

Where a is the average relative distance of travel during the collision, ΔE is the energy of the transition, h is

Planck's constant, and V_{max} is the relative velocity of the particles. The maximum kinetic energies for various exchange processes in a medium can then be calculated by $E_{max} = 1/2\ mV_{max}$. This hypothesis has been applied for predicting the charge state of recoil T,[24] ^{11}C,[25] ^{39}Cl,[26] and ^{127}I,[27] when it reaches the chemical region (~10 eV) in various media. Generally, high energy (~10^4 eV) recoil species which are produced by the particle emission process, such as (n,2n), (n,p), etc. can be expected to reach chemical energies as atoms. However, for species produced by (n,γ) process having recoil energies of only hundreds of electron volts, the possibility exists that some of them remain charged until they react.

Recoil chlorine atoms produced by $^{40}Ar(\gamma,p)^{39}Cl$ possess recoil energy of up to 0.27 MeV. With such a high recoil energies ^{39}Cl will eventually react as neutral ground state atom. A comparison of yields of ^{38}Cl and ^{39}Cl labeled species have shown no differences.[28] This indicates that ^{38}Cl atoms which are produced by a (n,γ) reaction do react as neutral atoms.

Other evidence supporting the contention that ^{38}Cl reacts as an atom but not as an ion is that n- and iso-propyl chloride do not isomerize in their reaction with recoil ^{38}Cl.[29,30]

In the case of bromine, it has been found that the reactive bromine species generated via the (n,γ) nuclear process are atoms but not ions.[31,32] However, the bromine species formed as a result of isomeric transition are highly charged and were found to react as (singly) charged ions. Hot bromine ions carrying charge of up to +13 have been observed.[22]

E. Criterion for Hot Atom Reactions

The high kinetic energy associated with the formation of the recoil atom in a nuclear reaction can be dissipated by the hot atom collisions with its surrounding molecules. At energies less than 20-50 eV chemical reactions may take place. Such reactions are considered as hot reactions. However, not all recoil atoms react while they still have excess energy. Eventually some of these recoil atoms will reach and react at thermal energy levels.

There are various criteria that can be used for distinguishing hot from thermal reactions.

(1) The addition of a small amount of radical scavengers will suppress or eliminate thermalized hot species whose reaction otherwise would interfere with the results, but have little effect on hot reactions. The use of a scavenger is possible because the reactions of hot atoms have high collision efficiencies. The low concentration of scavengers in the reaction system will

not significantly effect hot reactions since a hot atom is unlikely to encounter them in the few collisions of its chemically effective existence.

In the recoil halogen reactions, the scavengers that most often have been used are oxygen, bromine, and iodine. They can react effectively both with thermalized halogen atoms and other radicals produced by the radiation processes. Figure 3 shows an example of scavenger effect.[33] The percent of ^{80m}Br labeled organic products was plotted as a function of concentration of Br_2 scavenger following neutron irradiation of ethyl bromide. This result indicates that in the presence of small amount of Br_2, the thermal reaction can be eliminated almost completely. The hot products can be estimated by extrapolating the line back to zero Br_2 concentration.

(2) In the gas phase, inert moderators may also serve to distinguish hot and thermal reactions. In this case the excess kinetic energy of the hot atom will be removed in collisions with the moderator. Generally, noble gases are often used as moderators due to their chemical inertness. Collisions between the inert gas atoms and the hot atoms have been considered as elastic. Thus, the maximum amount of energy that a hot atom can transfer in an elastic collision can be calculated by

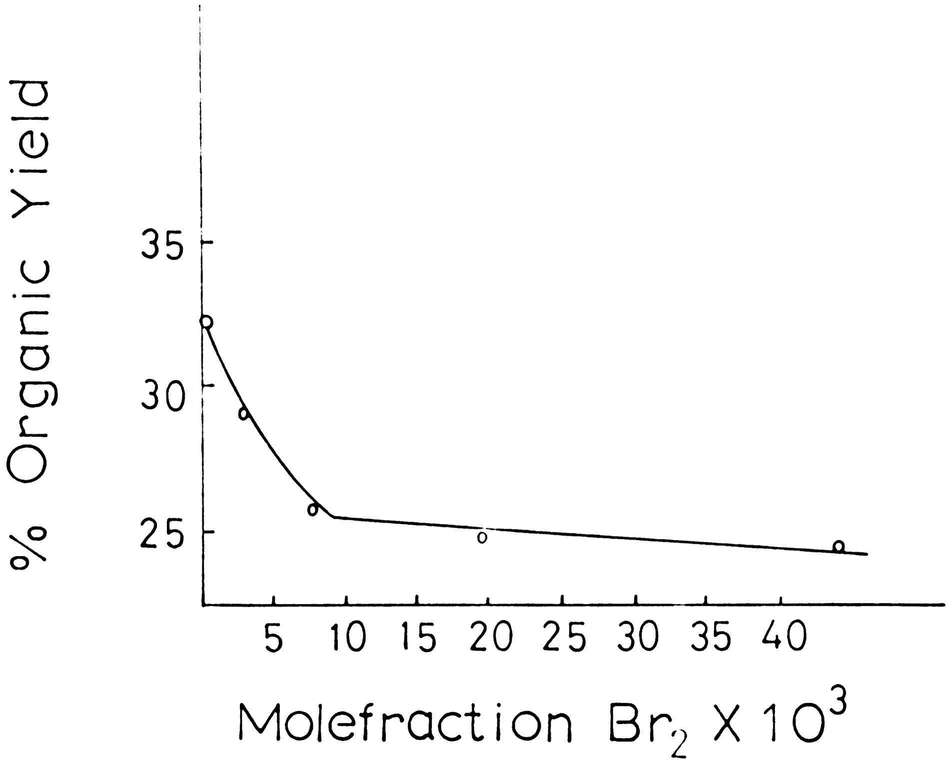


Figure 3. % Organic Yield in Neutron Irradiated Ethyl Bromide as a Function of Mole Fraction of Bromine.

using the following equation:

$$E_{max} = \frac{4\ m_1\ m_2}{(m_1\ +\ m_2)^2}\ E_I \qquad (2)$$

Where E_I = the kinetic energy of the incident atom, m_1 = the mass of the incident atom, and m_2 = the mass of the struck atom. From equation (2) it can be seen that if the incident atom and struck atom have the same mass, the maximum amount of energy will be transferred from the hot atom to the other nuclide. Thus, in this case it will undergo the smallest number of collisions before it reaches thermal equilibrium with its surroundings. Therefore, Ne, Ar, Kr, and Xe will be the best choice as moderators for ^{18}F, ^{38}Cl, ^{80}Br, and ^{128}I systems, respectively.

The addition of a moderator not only can remove energy from the hot atom but also can reduce the number of collisions of the hot atom with the reactive species at the appropriate energy range. Thus, if the yield of a given product decreases and is finally eliminated by the presence of increasing amounts of moderator it can generally be assumed that the product was formed by hot reactions.

(3) In a thermal reaction, the reaction will proceed via a pathway which requires the least amount of activation energy, so usually there is only a small number of

possible reaction pathways. However, in a hot atom reaction, the initially formed hot atom possesses a very high kinetic energy, which allows the reaction to proceed via many more pathways as schematically shown in Figure 4. Therefore, the formation of any product which is not observed in a thermal reaction may be assumed to be formed by a hot reaction. For example, the formation of $CH_3{}^{18}F$ from the hot reaction between ^{18}F and CH_4 is unknown in the thermal reaction.

(4) Hot reactions are in general temperature independent, since the energy required is supplied by the hot species. However, if a particular product yield shows temperature dependence, this does not necessarily indicate that a hot reaction is not involved. For example, the primary products of hot reaction may undergo secondary reaction which is a temperature dependent process.

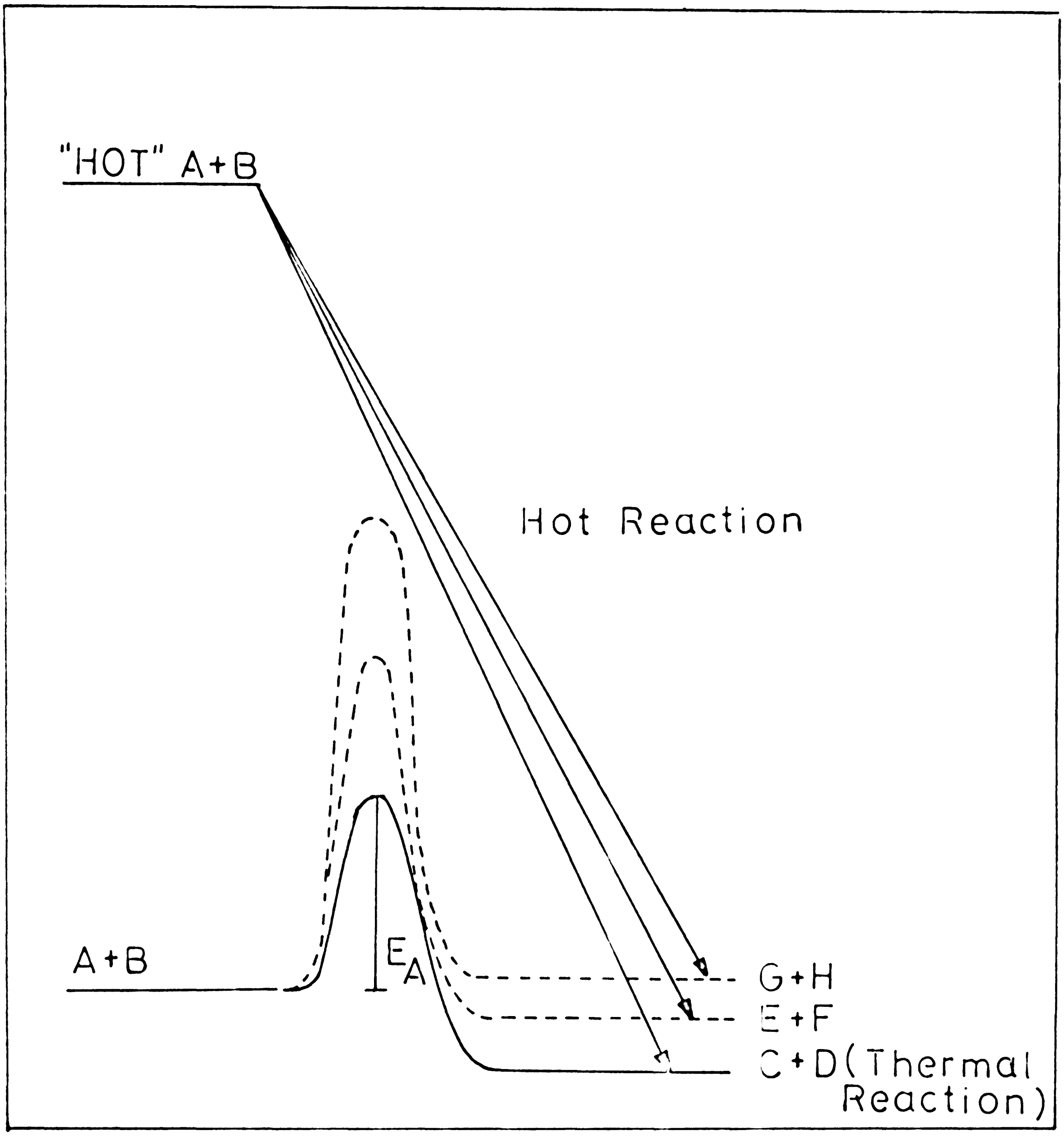
F. Types of Hot Atom Reactions

With high recoil energy, hot atoms can react in several ways. In this section, the discussion will focus on the type of reaction of recoil halogen.

1. Abstraction Reaction

$$[\cdot Y^*]^\ddagger + RH \longrightarrow HY^* + R\cdot \qquad (3)$$

$$[\cdot Y^*]^\ddagger + RX \longrightarrow XY^* + R\cdot \qquad (4)$$



Reaction Coordinate

Figure 4. Schematic Diagram of Hot Atom Reaction.

Recoil halogen can abstract hydrogen and halogen according to equations (3) and (4), but the abstraction of hydrogen by fluorine and chlorine are not typical hot reactions. As shown in Table II, thermal fluorine and chlorine atoms also favor hydrogen abstraction due to their exothermicity.

2. Substitution Reaction

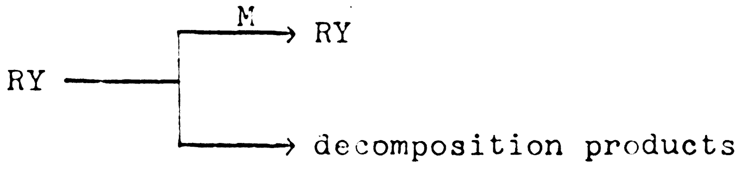
Recoil halogen atoms are able to substitute for hydrogen, halogen or a functional group as shown in equations (5), (6), and (7).

$$[\cdot Y^*] + RH \longrightarrow RY^* + H\cdot \tag{5}$$

$$[\cdot Y^*] + RX \longrightarrow RY^* + X\cdot \tag{6}$$

$$[\cdot Y^*] + RR_1 \longrightarrow RY^* + R_1\cdot \tag{7}$$

The excited product molecule RY^* can either decompose or become collisionally de-excited.



In the hot halogen substitution reaction it is a general trend that the yield of substituted products

Table II. Enthalpy Change ΔH^{o}_{25} (kcal/mole) in Various Types of Hydrogen Abstraction Reaction by Halogen.*

Bond Type	F	Cl	Br	I
Primary C-H	-55	-4.9	10.6	26.6
Secondary C-H	-58.5	-8.6	7.1	23.1
Tertiary C-H	-62	-11.9	3.6	19.6

* From reference 91.

increase from gas to liquid to solid transition. The increases in yield in the condensed phase are due to the ease of dissipation of excitation energy and also to the cage effect which allows radical recombination reactions.

The effect of bond strength on the yields of ^{18}F substitution reaction has also been investigated.[34] It was found that the yield of $R^{18}F$ increases as D(R-X) decreases, where X = F, Cl, Br, or I. The same trend was observed in the reaction of ^{82}Br with chlorofluoromethanes.[35] It has been shown that higher yields are associated with the Br for Cl reaction than Br for F.

3. Addition to C=C or C≡C Bonds

Hot halogen atoms can react with unsaturated hydrocarbons to form addition products. However, these hot addition reactions are usually accompanied by abstraction or substitution.

For example, the reaction of near thermal hot ^{18}F atoms produced from $^{19}F(n,2n)^{18}F$ nuclear reaction with acetylene[36] follows three pathways:

(a) Substitution of ^{18}F for H

$$^{18}F + CH{\equiv}CH \longrightarrow CH{\equiv}C^{18}F + H$$

(b) Abstraction of H

$$^{18}F + CH{\equiv}CH \longrightarrow H^{18}F + \cdot C_2H$$

(c) Addition to the π Bond

$$^{18}F + CH{\equiv}CH \longrightarrow \cdot CH{=}CH^{18}F$$

The addition product $\cdot CH{=}CH^{18}F$ is in the highly excited state, so it will either decompose to $CH{\equiv}C^{18}F$ and $CH{\equiv}CH$ or collisionally stablize to $\cdot CH{=}CH^{18}F$ followed by hydrogen abstraction from its surrounding molecules to form the stable product $CH_2{=}CH^{18}F$.

G. Stereochemistry of Hot Substitution Reactions

The substitution reaction of recoil atoms at asymmetric carbon atoms may result in inversion, retention, or racemization of the configuration at the asymmetric atom. The study of these reactions will provide information on the basic mechanism of the hot atom reaction. The replacement of hydrogen by recoil tritium has been investigated by several groups with the results shown that the substitution is accompanied with nearly complete retention of configuration at an asymmetric carbon in both condensed and gaseous phases. Diastereomers as well as enatiomers have been used in these investigations. A summary of these experimental results is shown in Table III.

Table III. Previous Results of Recoil Tritium for Hydrogen Substitution at Asymmetric Carbon Atoms.

Phase	System Studied	Substitution Product	Retention (%)	Reference
Solid	Glucose	Glucose Galactose	99	41
	L-Alanine	L-Alanine D-Alanine	95	40
	d,l DCB*	d,l DCB meso DCB	95.5	38
Liquid	Glucose	Glucose Galactose	90	40
	d,l DCB	d,l DCB meso DCB	97.7	38
	d,l DCDFE**	d,l DCDFE meso DCDFE	80.4	39
	meso DCDFE	meso-DCDFE d,l DCDFE	94	39
	d,l DCDFE	d,l DCDFE meso DCDFE	80	18
	meso DCDFE	meso DCDFE d,l DCDFE	92	18

Table III (continued)

Phase	System Studied	Substitution Product	Retention (%)	Reference
Gas	D-2-Butanol	D-2-Butanol L-2-Butanol	90	37
	L-2-Butanol	L-2-Butanol D-2-Butanol	95	37
	d,l DCB	d,l DCB meso DCB	93	38
	meso DCB	meso DCB d,l DCB	80	38
	d,l DCDFE	d,l DCDFE meso DCDFE	97.6	39
	meso DCDFE	meso DCDFE d,l DCDFE	99.5	39
	d,l DCDFE	d,l DCDFE meso DCDFE	96	18
	meso DCDFE	meso DCDFE d,l DCDFE	96	18

* DCB = 2,3-Dichlorobutane

** DCDFE = 1,2-Dichloro-1,2-difluroethane

Based upon the fact that no inversion occurs in a tritium substitution reaction and the observation that HT/RT ratio increased as chain length increases in a reaction between tritium and alkanes, Wolfgang and his coworker[38] proposed the "impact model". This model suggested that the product distributions depend on the point and direction of impact. The time of impact was estimated to be approximately equal to 10^{-14} second. This is in the same order as C-H bond vibration. As a result, the collision is localized and only one or two bonds tend to be broken.

According to this model only three modes of substitution and abstraction are possible for the reaction of tritium and alkanes, as shown in Figure 5.

When the hydrogen atom attacks directly from the "front" side at the central carbon, the atom or group on the opposite side will be expected to be expelled which leads to a replacement product with inversion of configuration. This is the so-called Walden inversion. However, there are some inertial factors to be considered. From the extension of a general form of the Frank-Condon principle, the so-called golden rule of hot atom chemistry, it is stated: "Hot atom reactions requiring nuclear motions which are slow relative to the time of collision

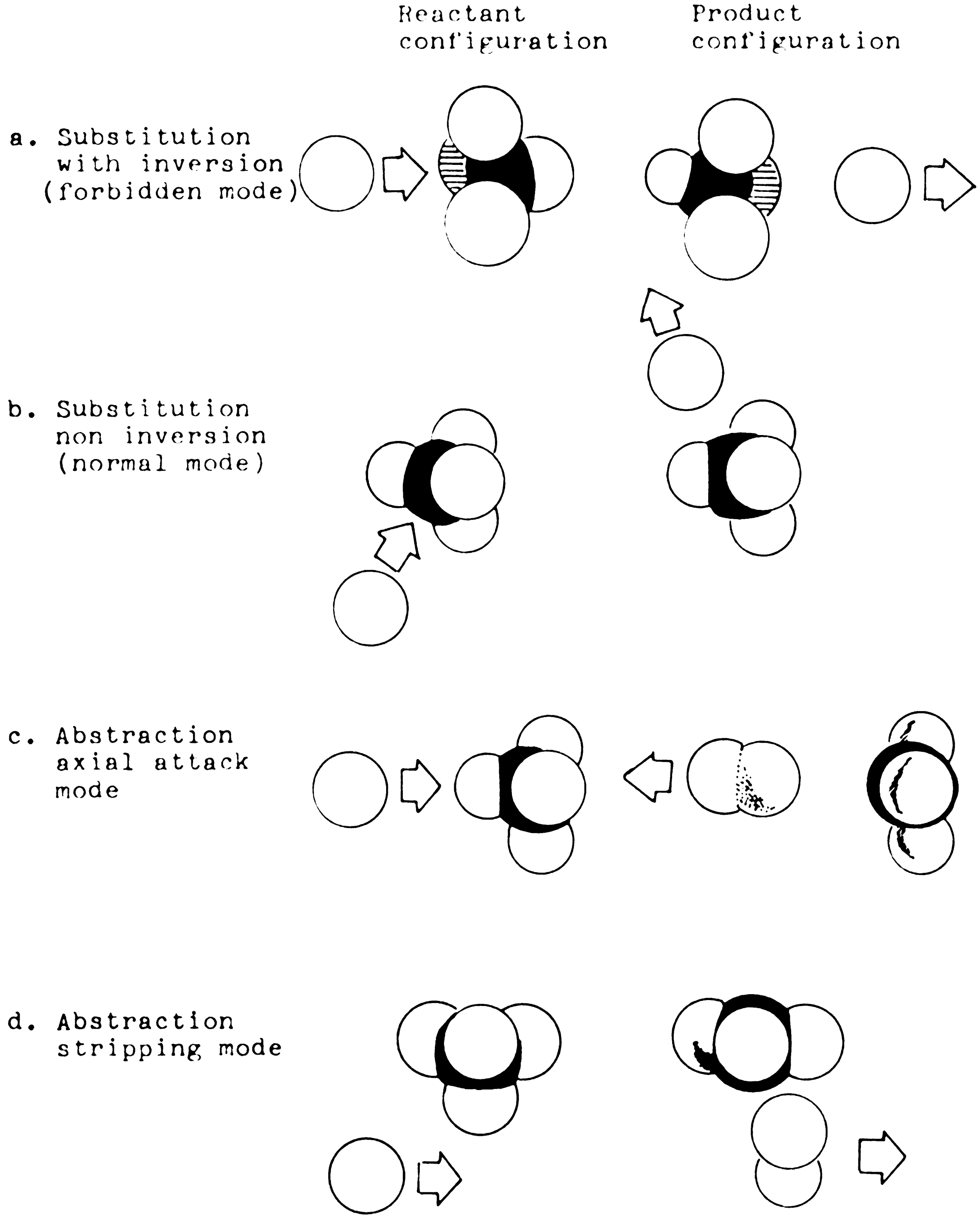


Figure 5. Modes of Reaction of Hot Hydrogen Atoms.

tend to be forbidden."[42] Therefore, if the three atoms or groups not replaced are heavy, substitution with the Walden inversion will be forbidden. For example, since the vibration time for OH and CH_3 is in the magnitude of 10^{-13} second. These groups will not be able to invert themselves within the time of collision (10^{-14} second), and there will be no vacant orbital available on the side of the carbon atom which the tritium is attacking. As a result the tritium is not captured and will escape as shown in Figure 5a.

When the recoil tritium attacks at a wide angle, within the time of collision the hydrogen atom can be expelled which leads to substitution without inversion (Figure 5b). However, when the tritium attacks along the bond axis, it can only form an abstraction product, HT (Figure 5c).

Such a glancing collision, although only small momentum or energy is transferred to the struck molecule if the collision is sufficiently close, will result in an abstraction by the stripping process (Figure 5d).

Unlike tritium substitution reactions, most of the stereochemical studies of the recoil halogen for halogen substitution were done with diastereomers. Since the recoil halogens of interest usually have relative short half lives (see Table I), one cannot afford the long resolution and degradation procedure which is usually required when optically active molecules are used.

Diastereomers, however, differ appreciably in both boiling point and dipole moment and can be readily separated by gas chromatography.

For many years, the experimental investigations of the stereochemistry of the halogen for halogen substitution have shown that in the gas phase the substitution is predominate with retention of configuration, whereas in the condensed phase the stereospecificity decreases, i.e. the retention/inversion ratio decreases.

The almost complete retention of configuration in the gaseous phase has been explained based on the impact model. It assumes a direct replacement process and the time for bond formation is less than time required for the motion of the substituent groups during the inversion process. Furthermore, these rapid motions involve so much vibrational excitation energy that the molecules thus formed will undergo decomposition within about 10^{-10} second.

The somewhat smaller stereospecificity observed in the condensed phase has been generally ascribed to a contribution from radical-radical cage combination reactions, allowing racemization of the intermediate radical.

Cage reaction was first introduced by Franck and Rabinowitch[43] to account for a situation created in solution when two radicals or atoms are formed simultaneously in the same location. Due to the slowness of the diffusion process in liquid, the orginal partners remain together for about 10^{-10} second, and this increases greatly the probability of their mutual interaction.

The Rabinowitch cage has long been considered a central concept in condensed phase hot atom chemistry.[1,44,45] Recently, Richardson and Wolfgang[46] approached the investigation of cage effects by studying the influence of a continuous increase in density from gas to a close packed liquid or solid on the yields of major products. Absolute yields of $CH_3{}^{18}F$ and $CH_2F^{18}F$ from the reaction of ^{18}F with CH_3F were measured for densities from 0.0014 g cm^{-3} (gas at 1.1 atm) to 1.1 g cm^{-3}. Both $CH_3{}^{18}F$ and $CH_2F^{18}F$ show sharp rises in yield starting from the lowest gas densities and leveling off at about 0.2 g cm^{-3} (50-100 atm). This indicates that due to increased collision de-excitation at increased densities, the highly excited primary products are stabilized. At higher densities a second rise in yields was observed. This phenomenon was described as the result of caging reactions involving the hot ^{18}F atom and organic radicals which has produced in the medium.

There are two types of immediate caged radical-radical reaction which occur either following the hot displacement of a halogen atom by a recoil atom with excess kinetic energy

$$[\cdot Y^*]^\ddagger + RX \longrightarrow \{R\cdot + X\cdot + \cdot Y^*\}_{cage} \longrightarrow RY^*$$

or the hot one-step substitution after excitation decomposition of the first formed product.

$$[\cdot Y^*]^\ddagger + RX \longrightarrow [RY^*]_{exc.} \longrightarrow \{R\cdot + \cdot Y^*\}_{cage} \longrightarrow RY^*$$

If the time scale for recombination of the radicals in the solvent cage becomes comparable to the time required for the radical to achieve planar configuration, the subsequent recombination would lead to the formation of products with both retention and inversion of configuration. This two-step cage reaction was the only mechanism considered in the early work of condensed phase hot atom reactions.

In the study of hot chlorine for chlorine substitution in liquid 2,3-dichlorobutane, Stöcklin and coworkers[17] observed a pronounced change on the configuration of substituted products by changing the type and the concentration of the solvent. By using infrared spectroscopy, the influence of the solvent on the relative equilibrium concentration of the rotational isomers was studied. They found that there is a correlation between equilibrium concentration of conformers and the stereochemical course of the substitution reaction. On the basis of this result the authors believed that a hot one-step process was involved, since two-step radical processes should not be affected by the conformation of the original substrate molecule. They suggested that the hot one-step substitution occurs via a collision complex which is collisionally stabilized and has a life time sufficiently long to allow also inversion of configuration.

The pressure dependence of the stereochemical course in hot chlorine for chlorine substitution in meso and d,l 1,2-dichloro-1,2-difluoroethane has also been studied by the same authors.[18] They found that substitution with inversion of configuration is almost negligible in the gas phase and substitution shows a strong phase effect.

From this study they derived at the same conclusion namely that the substitution occurs via a cage complex.

Pettijohn, Rack, and Wolf[47] have investigated the hot chlorine for chlorine substitution reactions with R- and S-2-chloropropanoyl chloride. This is the first experiment in which enantiomeric molecules have been used as substrates in the study of the stereochemical course of halogen for halogen substitution reactions. 81% inversion of configuration was found in the gas phase. This result is quite interesting, since previous results with diastereomeric compounds all indicate that substitution in the gas phase proceeds with almost complete retention of configuration. A list of previous studies on the stereochemical course of hot halogen for halogen substitution is given in Table IV.

In summary, tritium for hydrogen substitution predominantly occurs with retention of configuration either in gas phase or in condensed phase. These results indicate that caging is here unimportant. In the case of halogen substitution reactions, previous results show the stereospecificity decreases from the gas phase to the liquid phase transition. Two mechanisms have been suggested to explain the lower degree of stereospecificity observed in the liquid phase. (1) The two-step mechanism

Table IV. Previous Results of Recoil Halogen for Halogen Substitution at Asymmetric Carbon Atoms.

Phase	Recoil Halogen	System Studied	Substitution Product	Retention (%)	Reference
Solid	^{38}Cl	d,l DCB[1]	d,l DCB meso DCB	50	14
	^{38}Cl	meso DCB	meso DCB d,l DCB	60	14
	^{38}Cl	(S)-CPC[2]	(S)-CPC (R)-CPC	49.2	47
Liquid	^{18}F	d,l DCB	thero FCB[3] erythro FCB	73.3	17
	^{38}Cl	meso DCB	meso DCB d,l DCB	70	14
	^{38}Cl	d,l DCB	d,l DCB meso DCB	74	14
	^{38}Cl	d,l DCB	d,l DCB meso DCB	74.5	17

Table IV (continued)

Phase	Recoil Halogen	System Studied	Substitution Product	Retention (%)	Reference
Liquid	^{34m}Cl	(S)-CPC	(S)-CPC (R)-CPC	53	47
	^{34m}Cl	(R)-CPC	(R)-CPC (S)-CPC	53.4	47
	^{38}Cl	(S)-CPC	(S)-CPC (R)-CPC	52.7	47
	^{80m}Br	d,l DCB	threo BCB[4] erythro-BCB	92	12
	^{80m}Br	meso DCB	erythro BCB threo BCB	95	12
	^{80m}Br	d,l DCB	threo BCB erythro BCB	58.3	17
	^{80m}Br	meso DCB	threo BCB erythro BCB	74	13
	^{80m}Br	d,l DCB	threo BCB erythro BCB	72	13

Table IV (continued)

Phase	Recoil Halogen	System Studied	Substitution Product	Retention (%)	Reference
Liquid	^{82}Br	meso DCB	threo BCB erythro BCB	54	13
	^{82}Br	d,l DCB	erythro BCB threo BCB	52	13
	^{126}I	d,l DCB	threo ICB[5] erythro ICB	54	17
Gas	^{18}F	d,l DCDFE[6]	d,l DCDFE meso DCDFE	90	16
	^{18}F	meso DCDFE	meso DCDFE d,l DCDFE	90	16
	^{38}Cl	d,l DCB	d,l DCB meso DCB	93	15
	^{38}Cl	meso DCB	meso DCB d,l DCB	95	15
	^{38}Cl	d,l DCB	d,l DCB meso DCB	93	12

Table IV (continued)

Phase	Recoil Halogen	System Studied	Substitution Product	Retention (%)	Reference
Gas	^{38}Cl	meso DCB	meso DCB d,l DCB	95	12
	^{38}Cl	d,l DCDFE	d,l DCDFE meso DCDFE	91	18
	^{38}Cl	meso DCDFE	meso DCDFE d,l DCDFE	92	18
	^{38}Cl	(S)-CPC	(S)-CPC (R)-CPC	17.7	47
	^{38}Cl	(R)-CPC	(R)-CPC (S)-CPC	20.0	47
	^{34m}Cl	(S)-CPC	(S)-CPC (R)-CPC	18.8	47
	^{34m}Cl	(R)-CPC	(R)-CPC (S)-CPC	21.3	47
	^{80m}Br	d,l DCB	threo BCB erythro BCB	90	14
	^{80}Br	d,l DCB	threo BCB erythro BCB	71	48

Table IV (continued)

Phase	Recoil Halogen	System Studied	Substitution Product	Retention (%)	Reference
Gas	^{80}Br	meso DCB	erythro BCB threo BCB	73	48

1. DCB = 2,3-Dichlorobutane
2. (S)-CPC = 2(S)-Chloropropionyl Chloride
3. FCB = 2-Fluoro-3-chlorobutane
4. BCB = 2-Bromo-3-chlorobutane
5. ICB = 2-Iodo-3-chlorobutane
6. DCDFE = 1,2-Dichloro-1,2-difluoroethane

which involves the radical-radical combination in the solvent cage and (2) the one-step substitution processes which may proceed via a caged complex. However, the most fundamental question that still has not been answered is the role of the solvent in determing the mechanism of liquid hot reactions. Is it an indirect effect on the conformer population of the substrate molecule as indicated by Stöcklin or a direct effect of the solvent by participating in the de-excitation stabilization of the excited intermediate? This problem has been studied in the present research by undertaking the investigation of the solvent effect on the stereochemical course of 2,4-dichloropentane, 2,3-dichlorobutane, and 2-chloro-1-propanol.

CHAPTER II

EXPERIMENTAL

A. Preparation and Purification of Initial Materials

1. meso and racemic 2,3-Dichlorobutane

A diastereomeric mixture of 2,3-dichlorobutane was obtained from Aldrich Chemical Company. The meso and racemic forms of 2,3-dichlorobutane were separated by gas chromatography with purity greater than 99%. The separation conditions are shown in Table V.

2. meso and racemic 2,4-Dichloropentane

58.0 g of thionyl chloride were added slowly to 13.0 g of 2,4-pentanediol in the presence of a small amount of dry pyridine at 0°C. After refluxing for 3 hours, the excess thionyl chloride was destroyed with ice water. The mixture was then extracted with ether. The organic extracts were washed with aqueous sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. Pure 2,4-dichloropentane was distilled at 54-55.5°C at 20 torr. The yield was 10.8 g (61.3%). NMR (neat) δ 1.45 (d, J = 6 Hz, 3, $-CH_3$), 2.10 (m, 2, $-CH_2-$), 4.21 (m, 2, $-CH-$).

The products were separated by gas chromatography into the pure meso and racemic forms. Table V shows the separation conditions.

Table V. Conditions Used in Gas Chromatography for Separation of Diastereomeric 2,3-Dichlorobutane and 2,4-Dichloropentane.

	2,3-Dichlorobutane	2,4-Dichloropentane
Stationary phase	15% Igepal CO-800	15% Igepal CO-800
Solid support & particle size	Chromosorb W-AW 60/80 mesh	Chromosorb W-AW 60/80 mesh
Colume length	25 foot glass tubing	25 foot glass tubing
Column diameter	1/4" i.d.	1/4" i.d.
Effluent	Helium	Helium
Flow rate	80 ml/min	80 ml/min
Column temperature	65°C	80°C
Detector temperature	100°C	120°C

3. 2(S)-(+) and 2(R)-(-)-Chloropropanoyl chloride[50,51,52]

44.5 grams (0.5 mole) of high optical purity alanine was dissolved in 450 ml of 6N HCl at 0°C. The temperature of the solution was then adjusted to -5°C with an ice-salt freezing mixture. To this solution 57 grams (0.83 mole) of crystalline sodium nitrite was added slowly with rapid stirring at such a rate that the temperature of the reaction mixture did not exceed 0°C, and the evolution of brown fumes did not become too vigorous. Stirring was continued for 10 hours at 0°C after the addition of the sodium nitrate was finished. The solution was then extracted overnight with ether by using a continuous extractor. The extract was dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation. The S or R-2-chloropropanoic acid was distilled at 104-106°C at 35 torr.

The acid (about 0.17 mole) was then mixed with 35.1 g (o.25 mole) of benzoyl chloride in a round-bottomed flask surmounted by the fractionating column. The distillation apparatus was connected to the vacuum. The mixture was strongly heated to distill the acid chloride out of the reaction mixture as fast as possible by carefully controlling the pressure. The distillate which contained most of the acid chloride with a small amount of dissolved hydrogen chloride and benzoyl chloride was redistilled. b.p. 108-109°C. NMR (CCl_3D) δ 1.80 (d,J = 8 Hz, 3, $-CH_3$), 4.62 (q,J = 6 Hz, 1, -CH-). The amount of the other isomer varied from 2 to 5% for S-2-chloropropanoyl chloride, and 7 to 10% for R-2-chloropropanoyl chloride as determined by the method discussed in Section D.

4. 2(S)-(+)- and 2(R)-(-)-Bromopropanoyl bromide[50]

The same procedure was followed as described for the preparation of 2(S)-(+)- or 2(R)-(-)-chloropropanoyl chloride, except 6N HBr and benzoyl bromide were used instead of HCl and benzoyl chloride, respectively. b.p. 68-69°C at 30 torr. NMR (CCl_3D) δ 1.96 (d,J = 8 Hz, 3, $-CH_3$), 4.86 (q,J = 6 Hz, 1, -CH-). The amount of the other isomer was found to be varied from 85 to 87%.

5. 2(S)-(+)- and 2(R)-(-)-Chloro-1-propanol[52]

A solution of 12.7 g (0.1 mole) of either 2(S)- or 2(R)-chloropropanoyl chloride was added drop by drop to 2.28 g (0.06 mole) of lithium aluminum hydride in 100 ml of dry ether at 0°C. A period of about 20 minutes was required for this procedure, and the stirring was continued for 30 minutes. The excess hydride was destroyed with water and then with 10% sulfuric acid. The upper layer was separated and the aqueous layer was continuously extracted isopropyl ether for 2 hours. The extracts were combined with the organic layer and dried over Drierite. The distillation at 90 torr gave 6.1 g (65%) of 2-chloro-1-propanol. b.p. 76.5-77.5°C. NMR (CCl_3D) δ 1.50 (d, J = 6 Hz, 3, $-CH_3$), 2.43 (s, 1, -OH), 3.68 (m, 3, $-CH_2-$), 4.11 (m, 1, -CH-). The amount of S isomer of synthesized 2(S)-chloro-1-propanol was found to be from 90 to 94%.

6. 2(S)-(-)- or 2(R)-(+)-Acetoxy-4-methylvaleryl chloride[53,54]

High optically pure S-leucine, 37.6 g (0.287 mole), was dissolved in 400 ml of 1N H_2SO_4 solution at 0°C. To this solution 33 g (0.478 mole) of $NaNO_2$ was added slowly over a period of 2 hours, so that the temperature was kept between 0 and 2°C. After the addition was completed, the solution was stirred for 2 hours at 0°C and for 3 hours at room temperature. The solution was extracted overnight with ether by using a continuous extractor. The ether extract was dried over magnesium sulfate. Following removal of the ether by rotary evaporation, 47 g (0.6 mole) of acetyl chloride was stirred into the crude product of leucinic acid at 0°C. The reaction was continued with stirring for 10 hours. To the reaction mixture 35 ml of thionyl chloride was added slowly at 0°C. The solution was allowed to stand overnight at room temperature. The excess thionyl chloride and acetyl chloride was removed by distillation at 760 torr. The residue was fractionally distilled under reduced pressure to give 12.9 g of 2(S)-acetoxy-4-methylvaleryl chloride. b.p. 77-80°C at 5 torr. NMR (CCl_3D) δ 0.98 (q, J = 3.2 Hz, 6, two $-CH_3$), 1.80 (m, 3, $-CH-CH_2-$), 2.75 (s, 3, $COCH_3$), 5.40 (t, J = 5 Hz, 1, OCH-). The amount of opposite isomer was found to be about 3%.

7. Compounds obtained commercially

Iodine was obtained from Aldrich Chemical Company and bromine was purchased from J. T. Baker Chemical Company with a 99.8% purity and were used without further purification. CF_3Br and O_2 were obtained from Matheson Chemical Company with a stated purity level greater than 99.0%. The solvents used in this study were obtained from various companies and dried and purified when necessary. (S)-(+)-valine methyl ester was purchased from ICN Pharmaceuticals, Inc.

B. Sample Preparation and Irradiation

1. Liquid phase reaction

Liquid samples were prepared by introducing the desired amount of substrate and various amounts of solvents together with about 2 mole percent of I_2 as scavenger, an amount which was found as sufficient to suppress thermal diffusive reactions, into small quartz ampoules. The quartz ampoules were used in order to minimize the formation of long half-life ^{22}Na ($t_{1/2}$ = 2.58 years) during the irradiation. The amount of 2,3-dichlorobutane, 2,4-dichloropentane, 2-bromopropanoyl bromide, or 2-chloro-1-propanol used in each experiment was about 15 mg. The ampoules were then attached to the vacuum line, thoroughly degassed by freeze-thaw technique, and sealed under vacuum. The sample was immediately subjected to neutron irradiation. The neutron irradiation was carried out at the VPI&SU nuclear reactor with a neutron flux of 1.3 x 10^{12} n cm^{-2} sec^{-1} for 2 to 5 minutes at 40°C.

2. Gas phase reaction

In the study of the decay induced ^{80}Br exchange reaction in gas phase, CF_3Br was preferentially used as the ^{80}Br source because of its ionization potential of 12.3 eV, which lies above that of Br^+ and thus would not interfere with the Br^+ reaction by charge transfer.

About 35 milligrams of CF_3Br were trapped and sealed in a quartz capillary using a liquid nitrogen trap under vacuum. The quartz capillary was about three inches long and had a one millimeter internal diameter. The CF_3Br

sample was irradiated at a neutron flux density of about 10^{12} n cm^{-2} sec^{-1} for one hour at 50°C. After the irradiation, the sample was stored behind a lead shield for two hours to allow the decay of radioactivity to an acceptable limit for handling. The contents of the quartz capillary was then subjected to gas chromatographic purification on a 10 foot Poropak Q column. The separation conditions are listed in Table VI.

The CF_3Br fraction, containing ^{80m}Br-, ^{80}Br-, and ^{82}Br- labeled CF_3Br formed during the irradiation, was trapped and transferred by vacuum line technique into a reaction vessel. The other radioisotopes of bromine produced did not impose any problems, since they decayed to stable daughters.

The reaction was carried out in a spherical, specifically designed pyrex glass vessel with a total volume of 500 ml. In- and outlet valves were Kontes' greaseless high vacuum valves. The vessel was filled by the standard vacuum line technique with the desired amounts of reactants and additives. The reaction was kept in the dark for about 40 minutes at room temperature to permit ^{80}Br to obtain equilibrium with ^{80m}Br.

Table VI. Gas Chromotographic Purification of Neutron-irradiated CF_3Br.

Packing material	Parapak Q
Particle size	80/100 mesh
Column length	10 foot glass tubing
Column diameter	1/4" o.d.
Effluent	Helium
Flow rate	40 ml/min
Column temperature	100° C
Detector temperature	120° C

C. Sample Analysis

1. System of 2,3-dichlorobutane (DCB) and 2,4-dichloropentane (DCP)

When a dichloro-compound such as DCB or DCP is subjected for neutron bombardment ^{38}Cl is produced. The reaction of ^{38}Cl with DCB or DCP gives various products. Among these, two products form as the result of ^{38}Cl for Cl substitution in the parent molecule. Figure 6 shows a typical example of neutron irradiation of meso DCP. After irradiation, about 10^8 hot ^{38}Cl atoms are produced in the presence of 10^{20} molecules of substrate DCP. The reaction of hot ^{38}Cl with DCP gives abstraction product, $H^{38}Cl$, decomposition products such as $CH_3CHClCH_2{}^{38}Cl$, $CH_3{}^{38}Cl$, etc.. Only about 5% of the generated ^{38}Cl forms substituted products with either retention or inversion of configuration. The inversion at one optical center produces the d,l DCP from meso DCP.

The irradiated samples were transferred to a vial containing about 1 ml of ether and 0.5 ml of 10% aqueous solution of a 1 : 1 mixture of Na_2SO_3 and Na_2CO_3. The organic layer was separated, transferred to another vial, washed with distilled water and dried with anhydrous Na_2SO_4. After addition of a mixture of inactive carriers the organic products were subsequently analyzed by gas

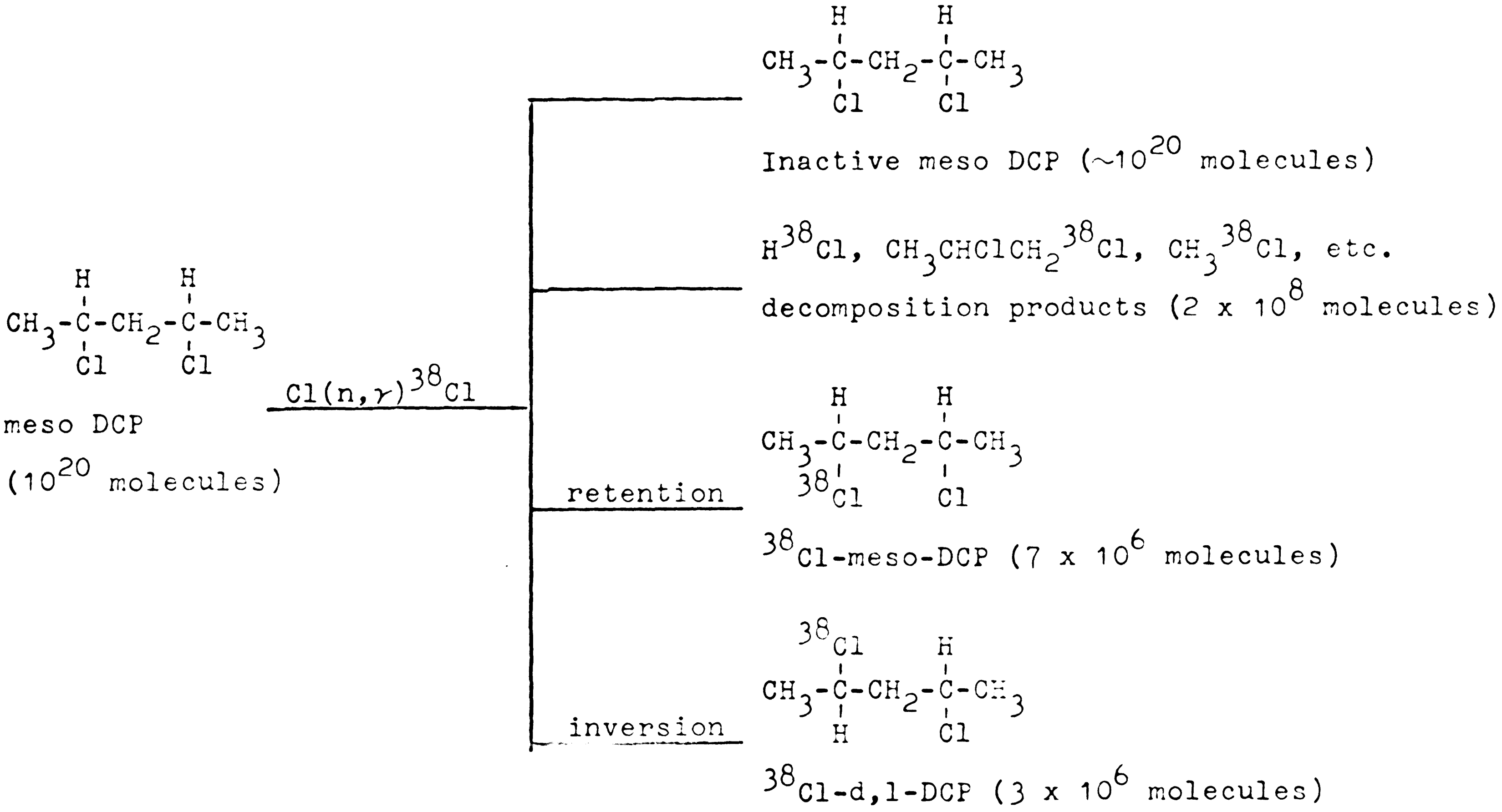


Figure 6. Typical Example of Neutron Irradiation of meso DCP.

chromatography. Several columns were used in this study for the separation of the products formed in the neutron irradiation of 2,4-dichloropentane and 2,3-dichlorobutane. The column packings and operating conditions for the separation of the irradiated products of 2,4-dichloropentane and 2,3-dichlorobutane systems are given in Tables VII and VIII, respectively.

The ^{38}Cl labeled products separated by gas chromatography were absorbed in charcoal directly from the effluent gas stream at one minute intervals. The relatively low ^{38}Cl activity made it necessary to use a discontinuous technique. The radioactivity of the products was subsequently measured in a well type scintillation counter.

The ^{38}Cl decays by gamma-ray emission with radiation energy of 1.64 MeV and 2.17 MeV which was detected with a NaI (TI) scintillation counter. ^{128}I formed as the consequences of the neutron irradiation of iodine which was added in the sample as radical scavenger also decays by gamma-ray emission with energies of 0.44 MeV and 0.53 MeV. Therefore, energy discrimination was required and was applied to avoid interferences in the measurement of ^{38}Cl activities by ^{128}I activities.

The radioactivity decay was accounted for by using

Table VII. Gas Chromatographic Separations of Products Formed in Neutron-irradiated 2,4-Dichloropentane.

% Liquid phase	15% DEGS
Solid support & particle size	Chromosorb W-AW, 60/80 mesh
Column length	35 foot stainless steel
Column diameter	1/4" i.d.
Effluent	Helium
Flow rate	80 ml/min
Column temperature	75°C
Detector temperature	100°C

Table VIII. Gas Chromatographic Separations of Products Formed in Neutron-irradiated 2,3-Dichlorobutane.

	Column A	Column B
% Liquid phase	15% Igepal CO-800	15% DEGS
Solid support & particle size	Chromosorb W-AW 60/80 mesh	Chromosorb W-AW 60/80 mesh
Column length	25 feet	35 feet
Column diameter	1/4" i.d.	1/4" i.d.
Effluent	Helium	Helium
Flow rate	80 ml/min	80 ml/min
Column temperature	70°C	65°C
Detector temperature	100°C	100°C

the decay equation $A = A_oe^{-\lambda t}$, where A is the radioactivity at time t, λ is the decay constant which can be calculated by $\lambda = \frac{0.639}{t_{1/2}}$ from the known half-life ($t_{1/2}$) of the decaying nuclide. A_o is the amount of radioactivity at time zero.

2. System of 2-chloro-1-propanol

The irradiated 2(R)- or 2(S)-chloro-1-propanol was first purified by gas chromatography using a 25' stainless steel column (1/4" i.d.) with 9% DEGS on Anakrom 80/90 mesh at 70°C and 75 ml/min He flow. As shown in Figure 7, the ^{38}Cl for Cl substitution of optically active 2(R)-(-)-chloro-1-propanol may result in ^{38}Cl labeled 2(S)-(+)-chloro-1-propanol and 2(R)-(-)-chloro-1-propanol through retention or inversion of configuration, respectively.

Because of the short half-life of ^{38}Cl ($t_{1/2}$ = 37 minutes) the resolution has to be fast and efficient. Among several types of resolution methods, the conversion of enantiomers into diastereomers by reaction with a chiral regent followed by chromatographic separation of the diastereomeric mixture proved to be an excellent and the most suitable method for this study. The use of 2-(S)-(-)-acetoxy-4-methylvaleryl chloride as resolving agent in the formation of diastereomers is shown in Figure 8.

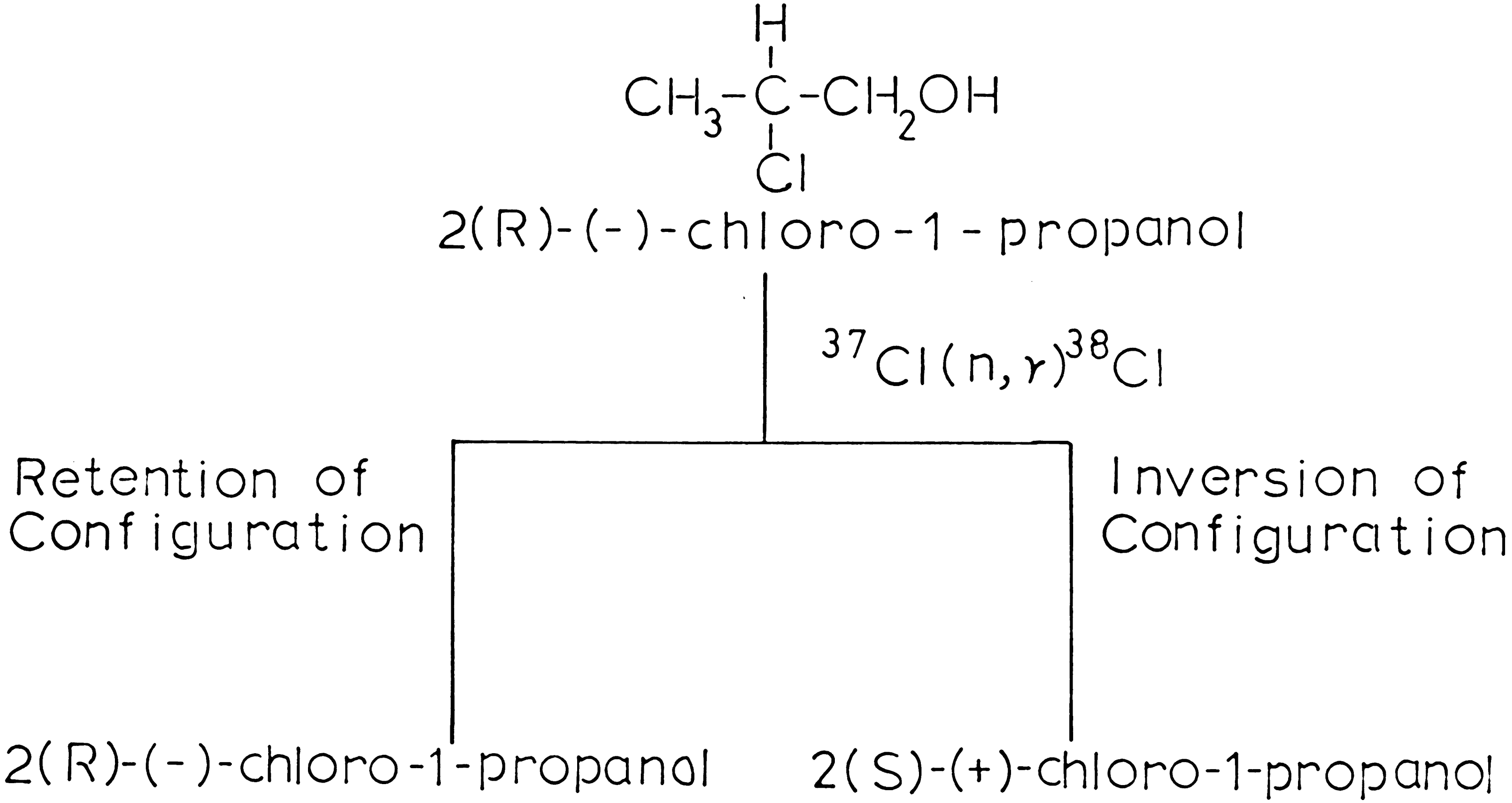


Figure 7. ^{38}Cl for Cl Substitution in 2(R)-(-)-Chloro-1-propanol.

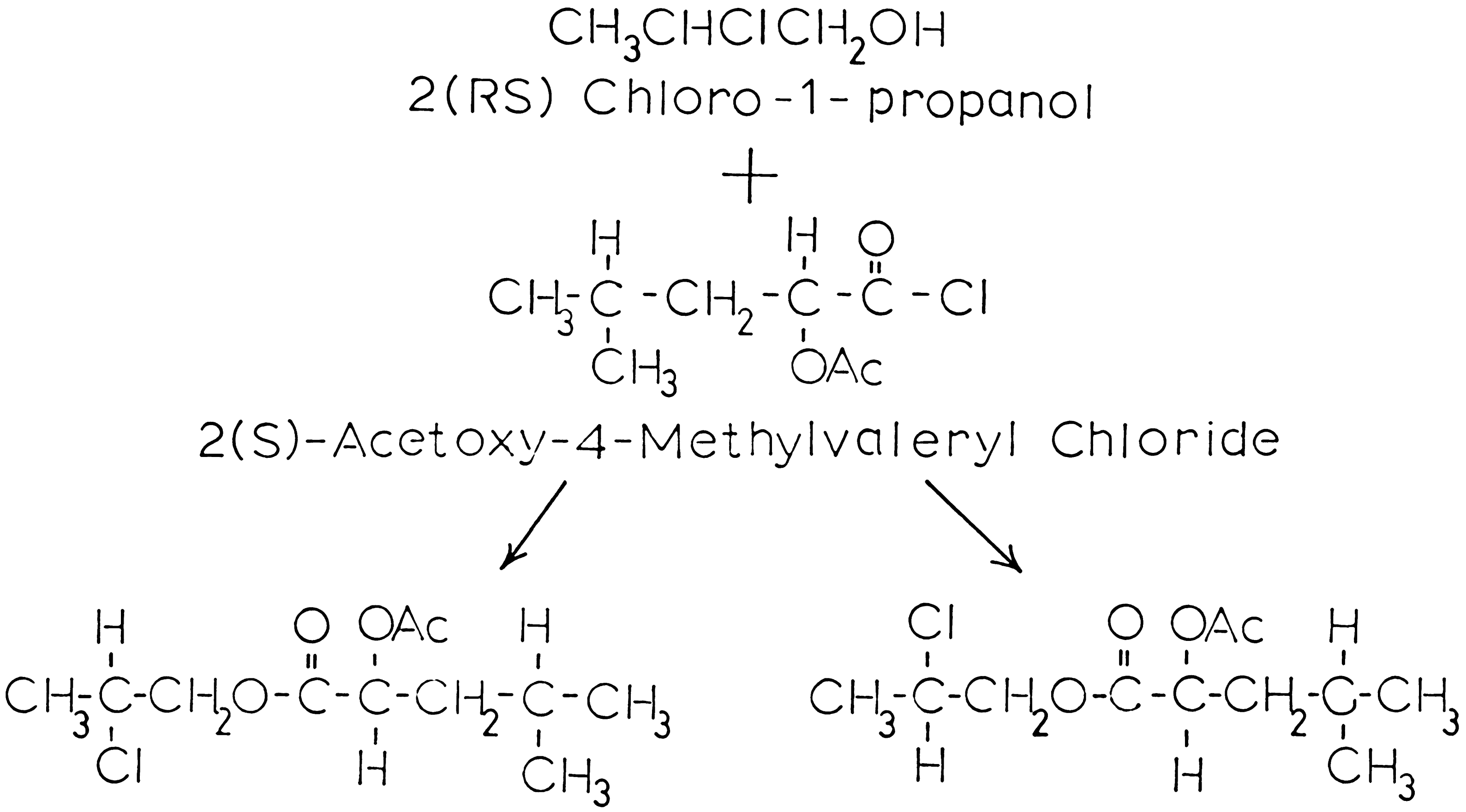


Figure 8. Resolution of 2-Chloro-1-propanol by 2(S)-(-)-Acetoxy-4-methylvaleryl Chloride.

To the purified 2-chloro-1-propanol, about 100 μl CH_2Cl_2 and 30 μl of pyridine were added. To this solution, an amount of 30 μl 2(S)-(-)-acetoxy-4-methylvaleryl chloride was slowly stirred in at 0°C. After the reaction mixture was warmed up to 50°C for 2 minutes, a few drops of methanol were added. The solution was washed with distilled water and the organic products extracted with ether then dried with anhydrous magnesium sulfate. The products were injected into a gas chromatograph for analysis. The column and separation conditions are included in Table IX.

3. System of 2-bromopropanoyl bromide

After irradiation 2(R)- or 2(S)-bromopropanoyl bromide was resolved into diastereomers with (S)-(+)-valine methyl ester as shown in Figure 9 then separated by gas chromatography.

The irradiated 2(R)- or 2(S)-bromopropanoyl bromide was added to a solution of 0.05 g of (S)-(+)-valine methyl ester hydrochloride, dissolved in 0.5 cc of chloroform at 0°C. 0.1 cc triethylamine was slowly stirred in. After 5 minutes, 0.1 cc of methanol was added, the solution was then washed with water, extracted by ether, dried with anhydrous magnesium sulfate, and injected into a gas chromatograph.

Table IX. Conditions Used in Gas Chromatography for Separation of (2-Chloropropyl) 2-Acetoxy-4-methylvalerate.

Stationary phase	10% DEGS
Solid support & particle size	Chromosorb p-NAW 60/80 mesh
Column length	15 foot glass tubing
Column diameter	1/4" i.d.
Effluent	Helium
Flow rate	80 ml/min
Column temperature	130°C
Detector temperature	150°C

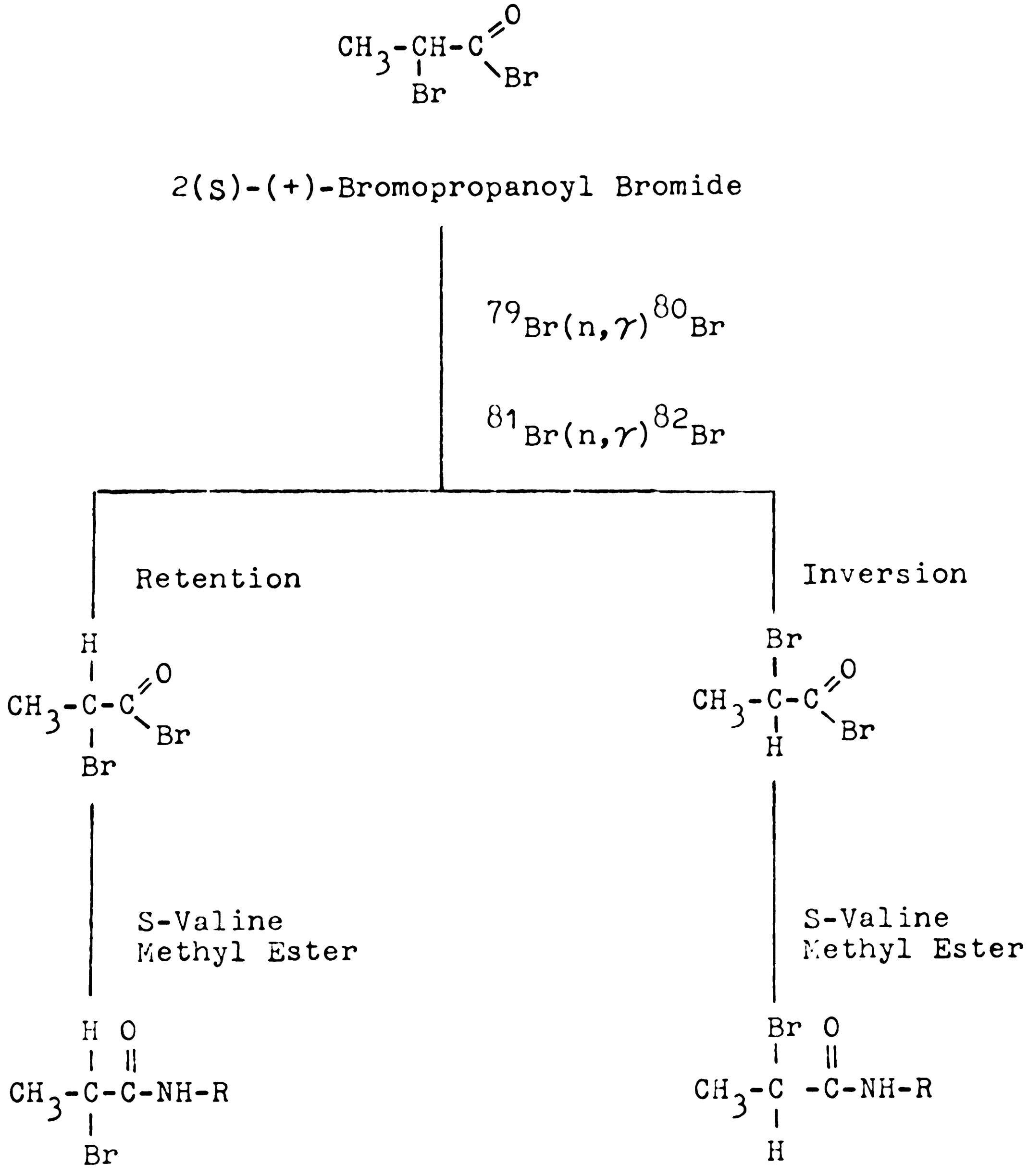


Figure 9. Resolution of Neutron Irradiated 2-Bromopropanoyl Bromide by S-(+)-Valine Methyl Ester.

The ^{82}Br labeled products separated by gas chromatography were collected at one minute intervals conseautively on charcoal directly from the effluent gas stream. The counting was carried out 24 hours after collection by using a well type NaI detector. The 24 hours waiting period allowed the complete decay of ^{80}Br or ^{80m}Br. Thus, the activity counted was solely due to ^{82}Br decay.

In the case of decay induced ^{80}Br substitution reaction with 2-bromopropanoyl bromide, $CF_3{}^{80m}Br$ was used as ^{80}Br source. After the reaction time of about 40 minutes, the residual radioactive CF_3Br was removed and stored for complete decay. The contents of the reaction vessel were transferred to a vial containing one ml of chloroform as solvent. The solution was allowed to react with (S)-(+)-valine methyl ester to form diastereomers and was subsequently separated by gas chromatography. The effluent from the gas chromatograph was collected discontinuously in vials containing 10 ml of toluene scintillator solutions. The scintillation solution was prepared by dissolving 4 g of PPO (2,5-diphenyloxazole) and 0.2 g of POPOP 1,4-bis-2-(5-phenyloxazolyl)-benzene in toluene to make 1000 ml solution. The ^{80}Br counting was done by liquid scintillation spectrometry with the appropriate energy discrimination. The appropriate decay corrections were made.

D. Determination of Optical Purity

When a solution of optically active compound which contains enantiomer R_1 with a small amount of opposite isomer S_1 is allowed to react with a mixture of enantiomers (resolving agent) R_2 and S_2, four different reactions will take place:

(a) $R_1 + R_2 \longrightarrow R_1R_2$

(b) $S_1 + S_2 \longrightarrow S_1S_2$

(c) $R_1 + S_2 \longrightarrow R_1S_2$

(d) $S_1 + R_2 \longrightarrow S_1R_2$

R_1R_2 and S_1S_2 are enantiomers, they are not distinguishable by gas chromatography. The same is true for R_1S_2 and S_1R_2. Therefore, the resolution of R_1R_2, S_1S_2, R_1S_2, and S_1R_2 in gas chromatography should give two peaks. One of the two peaks contains both the R_1R_2 and S_1S_2, the other contains R_1S_2 and S_1R_2. The percentage of $R_1R_2 + S_1S_2$ and $R_1S_2 + S_1R_2$ can be determined from the integration of the two peaks. If we assume that $R_1R_2 + S_1S_2 = A\%$, then the % of isomer (F) to be determined can be calculated by the following equation:

$$F = \frac{A - X}{100 - 2X} \times 100 \qquad (8)$$

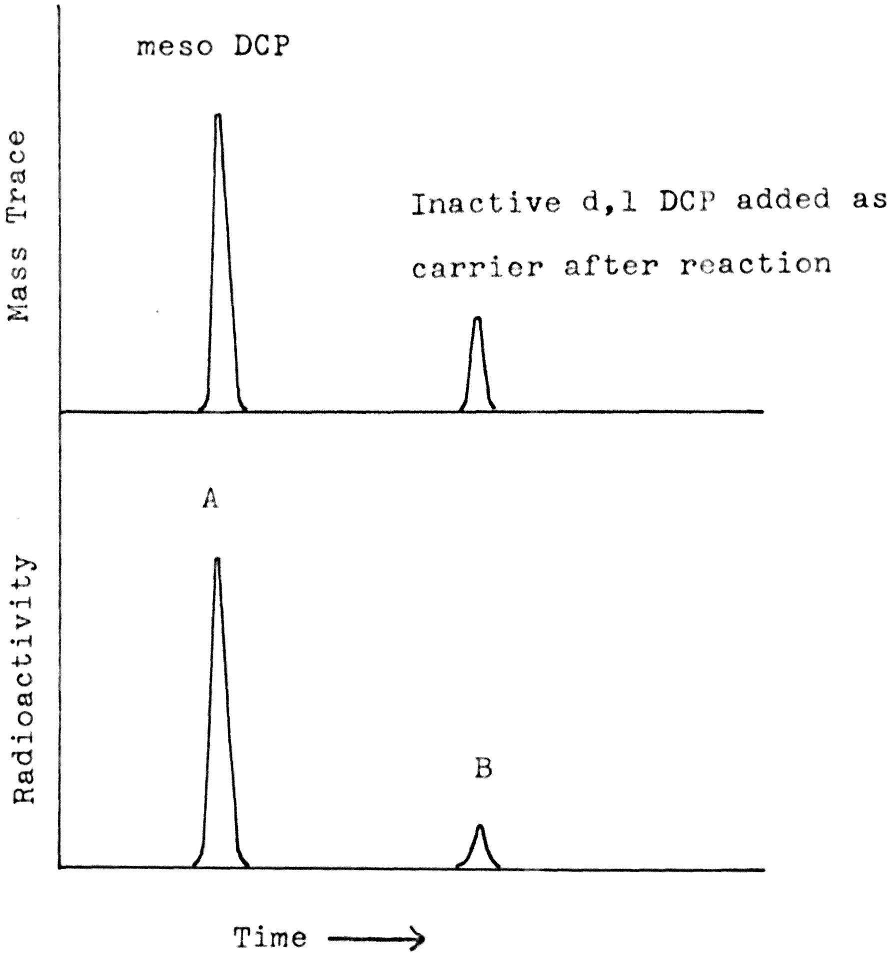
Where X is the known percentage of the opposite isomer in the resolving agent, unless X is 0.5 or close to 0.5.

The optical purities of the synthesized 2-chloropropanoyl chloride, 2-bromopropanoyl bromide, and 2-acetoxy-4-methylvaleryl chloride were determined by equation (8) by resolution with S-valine methyl ester. Using the same method, the optical purity of 2-chloro-1-propanol was determined with 2-acetoxy-4-methylvaleryl chloride.

E. Determination of Retention/Inversion Ratio

Under present experimental conditions it is difficult to obtain a meaningful result of the absolute radiochemical yields of the reaction products. Because in a solution reaction, the solvent molecules will compete with the solute for hot ^{38}Cl atom and react with them in the formation of a variety of products. Geissler and Willard[55] have shown that there are more than ten organic ^{38}Cl products formed by ^{37}Cl(n,γ)^{38}Cl activation of n-C_3H_7Cl in 99.9% n-pentane solution. It is clearly impractical to identify all these products resulting from the reaction of ^{38}Cl with solvent and solute. Therefore, no attempt was made to determine the individual radiochemical yields in each experiment. The radio halogen-labeled compound formed under retention of configuration was compared to the product formed under inversion of configuration and the ratio of their radiochemical yields was determined.

In the case of ^{38}Cl for Cl exchange in diastereomers such as meso 2,4-dichloropentane, the substituted products are formed either via retention of configuration or inversion of configuration as shown in Figure 6. After reaction a small amount of inactive d,l DCP was added as carrier. The solutions were separated by gas chromatography and submitted to radioactivity determination. Figure 10 represents a typical example of mass and activity trace. The radioactivity peak which corresponds to the mass peak of starting material indicates the amount of ^{38}Cl substituted products formed with retention of configuration. On the other hand, the radioactivity peak which corresponds to the mass peak of inactive carrier indicates the amount of ^{38}Cl products formed with inversion of configuration. The retention/inversion ratio was then determined by the following equation:



$$R/I = \frac{A}{B}$$

Figure 10. Relation Between Mass and Activity Trace.

$$\frac{\text{Retention}}{\text{Inversion}} = \frac{\begin{array}{l}\text{radioactivity of } {}^{38}\text{Cl-for-Cl substituted}\\ \text{product with retention of configuration}\end{array}}{\begin{array}{l}\text{radioactivity of } {}^{38}\text{Cl-for-Cl substituted}\\ \text{product with inversion of configuration}\end{array}}$$

In order to determine the relative percent yields of retention or inversion of ^{38}Cl-for-Cl or ^{80}Br-, ^{80m}Br-, and ^{82}Br-for-Br substitution reaction in each enantiomer, the optical purity of the starting material and resolving agent must be known. It was determined by the method discussed in the previous section. If the starting material contains A_1 fraction of R_1 with small amount A_2 fraction of impurity S_1 and the resolving agent contains B_1 fraction of R_2 with B_2 fraction impurity of S_2. Assuming that in the course of substitution reaction, R fraction of the reaction takes place with retention of configuration, then $(1 - R)$ fraction of the reaction must take place with inversion of configuration. Therefore, the fraction of products formed with the same configuration as R_1 is equal to $R(A_1) + (1 - R)A_2$. On the other hand, the fraction of products formed with the same configuration as the optical impurity, S_1, is equal to $R(A_2) + (1 - R)A_1$. The products are separated by formation and subsequent gas chromatographic resolution of the diastereomers. The radioactivity is measured by the use of proper radiation counters. If the fraction of activities in the peak which corresponds to the mass peak of $R_1R_2 + S_1S_2$ is equal to C, then C is given as:

$$C = \left[R(A_1) + (1 - R)A_2\right]B_1 + \left[R(A_2) + (1 - R)A_1\right]B_2$$

After expansion and rearrangement, one can get equation (9) which gives the percent of retention of configuration in a substitution reaction.

$$R = \frac{C - A_2B_1 - A_1B_2}{(A_1 - A_2)\ (B_1 - B_2)} \times 100\% \qquad (9)$$

With a pure resolving agent the above equation can be simpified to:

$$R = \frac{C - A_2}{A_1 - A_2}$$

The determination of optical purity and relative retention yield as discussed in Sections D and E requires that the mixture of enantiomers be quantitatively convertible into a pair of diastereomers. The mixture of diastereomers must be chemically and stereochemically stable under the conditions employed in the gas chromatography.

The test was performed by the reaction of 2(RS)-bromo-propanoyl bromide and 2(RS)-chloro-1-propanol with (R)-valine methyl ester and 2(R)-acetoxy-4-methylvaleryl chloride, respectively. In each case the products produce two peaks in gas chromatography. The first peak contained RS + SR diastereomers, the second peak contained both RR + SS diastereomers. The areas under these two peaks were equal within experimental error. This result indicated the enantiomers have been quantitatively converted into diastereomers under the experimental conditions.

Since the same ratio of the two mass peaks was observed before and after irradiation, no radiation induced racemization had occur during the neutron irradiation.

A further test for the accuracy of the applied experimental procedure was the determination of the percent retention in the substitution reaction which should be identical within experimental error, when either R or S enantiomers were used as starting materials.

CHAPTER III

RESULTS

A. ^{38}Cl for Cl Substitution in d,l and meso 2,4-Dichloropentane

The retention/inversion ratios obtained in ^{38}Cl for Cl exchange in d,l 2,4-dichloropentane and meso 2,4-dichloropentane, in the presence of different types of solvent with various concentrations, are summarized in Tables X and XI, respectively. These data represent the arithmetic mean of the results of two to three experiments. The retention/inversion ratios are further plotted as a function of molefraction additive for the various solutions containing d,l and meso 2,4-dichloropentane in Figures 11 and 12, respectively.

These results clearly indicate that the retention/inversion ratio is strongly influenced by the type and concentration of the solvent. The addition of bromine causes a drastic increase in retention/inversion ratio, whereas in the case of methanol and cyclohexanone this ratio also increases but to a lesser degree. However, cyclohexane and n-heptane reduce retention/inversion ratio below the value observed in the pure liquid d,l or meso 2,4-dichloropentane. This is in agreement with the

Table X. ^{38}Cl for Cl Substitution in d,l-2,4-Dichloropentane in Solution.

Additive	Mole Fraction	$\frac{\text{Retention}}{\text{Inversion}}$
Bromine	0.16	2.7 ±0.1
	0.28	3.0 ±0.1
	0.37	3.1 ±0.2
	0.40	3.4 ±0.3
	0.54	3.3 ±0.3
	0.61	3.7 ±0.3
	0.68	3.9 ±0.3
Methanol	0.14	2.3 ±0.2
	0.18	2.6 ±0.1
	0.32	2.82±0.07
	0.47	3.1 ±0.1
	0.65	3.3 ±0.2
	0.85	3.5 ±0.2
	0.90	3.8 ±0.1
Cyclohexanone	0.12	2.5 ±0.2
	0.30	2.6 ±0.1
	0.50	2.6 ±0.2
	0.66	2.7 ±0.2
	0.81	2.8 ±0.2
n-Heptane	0.21	2.2 ±0.2
	0.51	1.9 ±0.1
	0.74	1.6 ±0.1

Table X (continued)

Additive	Mole Fraction	$\frac{\text{Retention}}{\text{Inversion}}$
Cyclohexane	0.16	2.1 ±0.1
	0.37	2.0 ±0.2
	0.53	1.7 ±0.1
	0.67	1.6 ±0.1
	0.80	1.48±0.07
	0.84	1.3 ±0.1

Table XI. ^{38}Cl for Cl Substitution in meso-2,4-Dichloropentane in Solution.

Additive	Mole Fraction	$\frac{\text{Retention}}{\text{Inversion}}$
Bromine	0.15	2.4 ±0.2
	0.31	2.7 ±0.2
	0.39	2.6 ±0.2
	0.50	2.8 ±0.3
	0.58	2.9 ±0.3
Methanol	0.10	2.2 ±0.1
	0.17	2.2 ±0.1
	0.28	2.4 ±0.1
	0.49	2.4 ±0.2
	0.86	2.7 ±0.2
Cyclohexanone	0.16	2.3 ±0.2
	0.31	2.5 ±0.2
	0.48	2.2 ±0.2
	0.68	2.7 ±0.2
	0.80	2.4 ±0.2
	0.85	2.4 ±0.2
n-Heptane	0.22	1.4 ±0.1
	0.50	1.2 ±0.1
	0.79	0.85±0.05
Cyclohexane	0.12	1.6 ±0.1
	0.25	1.60±0.08
	0.47	1.31±0.05
	0.71	1.07±0.07
	0.91	0.52±0.05

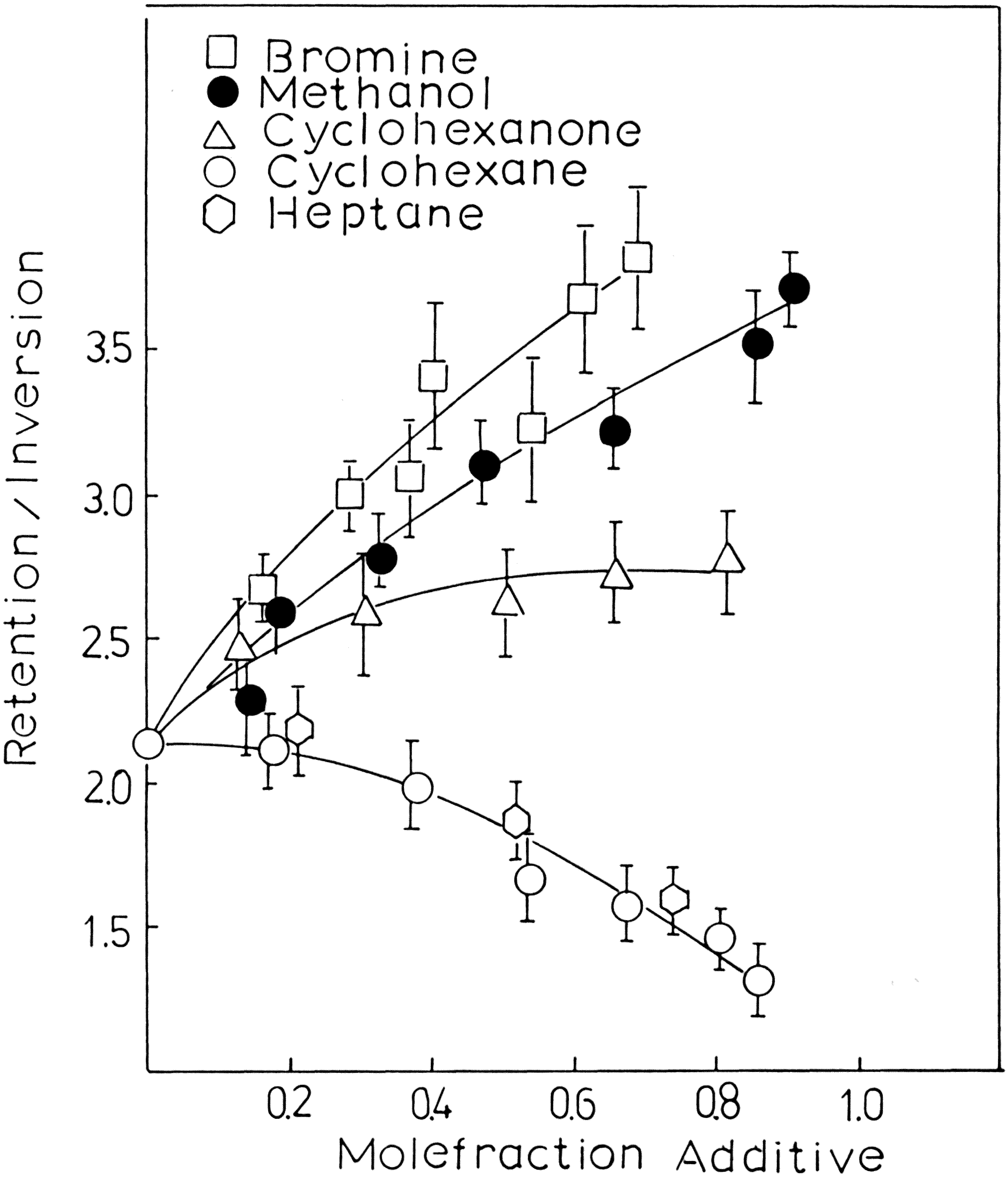


Figure 11. ^{38}Cl for Cl Exchange in d,l 2,4-Dichloropentane in Solution.

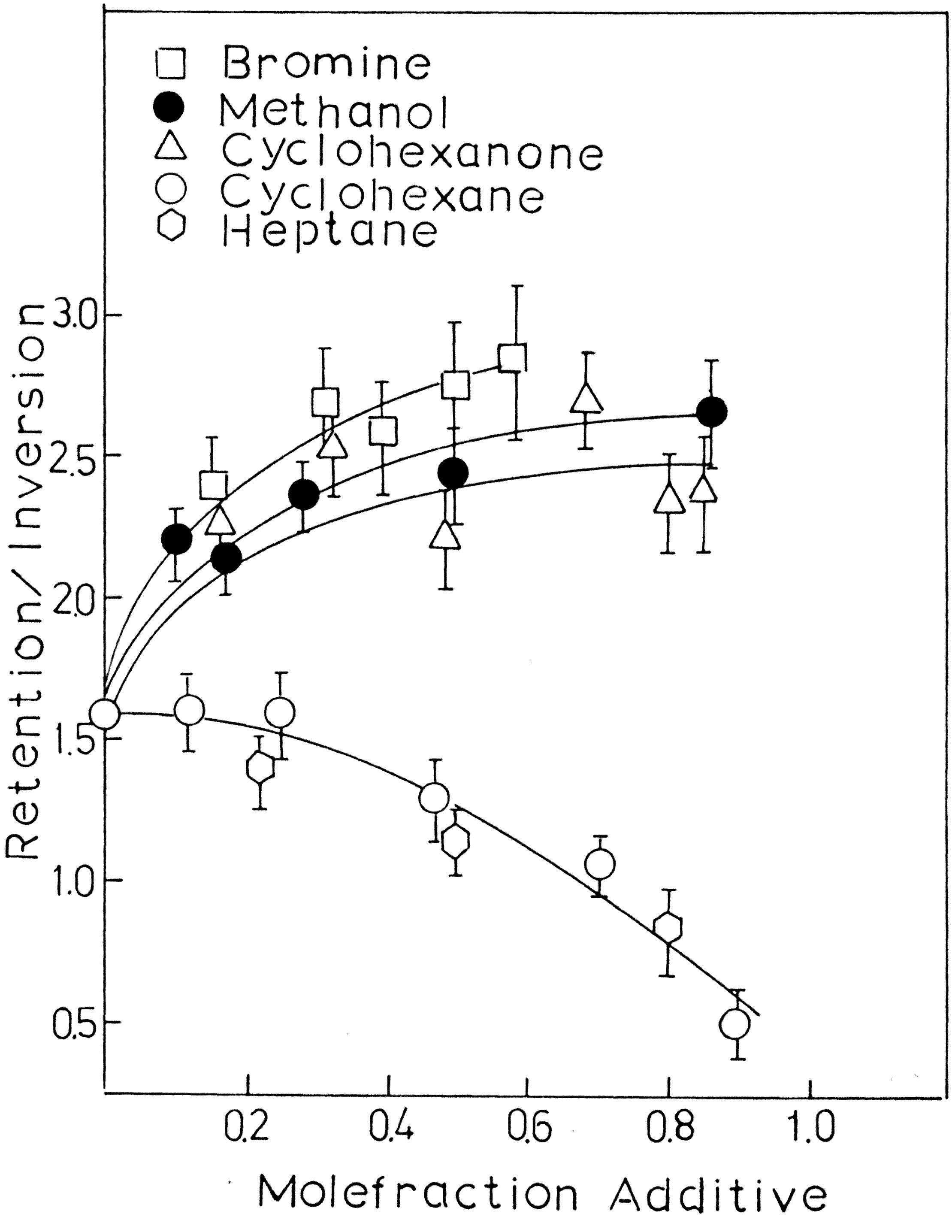


Figure 12. ^{38}Cl for Cl Exchange in meso 2,4-Dichloropentane in Solution.

results previously observed in the 2,3-dichlorobutane systems.[13,18]

B. ^{38}Cl for Cl Substitution in Diastereomeric 2,4-Dichloropentane and 2,3-Dichlorobutane in the Presence of 90% Solvent

In order to correlate the retention/inversion ratios to the physical and chemical properties of the solvent present, the investigation was extended by using a large number of different solvents to study the solvent effect in both the diastereomers of 2,3-dichlorobutane and 2,4-dichloropentane.

Samples were irradiated at about 40°C for 2 to 5 minutes in a solution containing 90 mole % solvent, and in the presence of a sufficient amount of I_2 as scavenger. The results are listed in Tables XII, XIII, XIV, and XV. These data represent the average of two to three experiments.

C. ^{80}Br, ^{80m}Br, and ^{82}Br for Br Substitution in 2(S)-(+)- and 2(R)-(-)-Bromopropanoyl Bromide

The ^{80m}Br and ^{82}Br for Br substitution in liquid 2-bromopropanoyl bromide were carried out by neutron irradiation of the substrate in the presence of I_2 as scavenger.

Table XII. ^{38}Cl for Cl Substitution in d,l 2,4-Dichloropentane in the Presence of 90% Additive.

Additive	Retention / Inversion
Methanol	3.8 ±0.1
Ethanol	3.7 ±0.2
n-Propanol	3.2 ±0.1
2-Propanol	3.5 ±0.1
i-Butanol	2.7 ±0.3
t-Butanol	2.6 ±0.2
n-Pentanol	3.2 ±0.3
n-Hexanol	3.1 ±0.1
n-Heptanol	2.7 ±0.1
Acetic Acid	3.0 ±0.1
Propanoic Acid	2.7 ±0.1
Cyclohexanone	2.8 ±0.2
Carbon Disulfide	2.46±0.06
Cyclohexane	1.28±0.06
n-Heptane	1.3 ±0.1
Bromine	4.2 ±0.3

Table XIII. ^{38}Cl for Cl Substitution in meso 2,4-Dichloropentane in the Presence of 90% Additive.

Additive	$\frac{\text{Retention}}{\text{Inversion}}$
Methanol	2.7 ±0.2
i-Propanol	2.2 ±0.1
Carbon Disulfide	1.79±0.08
Cyclohexanone	2.8 ±0.2
Acetic Acid	2.7 ±0.1
Propanoic Acid	1.8 ±0.1
Cyclohexane	0.54±0.05
n-Heptane	0.60±0.04
Bromine	3.0 ±0.3

Table XIV. ^{38}Cl for Cl Substitution in d,l 2,3-Dichlorobutane in the Presence of 90% Additive.

Additive	$\frac{\text{Retention}}{\text{Inversion}}$
Methanol	4.3 ±0.3
Ethanol	3.93±0.04
n-Propanol	3.3 ±0.1
2-Propanol	3.3 ±0.1
n-Butanol	3.3 ±0.1
2-Butanol	3.18±0.02
t-Butanol	3.14±0.04
n-Pentanol	3.10±0.08
n-Hexanol	3.04±0.05
Carbon Disulfide	1.9 ±0.1
Acetic Acid	2.59±0.04
Propanoic Acid	2.4 ±0.1
Butyric Acid	2.7 ±0.2
Benzene	1.43±0.04
Toluene	1.58±0.04
Ethylbenzene	1.48±0.05
t-Butylbenzene	1.6 ±0.1
n-Pentane	0.77±0.05
n-Hexane	0.79±0.07
Acetonitrile	2.4 ±0.2
Bromine	5.8 ±0.3

Table XV. ^{38}Cl for Cl Substitution in meso 2,3-Dichlorobutane in the Presence of 90% Additive.

Additive	$\frac{\text{Retention}}{\text{Inversion}}$
Methanol	3.1 ±0.1
Carbon Tetrachloride	1.5 ±0.1
Benzene	2.55±0.05
Nitrobenzene	3.0 ±0.1
n-Pentane	1.8 ±0.1
Carbon Disulfide	2.3 ±0.1
Acetic Acid	2.17±0.08
Acetonitrile	2.2 ±0.3
Bromine	5.7 ±0.2

The ^{80m}Br species were generated via the ^{79}Br(n,γ)^{80m}Br nuclear process, whereas ^{82}Br species were either produced via ^{81}Br(n,γ)^{82}Br or by isomeric transition of ^{82m}Br. The results are shown in Table XVI.

The gas phase substitution reaction was also studied. In the gas phase the complicated cage effect can be eliminated. Thus, it may provide some important information on the reaction mechanism. Energetic ^{80}Br ions were generated via the ^{80m}Br(IT)^{80}Br nuclear process using CF_3^{80m}Br as source. As discussed in Chapter I Section C, in this case ^{80}Br is formed as an ionic species. The results are also listed in Table XVI.

It is important to point out that in the analysis of the irradiated sample, the opposite isomer is not needed as a carrier, because the small impurity of the opposite isomer in the sample can serve as an intrinsic carrier. However, it was found that when the opposite isomer was added after the termination of the reaction, the percentage of ^{80}Br labeled products with R or S configuration showed a strong dependence on the amount of isomer present in the solution. This finding clearly indicates that thermal or chemical exchange rather than the hot reaction was involved.

Table XVI. $^{80}\mathrm{Br}$, $^{80m}\mathrm{Br}$, and $^{82}\mathrm{Br}$ Substitution in 2-Bromopropanoyl Bromide.

Enantiomer	Recoil Bromine	Phase	Irradiation Time	Inversion (%)
S	$^{80m}\mathrm{Br}$	Liquid	2 min.	83.0±5.6
R	$^{80m}\mathrm{Br}$	Liquid	2 min.	76.2±4.5
S	$^{82}\mathrm{Br}$	Liquid	30 min.	74.6±2.8
R	$^{82}\mathrm{Br}$	Liquid	30 min.	80.5±7.5
S	$^{80}\mathrm{Br}$	Gas	60 min.	86.2±5.1
R	$^{80}\mathrm{Br}$	Gas	60 min.	89.1±6.3

D. ^{38}Cl for Cl Substitution in 2(S)-(+)- and 2(R)-(-)-Chloro-1-propanol

The retention/inversion ratios obtained in ^{38}Cl for Cl exchange in enantiomeric 2-chloro-1-propanol in the presence of different types of solvent with various concentrations are shown in Table XVII. The retention of optical configuration in neat 2(S)-(+)- and 2(R)-(-)-chloro-1-propanol in liquid phase are equal to 53 ± 3%. For comparison with the results obtained in 2,3-dichlorobutane and 2,4-dichloropentane systems, the retention/inversion ratios are plotted as a function of the mole fraction of the solvent added. A similar trend of solvent effect as obtained in diastereomeric systems is shown in Figure 13.

Table XVII ^{38}Cl for Cl Substitution in 2(S)-(+)-Chloro-1-propanol.

Additive	Mole Fraction	$\frac{\text{Retention}}{\text{Inversion}}$
Methanol	0.19	1.1 ±0.1
Methanol	0.36	1.2 ±0.1
Methanol	0.49	1.5 ±0.1
Methanol	0.75	1.5 ±0.2
Methanol	0.90	1.6 ±0.3
n-Pentane	0.13	1.4 ±0.2
n-Pentane	0.24	1.2 ±0.1
n-Pentane	0.90	1.0 ±0.1
Cyclohexane	0.53	1.1 ±0.1
Cyclohexane	0.90	1.0 ±0.1
Methylene Chloride	0.16	1.3 ±0.2
Methylene Chloride	0.45	1.2 ±0.1
Chloroform	0.15	1.3 ±0.1
Carbon Tetrachloride	0.34	1.2 ±0.1
Neat Solution	—	1.16±0.05

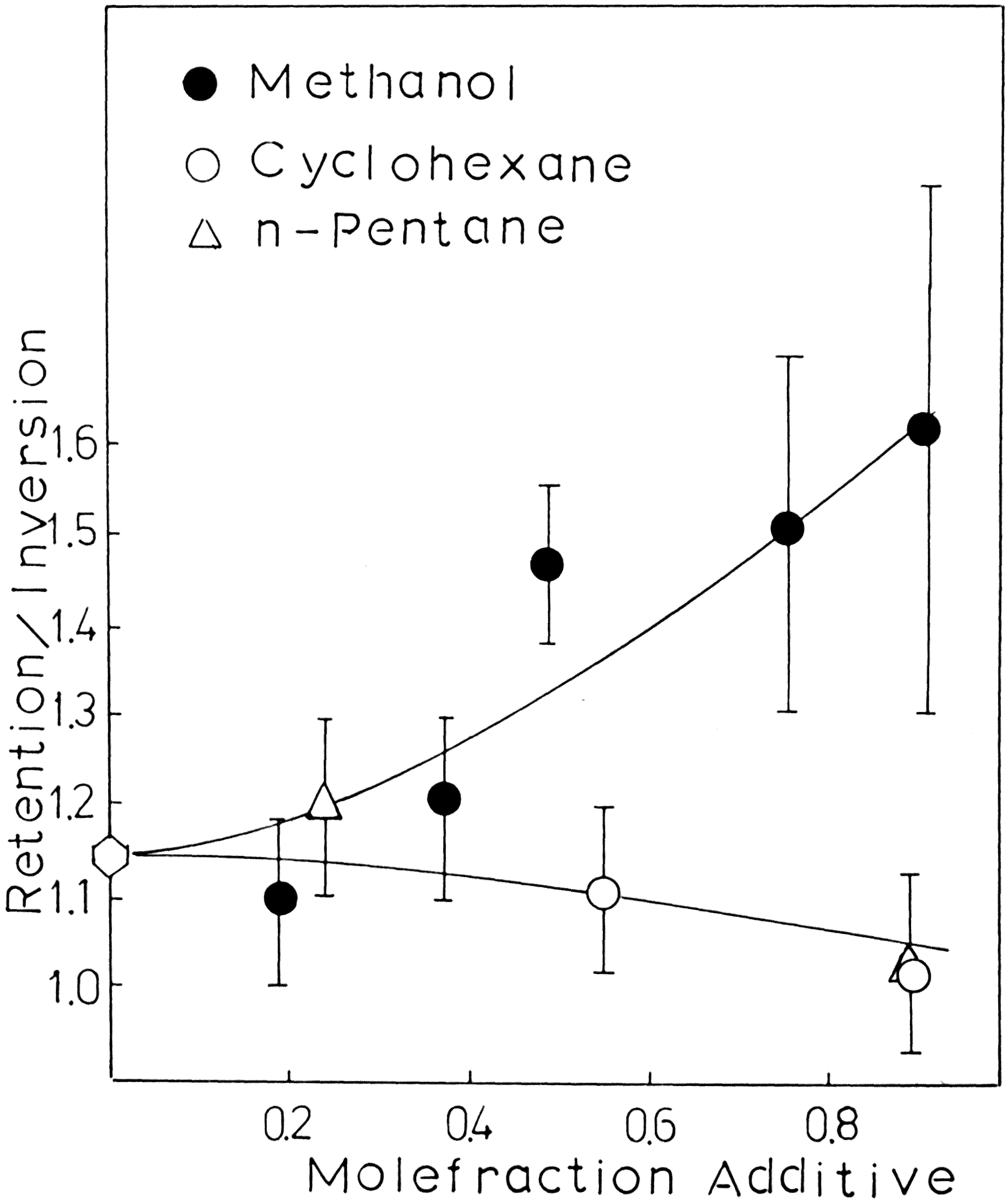


Figure 13. ^{38}Cl for Cl Substitution in 2(S)-(+)-Chloro-1-propanol in Solution.

CHAPTER IV

DISCUSSION

A. Conformational Analysis

As shown in Figures 11 and 12, the retention/ inversion ratios obtained as a result of ^{38}Cl for Cl substitution in diastereomeric 2,4-dichloropentane show a strong dependence on the type and concentration of the solvent.

In order to ascertain whether a conformational effect is controlling the stereochemical course of the reaction, the relative concentration of conformers of 2,4-dichloropentane in the reaction mixture was analyzed.

Based on the staggered molecular model, the structure of low energy conformers of d,l and meso 2,4-dichloropentane is presented on Figures 14a and 14b, respectively.

Earlier works[56-59] suggested the presence of only one form in the meso DCP, namely the TG conformer. Calculations using the "staggered approximation" predicated the relative energies for the next stable conformers to be (in kcal/mole) 18.6 for TT, 39.4 for TG', and 40.2 for GG[60], whereas the preferred forms for d,l DCP are predominantly TT, and also GG with some probabilities.

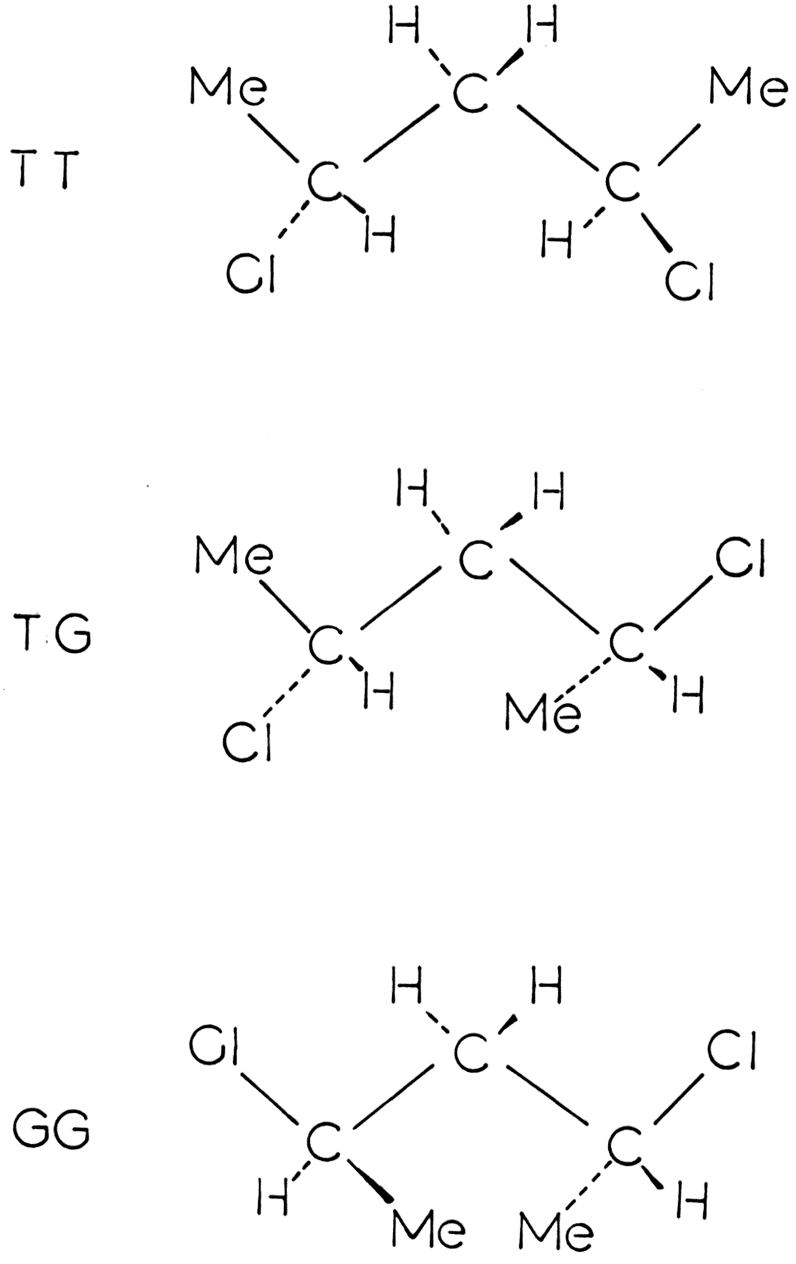
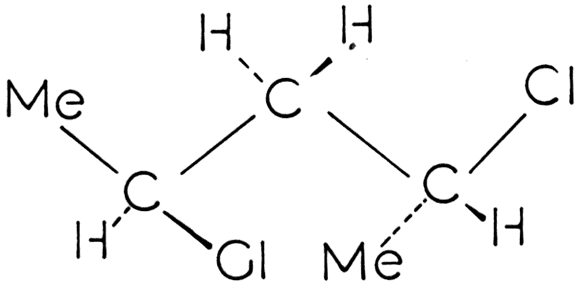
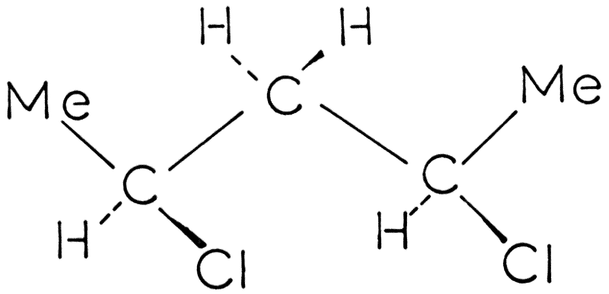


Figure 14a. Structure of Low Energy Conformers of d,l 2,4-Dichloropentane.

TG



T T



T G′

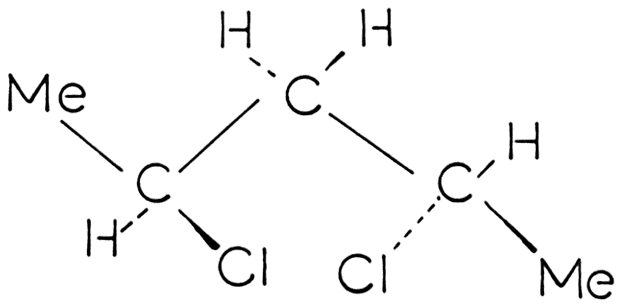


Figure 14b. Structure of Low Energy Conformers of meso 2,4-Dichloropentane.

From these results one would hardly expect any significant solvent effects, i.e. changes in the relative conformer concentrations upon addition of a solvent. This is in line with the results[58-60] of IR investigations of the pure liquid and in cyclohexanone which did not reveal any noticable changes in the IR spectra, a result which was further supported by NMR studies of the pure liquid DCP and DCP solutions in carbon tetrachloride and chlorobenzene.[56]

However, more recent NMR and IR investigations[61] of meso DCP revealed in addition to TG the possible existence of other conformers such as TT, TG', and GG, whose energies (relative to TG) were calculated to be (in kcal/mole) TT 2.9, TG' 1.7, and GG 2.8.[60] In the d,l DCP system, the most preferred conformer is TT form, with three minor conformers. Of these, the most favored one is GG, followed by TG and very small amounts of GG'. The energies relative to TT for these conformers were semiempirically calculated (in kcal/mole) as GG 1.5, TG 2.5, and GG' 3.7.

A quantitative experimental determination of the conformer concentrations by means of NMR and IR techniques is very difficult because of the relatively large number of conformers to be considered in the evaluation of these spectra. Therefore, the solvent effects on conformer population were estimated from semiempirical calculations based on Onsager's theory.[62-64]

If two conformers are in equilibrium and the population of these two conformers in any solvent are N_I and N_{II}, then the relative distribution of two conformers in a solution can be calculated from the following equation:

$$N_I/N_{II} = (f_I/f_{II}) \exp(-\Delta E^{solution}_{I/II}/RT) \qquad (10)$$

Where f_I/f_{II} is the ratio of the partition functions of the two conformers. It can be assumed to be approximately unity, $\Delta E^{solution}_{I/II}$ is the energy difference between the two rotational isomers in the solution, R is the gas constant and T the absolute temperature.

According to Onsager, when a molecule of dipole moment μ is transferred from vacuum into a medium of dielectric constant ϵ, the potential energy is lowered by:

$$E_r = \frac{\epsilon - 1}{2\epsilon - 1} \quad \frac{\mu^2}{a^3}$$

Where a is the radius of the solute molecule, it can be estimated from its density, d, molecular weight, M, and avogadro number, N, according to the following equation:

$$a^3 = \frac{M}{d} \quad \frac{3}{4\pi N}$$

Therefore, $\Delta E^{\text{solution}}_{I/II}$ can be obtained from the following relation:

$$\Delta E^{\text{solution}}_{I/II} = \Delta E^{\text{gas}}_{I/II} - \frac{\epsilon - 1}{2\epsilon + 1} \quad \frac{\mu^2_I - \mu^2_{II}}{a^3} \qquad (11)$$

$\Delta E^{\text{gas}}_{I/II}$ is the energy difference between the two conformers in the gas phase. Their values are obtained from reference 60, and listed in Table XVIII. The dipole moment of the various conformers were approximated by vector additive method[65,66] from the structure of the conformers (as shown in Figures 14a and 14b) by considering the bond angles as tetrahedral and the dipole moments for the C-Cl bond 1.85 D, $C\text{-}CH_3$ = -0.4 D, and C-H = 0 D.

As an example, the calculation is illustrated for the case of the TT conformer of meso 2,4-dichloropentane. First let us place the molecule on an arbitrarily chosen coordinate axes and label the atoms as shown in Figure 15. Secondly, find the projections of the vector of each group moment on the x, y, and z axis:

Table XVIII. Energy Differences Between the Rotational Isomers of 2,4-Dichloropentane in Gaseous State.*

Isomer	Energy Difference	Value (kcal/mole)
meso DCP	E^{gas}_{TT-TG}	2.9
	$E^{gas}_{TT-TG'}$	1.2
	$E^{gas}_{TG'-TG}$	1.7
d,l DCP	E^{gas}_{GG-TT}	1.5
	E^{gas}_{TG-TT}	2.5
	E^{gas}_{TG-GG}	1.0

---

* Obtained from reference 60.

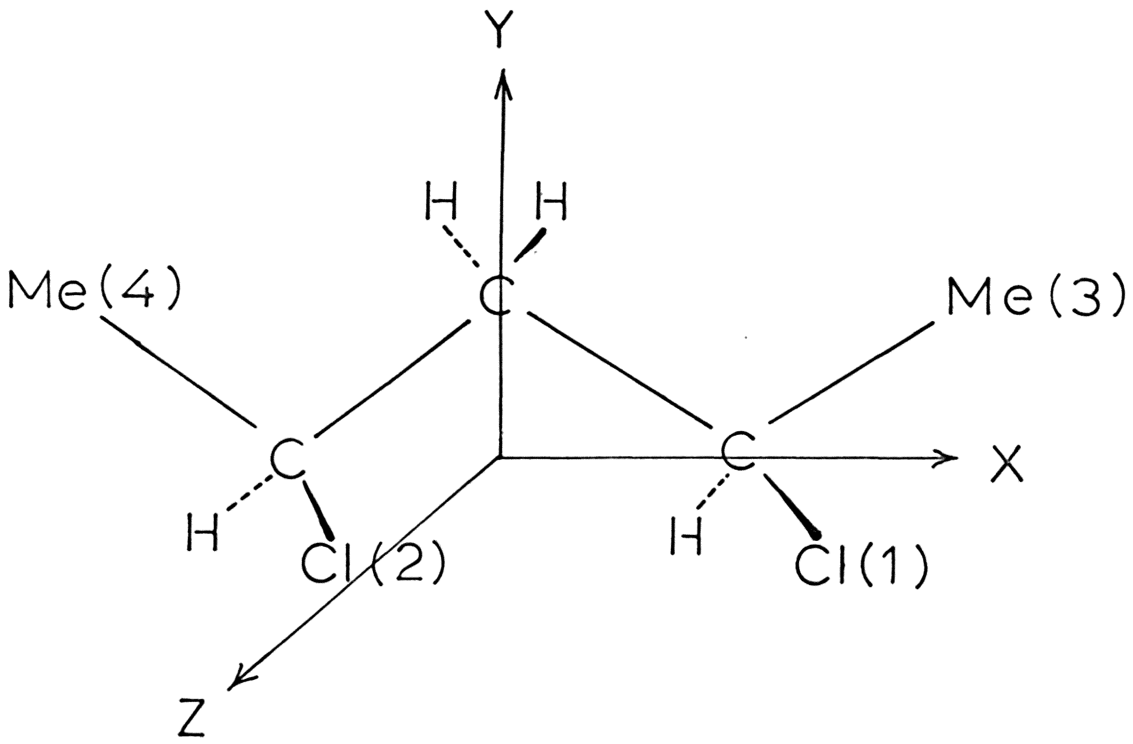


Figure 15. Scheme for the Calculation of the Dipole Moment of TT Conformer of meso 2,4-Dichloropentane.

Cl (1) $M_x = 0$
$M_y = -1.85 \cos 109.5/2$
$M_z = 1.85 \sin 109.5/2$

Cl (2) $M_x = 0$
$M_y = -1.85 \cos 109.5/2$
$M_z = 1.85 \sin 109.5/2$

$CH_3(3)$ $M_x = -0.4 \sin 109.5/2$
$M_y = -0.4 \cos 109.5/2$
$M_z = 0$

$CH_3(4)$ $M_x = 0.4 \sin 109.5/2$
$M_y = -0.4 \cos 109.5/2$
$M_z = 0$

Therefore, the momenta in each axis are:

$$\Sigma M_x = 0; \qquad \Sigma M_y = -2.60; \qquad \Sigma M_z = 3.02$$

Thus, the dipole moment, μ, of TT comformer of meso 2,4-dichloropentane is equal to:

$$\mu = \left[(\Sigma M_x)^2 + (\Sigma M_y)^2 + (\Sigma M_z)^2\right]^{1/2} = 3.98$$

By using the same method, the dipole moment of the low energy comformers of d,l and meso 2,4-dichloropentane were calculated. The results are listed in Table XIX.

Table XIX. Calculated Dipole Moment for meso and racemic 2,4-Dichloropentane.

Isomer	Conformation	Dipole Moment (D)
meso DCP	TG	2.60
	TT	3.98
	TG'	2.20
d,l DCP	TT	2.60
	GG	2.60
	TG	2.20
	TG'	3.98

By substituting appropriate values into equations (10) and (11), the concentration of various conformers can be estimated as a function of the solvents with a wide range of dielectric constants. For instance, the relative population of TG and TT conformers of meso 2,4-dichloropentane in methanol at 25°C can be calculated as follows:

$$\Delta E_{TG/TT}^{solution} = \Delta E_{TG/TT}^{gas} - \frac{\epsilon - 1}{2\epsilon + 1} \; \frac{\mu_{TG}^{2} - \mu_{TT}^{2}}{a^{3}}$$

$$= -2.9 - \frac{32.6 - 1}{2 \times 32.6 + 1} \times \frac{(2.60)^{2} - (3.98)^{2}}{5.258 \times 10^{-23}}$$

$$\times 1.44 \times 10^{13} \times 10^{-36}$$

$$= -1.7138 \text{ kcal/mole}$$

Substituting the above number into equation (10), the relative concentration of TG and TT is equal to:

$$\frac{N_{TG}}{N_{TT}} = e^{-1.7138 \times 10^{3}/1.987 \times 298} = 18.07$$

By using the same method, the relative concentration of TG' and TT conformers of meso 2,4-dichloropentane in methanol at 25°C can be calculated:

$$\frac{N_{TG'}}{N_{TT}} = 0.67$$

Thus, the relative population of TG, TG', and TT at above metioned conditions are: TG : TG' : TT = 18.07 : 0.67 : 1 or TG 91.5%, TG' 3.4%, and TT 5.1%. The relative population of major conformers of d,l and meso 2,4-dichloropentane in the presence of different solvents was also estimated, the results are shown in Table XX.

The validity of these calculations has been checked with the results published by Flory and Williams.[67] Based on the statistical weight parameters obtained in the stereochemical equilibration of 2,4-dichloropentane in DMSO, they calculated the major conformer populations for d,l and meso isomers in DMSO at 70°C. The comparison between their results and the results obtained by using this calculation for the same condition is given in Table XXI. The agreement between these data seems to support the validity of this approach.

From Table XX it appears that the presence of solvents with widely different dielectric constants has only a negligible effect on the relative amounts of the preferred form present in the mixture. Significant changes are only observed in the ratios of the conformer

Table XX. Equilibrium Concentrations of the Rotational Isomers in 2,4-Dichloropentane.

Solvent		Methanol	Cyclohexanone	Cyclohexane
Dielectric Constant		32.6	18.3	2.02
d,l DCP	TT(%)	91.8	91.8	91.6
	GG(%)	7.3	7.3	7.3
	TG(%)	0.9	0.9	0.9
meso DCP	TG(%)	91.5	91.8	93.9
	TG'(%)	3.4	4.7	4.4
	TT(%)	5.1	3.5	1.6

Table XXI. Percent Conformation Population in 90% DMSO at 70°C.

Isomer	Conformation	% Conformation Population A*	 B**
meso DCP	TG	86.3	87.8
	TT	7.6	7.3
	TG'	4.3	5.0
d,l DCP	TT	86.4	88.6
	GG	7.1	9.8
	TG	4.9	1.6

* Results obtained by this calculation.

** Data from reference 67.

population of the two minor components, e.g. GG and TG, if d,l 2,4-dichloropentane is the substrate, where the ratios change from approximately $C_{GG} : C_{TG} = 8.1$ in methanol to 6.6 in cyclohexane. However, the absolute amounts of these two conformers are less than 9% of the conformer population. All of these results indicate the relative conformer population of 2,4-dichloropentane is not affected to any significant degree by the nature of the solvent.

B. Solvent Effects on Stereochemical Course

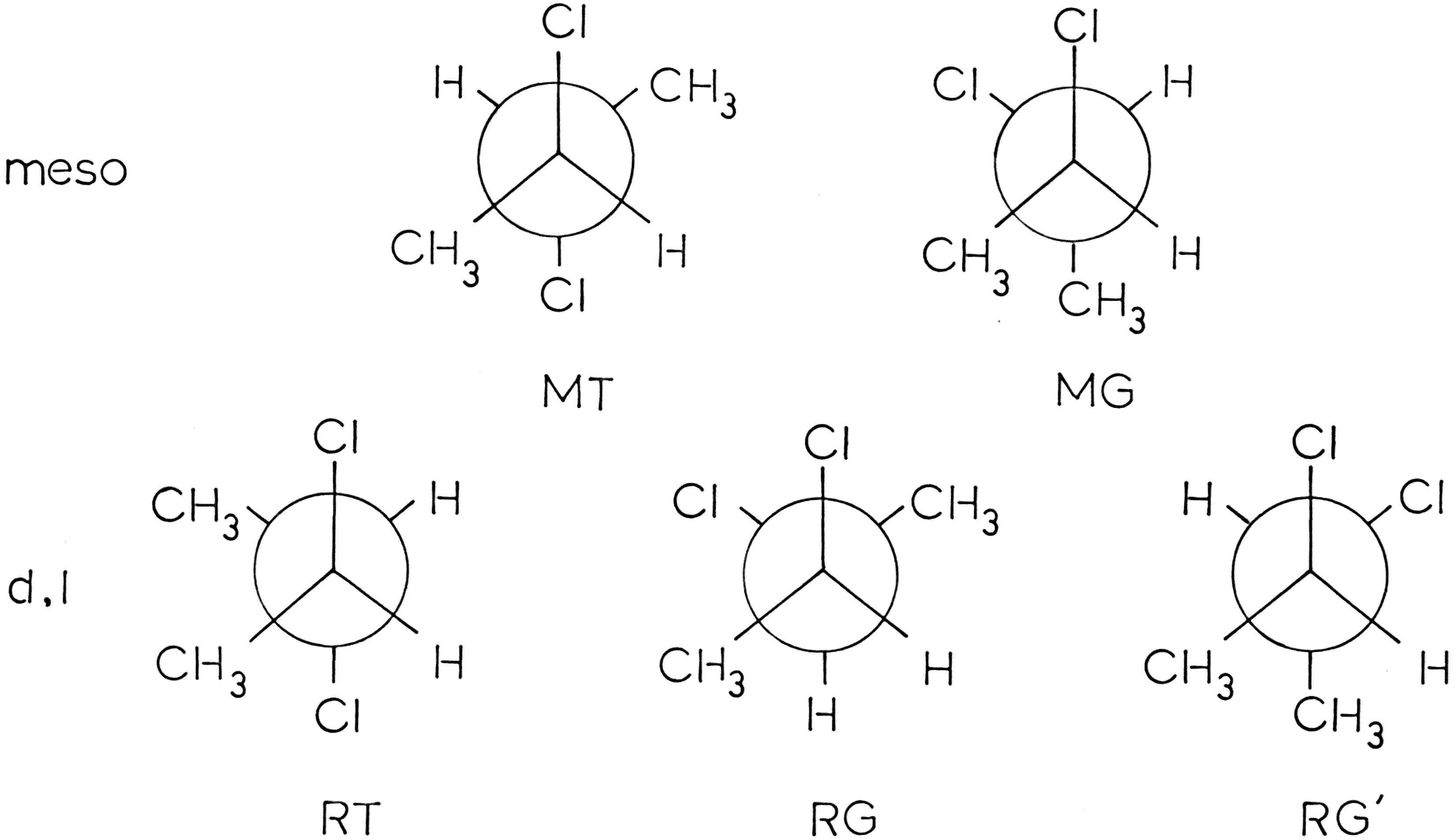
The results of ^{38}Cl for Cl substitution in d,l and meso 2,4-dichloropentane in solution are given in Tables X and XI, respectively. It indicates that the stereochemical course of the substitution exhibits a pronounced solvent effect. As shown in Figures 11 and 12 the ratio of retention to inversion is strongly dependent on the concentration and nature of the solvent added. An increase in this ratio with increasing bromine concentration was observed. With 90% bromine present the retention/inversion ratio increases from initially 2.1 for pure d,l 2,4-dichloropentane and 1.6 for pure meso form to 4.2 and 3.0, respectively. Similar trends with smaller degree increases have been found for the case of methanol and cyclohexanone as solvent. However, n-heptane and cyclohexane reduce the ratio to 1.3 and 0.6 for d,l and meso systems containing 90% n-heptane or cyclohexane, respectively.

Furthermore, this strong solvent effect was also observed in the study of the stereochemistry of ^{38}Cl for Cl exchange in diastereomeric 2,3-dichlorobutane and 2,4-dichloropentane in the presence of 90% solvent. The results are shown in Tables XII and XIV for 2,4-DCP and 2,3-DCB systems, respectively.

As discussed in the previous section, the relative conformer population of 2,4-dichloropentane is not significantly affected by the presence of solvents with different dielectric constant. Thus, we can conclude that the strong solvent dependence of the retention/inversion ratios observed cannot be correlated with the conformational composition of the reaction mixture.

This conclusion is further supported by the results obtained in neutron irradiation of neat diastereomers of 2,3-dichlorobutane in solid (crystalline) state.

On the study of conformational structure of stereoisomers of 2,3-dichlorobutane, Schneider and coworkers[68] have found that in the case of meso form, the population of conformer MT (the conformational structure of 2,3-dichlorobutane is shown in Figure 16) in which the two Cl



MT MG

RT RG RG′

Figure 16. Conformational Structure of 2,3-Dichlorobutane.

atoms are in trans position increases in the transition from the solid to liquid phase, whereas in the d,l form, all three conformers are present in liquid state, but with a high population of RT. In the solid state RT disappears and only RG and RG' remain. Thus, one would expect distinct changes in the retention/inversion ratio in the neutron irradiation of a neat sample going from the liquid state to the solid state if there is a conformational effect in the stereochemical course of substitution reaction. However, only small changes in the retention/inversion ratios were observed in the solid state as compared to the liquid state result, e.g. in d,l DCB: liquid 2.78, solid 2.57; in meso DCB: liquid 2.45, solid 2.21. These slight differences could be attributed to the concomitant variations of the dielectric constants with temperature. If conformational changes were responsible for this result an opposite trend in the retention/inversion ratios should be observed in the case of d,l system.

This result is clearly in disagreement with Stöcklin's argument, who related the solvent dependence of the retention/inversion ratio to the conformational composition of the substrate in solution. In their study of the ^{38}Cl for Cl substitution in liquid diastereomeric 2,3-dichlorobutane they found that the stereochemical course can be drastically influenced by the nature and concentration of the solvent present in the reaction mixture. IR spectra and theoretical calculations provided coincidence that the presence of these additives causes a pronounced change of the relative rotational isomer concentration of 2,3-dichlorobutane in these solutions. In the case of d,l form there are three rotational isomers, namely RT, RG, and RG' (see Figure 16). In the presence of nonpolar solvents such as cyclohexane the nonpolar RT form is stabilized, while the polar RG and RG' forms are destabilized, whereas in polar solvent, methanol, the opposite effect was observed. Furthermore, by using steric argument they suggested that the recoil chlorine attacks from the opposite side of the halogen to be replaced can only be successful at the RT and especially at the RG form, where the asymmetric carbon atoms are relatively free. But in the RG' form the carbon atoms are obscured by the methyl groups for back side attack. The front side attack can occur with all three forms leading to retention of configuration. Therefore, they believed that the stereochemical course in hot halogen for halogen replacement at asymmetric carbon atoms depends on the conformation of the substrate. However, our results clearly indicate that the stereochemical course is not controlled by the conformational effect but rather by a direct effect, which the solvent exerts on the intermediates involved in the substitution process.

In the following the physical and chemical properties of the solvent which could be responsible for the drastic changes inflicted upon the stereochemistry of ^{38}Cl for Cl substitution in dichlorinated alkanes were examined. Several molecular parameters of the solvents, such as density, surface tension, viscosity, polarization, dipole moment, polarizability, ionization and first excitation potentials, molecular diameter, and dielectric constant were considered. Among these parameters only the latter property of the solvent showed a reasonably good correlation with the experimental data.

As shown in Figures 17 and 18, a smooth correlation between the retention/inversion ratios and $(\epsilon - 1)/(2\epsilon - 1)$ for most of the solvents studied was observed. In this study 29 different solvents were utilized, they are: 1. methanol, 2. ethanol, 3. n-propanol, 4. 2-propanol, 5. n-butanol, 6. 2-butanol, 7. 2-methyl-2-propanol, 8. n-pentanol, 9. n-hexanol, 10. n-heptanol, 11. carbon tetrachloride, 12. nitrobezene, 13. carbon disulfide, 14. benzene, 15. toluene, 16. ethylbenzene,

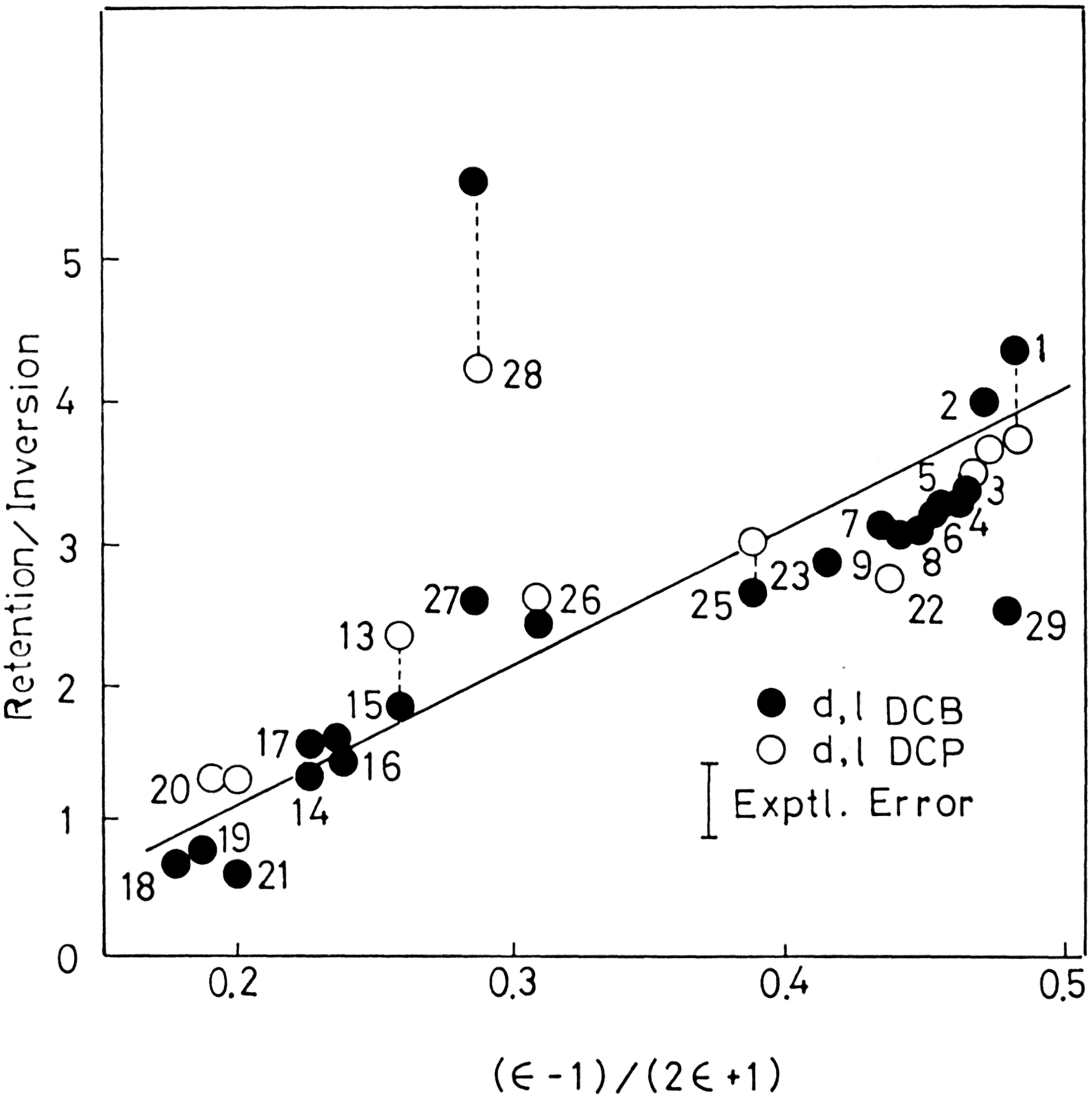


Figure 17. Retention/Inversion Ratios vs $(\epsilon - 1)/(2\epsilon + 1)$ Following ^{38}Cl for Cl Substitution in d,l 2,3-Dichlorobutane and d,l 2,4-Dichloropentane in Solution with 90% Additive.

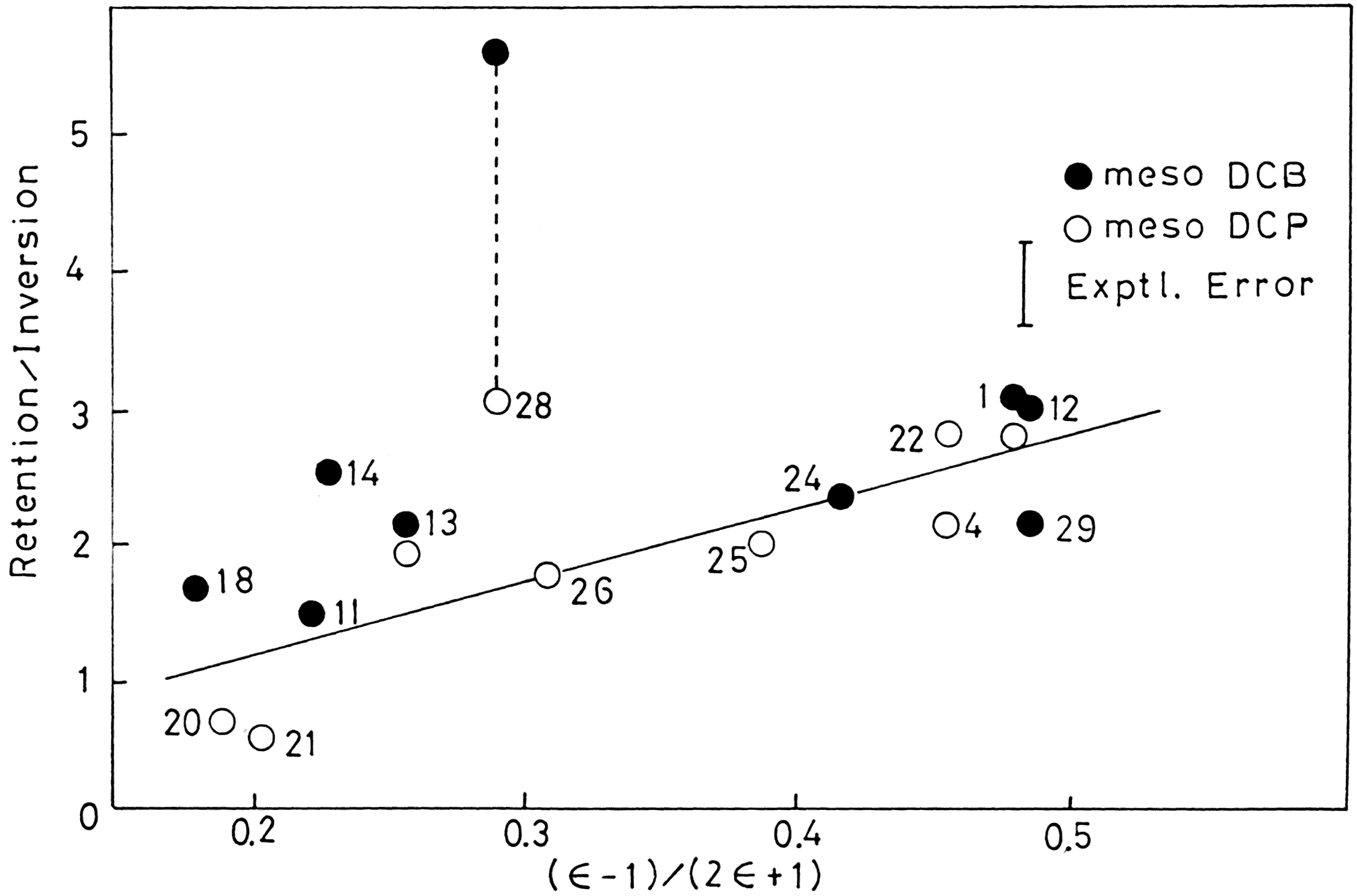


Figure 18. Retention/Inversion Ratios vs (ϵ - 1)/(2ϵ + 1) Following ^{38}Cl for Cl Substitution in meso 2,3-Dichlorobutane and meso 2,4-Dichloropentane in Solution.

17. tert-butylbenzene, 18. n-pentane, 19. n-hexane, 20. n-heptane, 21. cyclohexane, 22. cyclohexanone, 23. d,l 2,3-dichlorobutane, 24. meso 2,3-dichlorobutane, 25. acetic acid, 26. propanoic acid, 27. butyric acid, 28. bromine, 29. acetonitrile. However, this correlation does not hold when Br_2 and CH_3CN were used as solvent. The strong deviations observed in the presence of highly reactive Br_2 as solvent are probably not the result of the physical properties of this "solvent" but they appear to be the consequence of a chemical interference with the reactant. This may be due either to highly efficient scavenging of the ^{38}Cl (in the cage) by Br_2 or caused by the different reaction channel by which BrCl, formed as an intermediate, reacts with substrate molecules. The source of deviation caused by the presence of acetonitrile is not clear. It might be due to the formation of a complex $[CH_3C{\equiv}NI]^+Cl^- \rightleftharpoons CH_3C{\equiv}NI^+ + Cl^-$ which then interferes or suppresses one of the reaction channel. This complex was proposed by Popov and coworkers[69,70] in order to explain the fact that in the presence of iodine monochloride in pure acetonitrile, the electric conductance increased with time and the visible absorption spectra changed.

C. The Physical Significance of $(\epsilon - 1)/(2\epsilon + 1)$

The parameter $(\epsilon - 1)/(2\epsilon + 1)$ can be related to the magnitude of the intermolecular interaction between the reactants and the surrounding solvent molecules.

An estimate of the magnitude of these interactions may be obtained from the free energy change which occurs when a solute molecule is transferred from a vacuum to a solvent. The free energy change[71] is mainly controlled by two terms: the cavity term and perhaps more importantly by the interaction term. The cavity term represents the energy required to separate the solvent molecule from one another to create a hole in the liquid which is a function of surface tension, whereas the interaction term is due to the action of the medium on the molecule when a solute molecule is introduced into the hole. This term is related to the dipole and multipole moments of the solute molecule, its molecular volume a^3 and the term $(\epsilon - 1)/(2\epsilon + 1)$.

Thus, if the magnitude of interaction between solute and solvent molecules can indeed be represented by this free energy change, one might expect to see for a given solute molecule a correlation between individual product yields or, as in this case, between the retention to inversion ratio and $(\epsilon - 1)/(2\epsilon + 1)$.

Such a correlation is borne out in Figure 17 for the d,l diastereomers of 2,3-dichlorobutane and 2,4-dichloropentanes, and to a lesser degree in Figure 18 for the corresponding meso systems.

Similar attempts to correlate the solvent-solute interaction with ϵ and other parameters have previously been made by Nakajima.[72-75] From fluoresence and absorption spectra of pyrene, he observed a strong solvent dependence of vibronic band intensities. In the presence of polar solvents there is an enhancement in the intensity of the 0-0 band at the expense of others. In an attempt to correlate this intensity enhancement with the properties of the solvent, Nakajima investigated several parameters of the solvent, such as the solvent dielectric constant, ϵ, Grunwald's parameter $(\epsilon - 1)/(2\epsilon + 1)$, and a factor, f', that takes into account the polarizability of the solvent dielectric by the permanent dipole moment of the solvent when the dielectric is present in a high-frequency field (region of visible light)

$$f' = \frac{(\epsilon - 1)}{(2\epsilon + 1)} - \chi \cdot \frac{(n^2 - 1)}{(2n^2 + 1)}$$

Where χ is a variable parameter and n is the refractive index on the solvent. A correlation between the intensity of the 0-0 band and $(\epsilon - 1)/(2\epsilon + 1)$ was observed. However, an even better correlation was obtained between the intensity and f' with $\chi = 0.5$.

The solvent effect on the absorption bands appears to be a general case.[76,77,78] Suppan[79] has studied the solvent effect on the absorption spectra of 4-nitroaniline. The result indicated that the only property of the solvent which showed a reasonable degree of correlation with the transition energy is the static dielectric constant, ϵ, or more precisely a function of it as in equations (12) and (13):

$$f(\epsilon) = \frac{2\ (\epsilon - 1)}{2\epsilon + 1} \tag{12}$$

$$\phi(\epsilon) = \frac{\epsilon - 1}{\epsilon + 2} \tag{13}$$

These results indicate that the solvent-solute interaction plays an important role in determining the intensity of the absorption and fluorescene spectra which resembles our case in so far as in both studies excited molecular states may be involved.

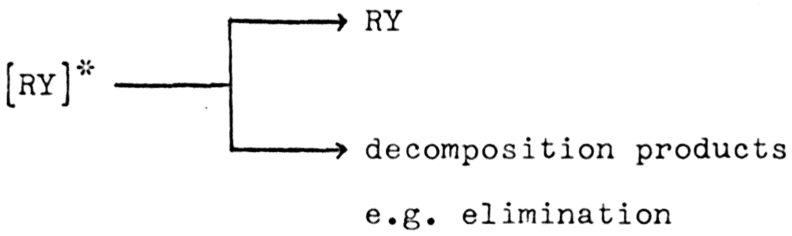
We used several of the above parameters to correlate the retention/inversion ratios with the solvent parameters, however, none of them provided any significant improvements over the correlation shown in Figure 17.

D. Mechanism of ^{38}Cl for Cl Substitution in Solution

In the previous study[12-16] of the stereochemistry of hot halogen for halogen substitution in liquid phase, a one-step substitution mechanism as well as a two-step mechanism involving the radical-radical recombination in the solvent cage have been suggested:

1. One-step molecular reaction or hot direct replacement

$$[\cdot\mathrm{Y}] + \mathrm{RX} \longrightarrow [\mathrm{RY}]^{*} + \mathrm{X}\cdot$$



The primary hot substitution product $[\mathrm{RY}]^{*}$ with high kinetic energy can either decompose or stabilize through collisional de-excitation.

2. Caged radical-radical combination

The radical-radical cage reaction occurs either following a hot displacement of a halogen atom by a recoil atom with excess kinetic energy

$$[\cdot\mathrm{Y}^{*}]^{\ddagger} + \mathrm{RX} \longrightarrow \{\mathrm{R}\cdot + \mathrm{X}\cdot + \cdot\mathrm{Y}^{*}\}_{\mathrm{cage}} \longrightarrow \mathrm{RY}^{*}$$

or a hot one-step substitution after excitation decomposition of the first formed product

$$[\cdot Y^{*}]^{\ddagger} + RX \longrightarrow [RY^{*}]_{exc.} \longrightarrow \{R\cdot + \cdot Y^{*}\}_{cage}$$

$$\longrightarrow RY^{*}$$

A cage effect has been postulated by Richardson and Wolfgang[46] in their study of density effect on the yield of hot ^{18}F reacts with CH_3F. Experimental results have shown that there is a sharp increase in the yield of $CH_3{}^{18}F$ and $CH_2F^{18}F$ from the lowest gas densities, this increase levelling off at intermediate densities. At higher densities a second rise was observed and ascribed as cage effect. The identical behavior has been shown in the subsequent investigations such as $^{38}Cl/CHFClCHFCl$,[18] $^{80}Br/CH_3F$,[80] $^{123}I/C_2H_6$,[81] $^{128}I/C_2H_2$,[82] and $^{18}F/CH_3CF_3$[83] systems. This density effect on substitution product yield is illustrated in Figure 19. This phenomenon has been explained by assuming that in a system with low density (region I), the yield increases with increasing density due to enhanced de-excitation-stabilization of the highly excited primary products which are formed by direct substitution reaction. The yield levels off when all excited species has been stabilized (region II). At higher densities (region III) the yield increases further due to caged radical-radical recombination. Recently, Manning and Root[84] have studied the ^{18}F for F substitution

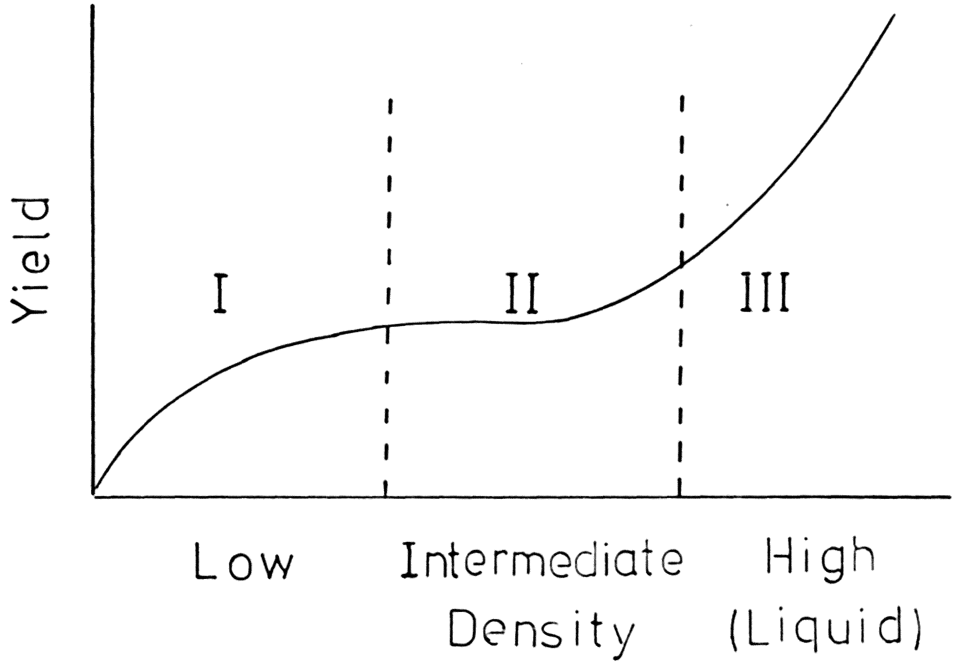


Figure 19. Density Effect on Substitution Product Yield.

reaction in CH_3CF_3 and CH_3CHF_2 by using a combined density-variation, mechanism-elucidation technique. With this procedure, they found that all five hot ^{18}F substitution channels in CH_3CF_3 and CH_3CHF_2 exhibit caging at high densities. The total caging yields at 195°K was estimated.

The decrease of stereospecificity from gas to liquid phase in the recoil halogen for halogen substitution at asymmetric carbon atoms[12-14,17,18] was in the past frequently used as evidence for a caged radical reaction which allows the racemization of the intermediate radical, and the early work of hot halogen reactions in the condensed phase only the caging mechanism was considered.[1,44,45]

However, it has been postulated[17] that fluorine and chlorine atoms formed as a result of the breakup of the primary reaction products should immediately be scavenged via H abstraction from one of the hydrogen-containing solvent molecules. This should occur because the activation energy for gas phase hydrogen abstraction of a primary hydrogen by a chlorine atom is about 1 kcal/mole, whereas by a fluorine atom it is approximately equal to zero. Thus, due to the fast competing hydrogen abstraction, fluorine and chlorine atoms may not be subject to cage radical-radical recombination reaction. This argument was used in the past to exclude the presence of caged radical-radical recombination. But more recently, the efficiency of this self-scavenging process has been seriously questioned.[85] It has been found that in the ^{18}F reaction with a liquid mixture of CH_3CF_3/H_2S system even the efficient F-to-HF processes do not interfere with the primary ^{18}F cage effect.[84] Thus, self-scavenging may not always be that highly efficient and caged radical-radical recombination may indeed occur in some of the systems under study.

As mentioned above, Stöcklin et al.[17] who studied the stereochemical course of ^{38}Cl for Cl substitution in liquid diastereomeric 2,3-dichlorobutane suggested on the basis of the observed solvent effect and additional evidence that the substitution occurs via a direct replacement with collisional stabilization of a "caged complex". Additional evidence supporting the "caged complex" model was presented by Rack et al..[82] In their study of the reaction of hot iodine species with acetylene, they found a sharp increase of combined C_2H_5I and C_2H_3I product yield with decreasing normalized intermolecular distance (λ/σ), where λ represents the intermolecular distance between centers of spheroidal molecules of diameter σ. Furthermore, a decrease in the number of products from the gas to condensed phase transition rather than increase was observed. Therefore, the enhanced yield was suggested to be due to the caging of the "electronically excited complex".

Although the experimental evidence from the present investigation unambiguously indicates that the stereochemical course is not controlled by the conformational composition of the reaction mixture, it does not rule out the possibility of a hot one-step reaction mechanism which may involve a direct replacement step or a "caged complex" or for that matter a caged radical-radical recombination mechanism. Thus, it seems interesting to see whether and how the present results can be interpreted in terms of either of these two models.

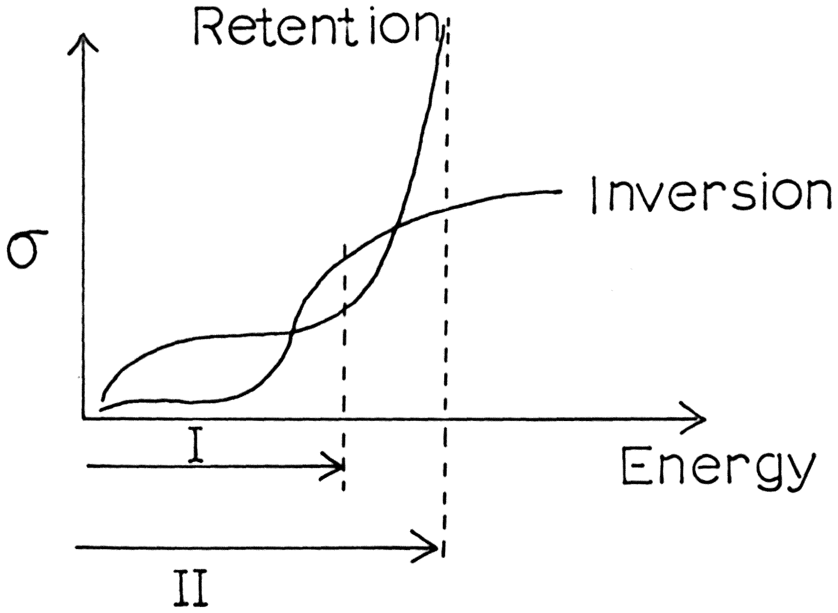
In the case of a hot one-step mechanism one could assume that a strong interaction between the excited substitution product and the solvent could prevent the former from decomposition, or in other words the strong interaction could lead to enhanced collisional de-excitation-stabilization of the intermediate product.

Therefore, if one assumes two or more energy dependent reaction channels for the formation of the retained and inverted product, respectively, the ratio in which these products are formed will depend on the relative cross section for these processes as a function of energy. This is illustrated in Figure 20, where certain arbitrary assumptions about the energy dependence of these reaction channels are being made, which could explain the observed results.

More information about the validity of these hypothesis could be obtained by measuring independently the radiochemical yields of the retained and inverted product.

Unfortunately, however, as discussed in Chapter II Section E, the absolute radiochemical yields of the substitution products cannot be determined, and only the retention/inversion ratios were measured. So it is not clear whether the variation in these ratios is caused by an increase of the yield of the retained form or by a reduction of the inverted product or by both. This inherent deficiency of solution experiments makes it difficult to draw any final conclusions as to whether it is justified to interpret the experimental results in terms of a hot one-step mechanism.

However, in the density variation studies of diastereomeric 1,2-dichloro-1,2-difluoroethane system,[18] the results indicated that the reaction channel leading to an inverted product is low energetic, this could be



I Products stabilized in weakly interacting solvent, e.g. pentane R/I < 1

II Products stabilized in strongly interacting solvent, e.g. alcohols R/I >> 1

Figure 20. Schematic Diagram of Assumed Substitution Cross Section - Energy Dependence of One Step Mechanism.

because the inversion process is relatively slow, so only low energetic ^{38}Cl will remain long enough in the vicinity of the substrate molecule to react with the substrate after inversion has occured. The yields of the retained product increase monotonically with increasing density, due to the more efficient excitation-stabilization at higher density of the higher energetic reaction channel yielding the retained product.

Therefore, the fact that the retention to inversion ratio increases with $(\epsilon - 1)/(2\epsilon + 1)$ could then be interpreted by assuming that in those cases where the reactants interact strongly with the surrounding solvent molecules, the excess energy of the retained product formed in a hot one-step substitution at higher energies is quickly dissipated and the product stabilized. This explanation is demonstrated in Figure 20. Whereas in those solvent which have a low dielectric constant, the energy dissipation proceeds less rapidly and less of the retained product formed in a high energy substitution becomes stabilized. Thus, the retention/inversion ratio remains small or even drops.

Alternatively, in terms of the immediate caged radical-radical recombination of the type

$$R\text{-}X + Y^{*} \longrightarrow [RY]^{*} \longrightarrow [R\cdot + \cdot Y^{*}] \longrightarrow RY^{*}$$

recombination may occur following ^{38}Cl for Cl substitution and subsequent break-up of the excited intermediate state. This can occur either by retention or by inversion of configuration. The degree of retained or inverted product formed depends mainly on the time factor of the recombination of the radicals in the solvent cage. If the time scale for recombination of the radicals becomes comparable with the time required for the organic radical to achieve planar configuration, the subsequent recombination will lead to the formation of a mixture of the two diastereomers. In the case of strong interaction between the intermediate radical and the surrounding molecules the radical will most likely not achieve planarity before recombination takes place and recombination will occur resulting in a labeled molecule which maintains the same configuration as it achieved in the primary step, the direct displacement process. This is schematically demonstrated in Figure 21.

The results in Figure 17 and Figure 18 which show a drastically higher retention/inversion ratio for strongly interacting solvents would thus indicate that the primary step is the substitution via front side attack leading to

Strong Interaction Between Radical and Solvent Molecules Forming the Cage Prevents the Radical From Obtaining Planarity Before Recombination Occurs:

≡ Retention of Configuration

Weak Interaction ≡ Racemization

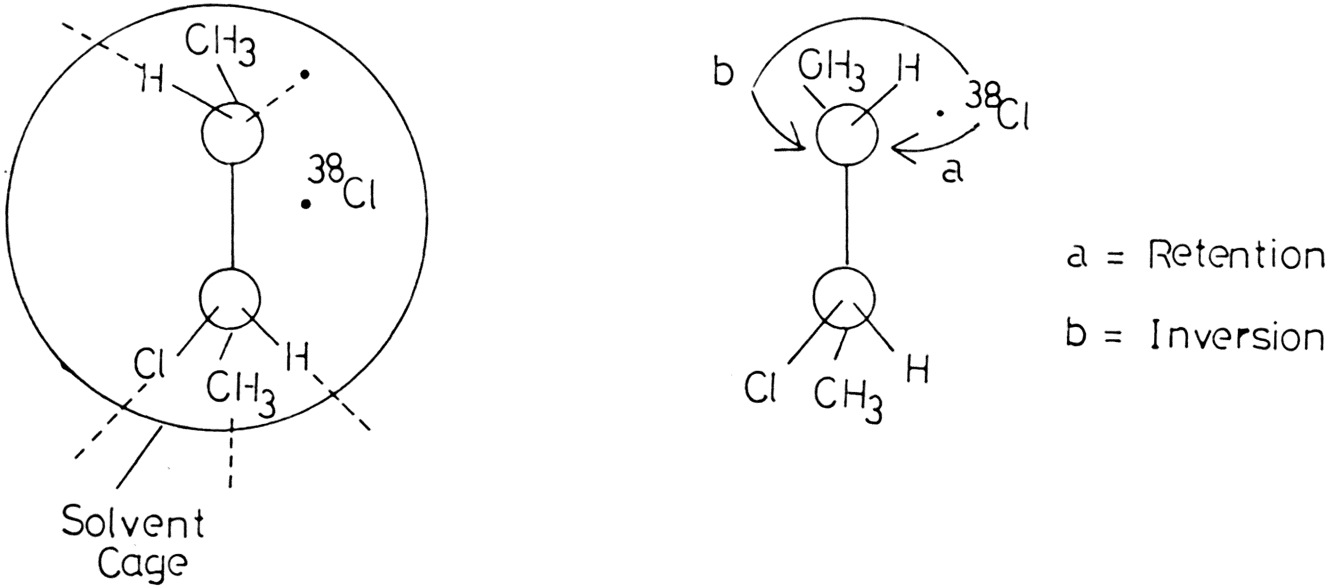


Figure 21. Caged Radical-Radical Recombination Mechanism.

retention of configuration.

In the case of weakly interacting solvents, racemization of the intermediate organic radical may eventually be achieved. As in the 2,3-dichlorobutane system, two conformers can be postulated for 3-chloro-2-butyl radical as shown in Figure 22. Because of lesser crowding between the methyl groups, one would expect conformation (I) to be more stable and hence more abundant than (II). The preferred attack from the bottom of conformation (I) by the chlorine atom which keeps the two chlorine atoms as far apart as possible in the transition state, would yield the meso product. Since the same 3-chloro-2-butyl radical is formed regardless of whether meso or d,l 2,3-dichlorobutane is used as the substrate, one should observe the same equilibrium concentration of d,l and meso in both systems if the planarity is reached. Indeed, when we calculated this value by using a retention/inversion ratio of 0.77 observed in the d,l DCB system in n-pentane solution and an average retention/inversion ratio of 1.8 observed in the meso DCB system in n-pentane and n-hexane solutions, an equilibrium population of 56% meso DCB, 44% d,l DCB and 64% meso DCB, 36% d,l DCB was found, respectively. The average of these two sets was 60% meso DCB and 40% d,l DCB. This is very similar to the product distribution obtained in the photochlorination

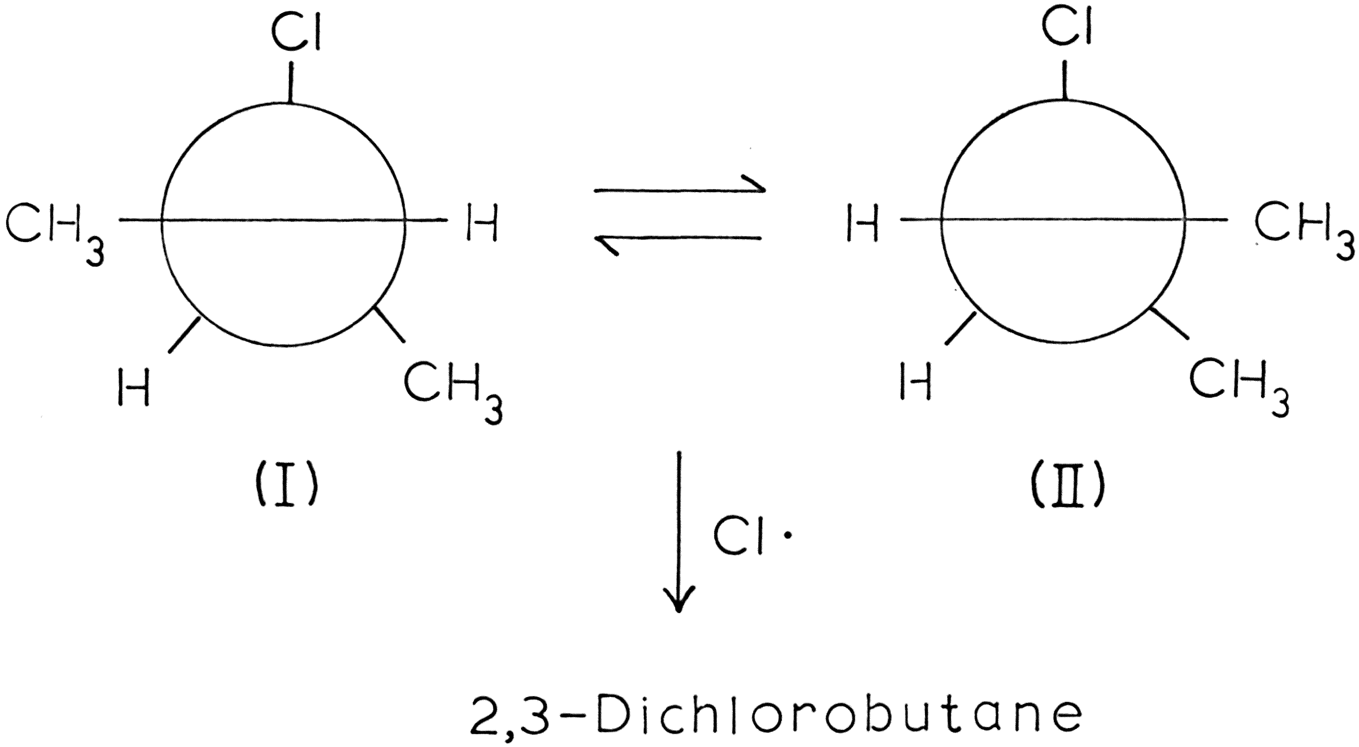


Figure 22. Conformers of 3-Chloro-2-butyl Radical.

of 2-chlorobutane.[86] In the case of 2,4-dichloropentane system, the corresponding values are: 40% meso DCP and 60% d,l DCP. This value was calculated from an average retention to inversion of 1.29 found in d,l DCP (an equilibrium population of 43% meso and 56% d,l DCP) and 0.57 in meso DCP (an equilibrium population of 36% meso and 64% d,l DCP) when n-heptane and cyclohexane were used as solvent. These numbers also compare favorably with the equilibrium concentration previously observed by Flory et al.[67] which is 36.4% meso DCP and 63.7% d,l DCP.

As shown in Figure 23, where the retention/inversion ratios for d,l DCB and d,l DCP are plotted as a function of $(1/\sigma) \times (\epsilon - 1)/(2\epsilon + 1)$ it appears that a suitable combination of both the molecular diameter, σ, and the term which would be indicated of the magnitude of intermolecular interaction, $(\epsilon - 1)/(2\epsilon + 1)$, may best fit the experimental results. The molecular diameter[87] and dielectric constant[88] used in this study appear in Table XXII.

In the Monte-Carlo simulation of the photochemical reaction of I_2 with CCl_4, Bunker and Jacobson[89] have suggested that the cage recombination is strongly influenced by recoil energy, solvent molecule size, and intermolecular forces. Our experimental results correlate well with their finding.

As shown in Figure 18, there is a less pronounced

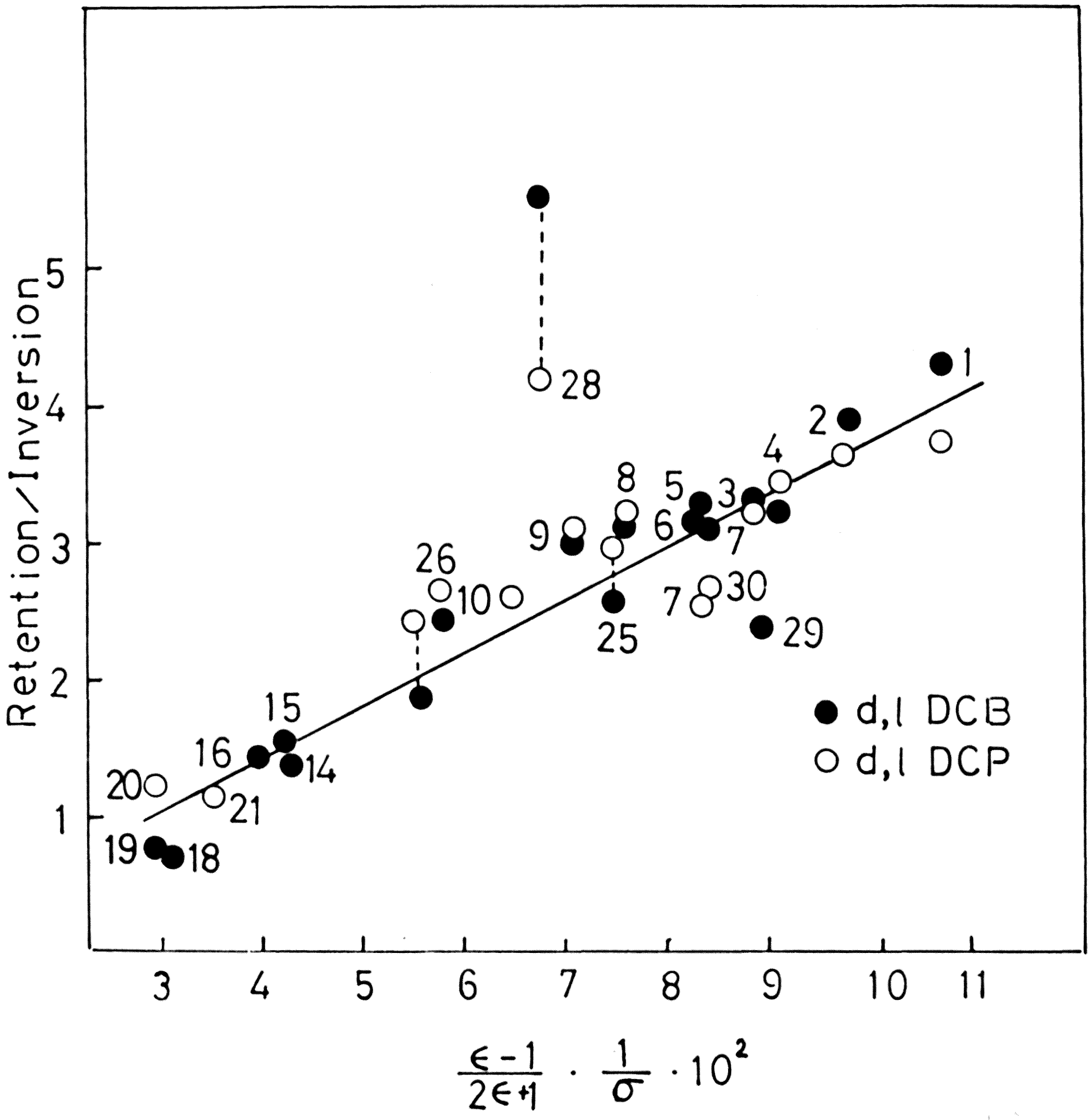


Figure 23. Retention/Inversion Ratios vs $(\epsilon - 1)/(2\epsilon + 1) \times \frac{1}{\sigma}$ Following ^{38}Cl for Cl Substitution in d,l 2,3-Dichlorobutane and d,l 2,4-Dichloropentane in Solution.

Table XXII. Molecular Diameter and Dielectric Constant of Solvent.

Solvent	Molecular* Diameter (Å)	Dielectric** Constant
Methanol	4.430	32.63
Ethanol	4.777	24.3
n-Propanol	5.221	20.1
2-Propanol	5.034	18.3
n-Butanol	5.448	17.1
2-Butanol	5.427	15.8
t-Butanol	5.167	10.9
n-Pentanol	5.88	13.9
n-Hexanol	6.26	13.7
Carbon Tetrachloride	5.478	2.238
Carbon Disulfide	4.641	2.641
Benzene	5.359	2.284
Toluene	5.746	2.379
Ethybenzene	6.060	2.412
n-Pentane	5.741	1.844
n-Hexane	6.105	1.890
n-Heptane	6.439	1.924

Table XXII (continued)

Solvent	Molecular Diameter (Å)	Dielectric Constant
Cyclohexane	5.679	2.023
Acetic Acid	5.170	6.15
Propanoic Acid	5.355	3.44
Bromine	4.268	3.09
Acetonitrile	5.345	37.5

* Obtained from Reference 87.

** Obtained from Reference 88.

dependence of the retention/inversion ratio on the interaction energy in the system compared with the corresponding values for the d,l diastereomers. This appears to occur in the case of the meso isomer, when a smaller number of the primary ^{38}Cl for Cl replacement lead eventually to substitution via frontside attack to give a smaller amount of product with retention of configuration than in the d,l isomer. Thus, even in the presence of strongly interacting solvents, the retention/ inversion will remain relatively small as compared with the d,l system. Alternatively, in terms of the caged radical-radical recombination model, one can argue that the radical formed by the break-up of the excited meso ^{38}Cl-product shows less interaction with the surrounding solvent molecules and therefore achieves planarity more easily than the corresponding radical formed by the fragmentation of the excited d,l ^{38}Cl-product. However, it is not certain that the easier frontside attack in d,l isomer is due to the steric effect nor that the easier-to-achieve planarity of the radical formed by the break-up of the excited meso ^{38}Cl-product is due to the different thermodynamic stability of two stereoisomers.

In order to minimize the steric effect and to overcome the difference in thermodynamic stability between the initial and final state of the reaction, the investigation was further extended by using enantiomeric molecules as substrate.

As shown in Table XVI, the ^{80}Br, ^{80m}Br, and ^{82}Br for Br substitution in R- or S-2-bromopropionyl bromide gave about 80% inversion product either in gas or in liquid phase reaction. This result was later found partly due to the exchange of radioactive bromine in the form of inorganic bromide with bromine atom attached in α carbon of propionyl bromide in the gas chromatographic column. This finding is in accordance with the result found by Cowdrey and co-workers.[90] They studied the exchange reaction of 2-bromopropionic acid with lithium bromide which contains a proportion of radioactive bromine in acetone solution at 22°C. They found that the displacement is accompanied by inversion in every bromine substitution. The instability of the bromine atom next to the carbonyl group and the high column temperature ($\sim$170°C) employed in the separation of diastereomeric 2-bromopropionyl bromide valine methyl ester apparantly caused the exchange in the column. This obscured the true stereochemical course of decay-induced bromine for bromine substitution reaction.

The exchange problem was solved first by using 2-

chloro-1-propanol as substrate. In this compound the C-Cl bond is stronger than the C-Br bond, furthermore it is attached to C-OH instead of to an active carbonyl group (C=O). Secondly, the inorganic chloride formed as a result of the neutron irradiation of substrate molecules must be removed. This can be insured by low-temperature gas chromatographic purification of irradiated 2-chloro-1-propanol before subject to resolution via diastereomer formation and gas chromatographic separation.

The results of ^{38}Cl for Cl substitution in enantiomeric 2-chloro-1-propanol are shown in Table XVII. The retention of optical configuration in neat R or S form of the solution is equal to 53 ± 3%. This result seems to suggest that the reaction is via a radical process leading to racemization, even though a hot one-step substitution mechanism cannot be completely ruled out. However, from the steric point of view, it is very unlikely that the chlorine atom can have the same probability of attacking 2-chloro-1-propanol from the back and the front side.

Due to the relative long postirradiation analysis procedure ($\sim$150 minutes) and the competetion of ^{38}Cl between solute and solvent molecule, the ^{38}Cl labeled 2(R)- or 2(S)-chloro-1-propanol has a low radioactivity by the time the activity is measured. Together with the fact that the gas chromatographic resolution is less than 100%, the interpretation of the result is rather difficult especially in the presence of a high concentration of solvent. However, generally the same trend of solvent effect in stereochemical course as in 2,4-dichloropentane and 2,3-dichlorobutane systems was observed.

As shown in Figure 13, the ratio of retention to inversion of ^{38}Cl for Cl substitution in enantiomeric 2-chloro-1-propanol in solution is affected by the concentration and nature of the solvent added. An increase of methanol concentration causes the retention/inversion ratio to increase, while n-pentane and cyclohexane additives show almost no effect.

In the presence of a strong interacting solvent, methanol, the radical formed as a result of the break-up of the excited intermediate has probably not been able to achieve planarity before recombination takes place. Thus, the recombination will occur resulting in a labeled molecule with retention of its orginal configuration. However, in the case of weakly interacting solvents, i.e. n-pentane and cyclohexane, the radical may eventually reach the planarity. Since there is no energy difference between R and S form of 2-chloro-1-propanol, we should expect the same amount of each enantiomer will be formed. Indeed, the formation of 50% of each enantiomer was observed.

E. Summary

The results presented in this study clearly indicate that the stereochemistry is predominantly and directly governed by the properties of the solvent and not by an indirect solvent effect on the relative rotamer populations of the substrate molecule. The parameters most likely responsible are related to the intermolecular interactions between reactants and the surrounding solvent molecules. They are in particular the dielectric constant and to a minor extent the size of the solvent molecules.

Although the experimental results do not allow a conclusive distinction between the relative contribution of the hot one-step substitution mechanism and the caged radical-radical conbination model, they strongly suggest that the latter mechanism is preferred in liquid phase hot substitution reactions. In terms of the caged radical-radical recombination model the strong solvation will prevent the intermediate radical from obtaining planarity and recombination will result in a labeled molecule having the same configuration as the product formed in the primary displacement step (retention). Whereas in terms of the hot one-step substitution mechanism the strong interaction between solvent and reactants may enhance a rapid transfer of excitation energy and thus excitation-stabilize the product formed via retention of configuration.

REFERENCES

1. J. E. Willard, Ann. Rev. Phys. Chem., 6, 141 (1955).
2. J. E. Willard, Nucleonics, 19, 61 (1961).
3. G. Harbottle and N. Sutin, J. Phys. Chem., 62, 1344 (1958).
4. A. P. Wolf, Advan. Phys. Org. Chem., 2, 201 (1964).
5. J. G. Campbell, Adv. Inorg. Chem. Radiochem., 5, 135 (1963).
6. R. Wolfgang, Progr. Reaction Kinetics, 3, 97 (1965).
7. R. Wolfgang, Ann. Rev. Phys. Chem., 16, 15 (1965).
8. G. Stocklin, Chemie Heisser Atome, Verlag Chemie, Weinheim, 1969.
9. D. S. Urch, Inorg. Chem., Ser. One, Vol. 8, 149 (1972).
10. D. S. Urch, Inorg. Chem., Ser. Two, Vol. 8, 49 (1975).
11. C. M. Wai and F. S. Rowland, J. Phys. Chem., 71, 2752 (1967).
12. F. S. Rowland, C. M. Wai, C. T. Ting, and G. Miller in Chemical Effects of Nuclear Transformations, Vol. 1, IAEA, Vienna, 1965, p. 333.
13. Y. Y. Su and H. J. Ache, J. Phys. Chem., 80, 659 (1976).
14. C. M. Wai, C. T. Ting, and F. S. Rowland, J. Amer. Chem. Soc., 86, 2525 (1964).
15. C. M. Wai and F. S. Rowland, J. Phys. Chem., 74, 434 (1970).
16. G. F. Palino and F. S. Rowland, Radiochimica Acta, 15, 57 (1971).
17. L. Vasaros, H. J. Machulla, and G. Stöcklin, J. Phys. Chem., 76, 501 (1972).

18. H. J. Machulla and G. Stöcklin, J. Phys. Chem., 78, 658 (1974).

19. L. Szilard and T. A. Chalmers, Nature, 134, 462 (1934).

20. E. Glueckauf and J. Fay, J. Chem. Soc., 390 (1936).

21. D. Strominger, J. M. Hollander, and G. T. Seaborg, Res. Modern Phys., 30, pt. II, 649 (1958).

22. S. Wexler and G. Anderson, J. Chem. Phys., 33, 850 (1960).

23. H. S. W. Massey and E. Burhop, Electronic and Ionic Impact Phenomena, Oxford, p. 441, 1952.

24. M. A. El Sayed, P. J. Estrup, and R. Wolfgang, J. Phys. Chem., 62, 1356 (1958).

25. M. Marshall, C. Mackay, and R. Wolfgang, J. Amer. Chem. Soc., 86, 4741 (1964).

26. L. Spicer and R. Wolfgang, J. Chem. Phys., 50, 3466 (1969).

27. R. J. Cross and R. Wolfgang, Radiochim Acta, 3, 112 (1964).

28. C. M. Wai and F. S. Rowland, J. Amer. Chem. Soc., 90, 3638 (1968).

29. J. B. Evans, J. E. Quinlan, M. C. Sauer, and J. E. Willard, J. Phys. Chem., 62, 1351 (1958).

30. J. E. Willard, Chemical Effects of Nuclear Transformations, Vol. 1, IAEA, Vienna, 1965, p. 215.

31. E. P. Rack and A. A. Gordus, J. Phys. Chem., 65, 944 (1961).

32. M. Saeki and E. Tachikawa, Bull. Chem. Soc. Japan, 46, 839 (1973).

33. S. Goldhabor and J. E. Willard, J. Amer. Chem. Soc., 74, 318 (1952).

34. T. Smail, R. S. Lyer, and F. S. Rowland, J. Phys. Chem., 75, 1324 (1971).

35. T. Tominaga, Y. Makide, S. Okada, Y. Kunimasa, and K. Wada, Radioisotopes (Tokyo), 20, 541 (1971).

36. R. L. Williams and F. S. Rowland, J. Amer. Chem. Soc., 94, 1047 (1972).

37. M. Henchman and R. Wolfgang, J. Amer. Chem. Soc., 81, 2991 (1961).

38. Y. N. Tang, C. T. Ting, F. S. Rowland, J. Phys. Chem., 74, 675 (1970).

39. G. F. Palino and F. S. Rowland, J. Phys. Chem., 75, 1299 (1971).

40. J. G. Kay, R. P. Malsan, and F. S. Rowland, J. Amer. Chem. Soc., 81, 5050 (1959).

41. H. Keller and F. S. Rowland, J. Phys. Chem., 62, 1373 (1959).

42. D. Urch and R. Wolfgang, J. Amer. Chem. Soc., 83, 2982 (1961).

43. J. Franck and E. Robinowitch, Trans. Faraday Soc., 30, 120 (1934).

44. C. Lu and S. Sugden, J. Chem. Soc., 1273 (1939).

45. W. F. Libby, J. Amer. Chem. Soc., 62, 1393 (1940).

46. A. E. Richardson and R. Wolfgang, J. Amer. Chem. Soc., 92, 3480 (1970).

47. R. R. Pettijohn, E. P. Rack, and A. P. Wolf, 7th International Hot Atoms Symposium, Julich, 1973, p. 34.

48. S. H. Daniel, H. J. Ache, and G. Stöcklin, J. Amer. Chem. Soc., 78, 1043 (1974).

49. J. G. Pritchard and R. L. Volmer, J. Org. Chem., 28, 1545 (1963).

50. S. C. J. Fu, S. M. Birnbaum, and J. P. Greenstein, J. Amer. Chem. Soc., 76, 6058 (1954).

51. H. C. Brown, J. Amer. Chem. Soc., 60, 1325 (1938).

52. W. Fickett, H. K. Garner, and H. J. Lucas, J. Amer. Chem. Soc., 73, 5063 (1951).

53. H. Scheibler and A. S. Wheller, Ber. Deut. Chem. Ges., 44, 2684 (1911).

54. S. Matsuo and Y. Iwakura, Makromol. Chem., 152, 203 (1972).

55. P. R. Geissler and J. E. Willard, J. Phys. Chem., 67, 1675 (1963).

56. D. Doskočilová and B. Schneider, Coll. Czech. Chem. Commun., 29, 2290 (1964).

57. T. Shimanouchi and M. Tasumi, Spectrochim. Acta, 17, 755 (1961).

58. K. Iimura, T. Hama, T. Shibuya, and M. Takeda, Bull. Chem. Soc. Japan, 37, 1758 (1964).

59. F. A. Bovey, Pure Appl. Chem., 12, 525 (1966).

60. S. Sykora, Coll. Czech. Chem. Commun., 33, 3514 (1968).

61. B. Schneider, J. Štokr, D. Doskočilová, S. Sýkora, J. Jakeš, and M. Kolínský, J. Polymer Sci., Part C, 22, 1073 (1969).

62. L. Onsager, J. Amer. Chem. Soc., 58, 1486 (1939).

63. I. Watanabe, S. Mizushima, and Y. Morino, J. Chem. Soc. Japan, Pure Chem. Sect., 63, 1131 (1942).

64. I. Watanabe, S. Mizushima, and Y. Mashiko, J. Chem. Soc. Japan, 64, 962 (1943).

65. V. I. Minkin, O. A. Osipov, and Y. A. Zhdanov, Dipole Moments in Organic Chemistry, Plenum Press, 1975, p. 81.

66. O. Exner, Dipole Moments in Organic Chemistry, Georg Thieme Publishers Stuttgart, 1975, p. 29.

67. P. J. Flory and A. O. Williams, J. Amer. Chem. Soc., 91, 3118 (1969).

68. J. Štokr, D. Doskočilová, S. Sýkora, H. H. Hörhold and B. Schneider, Coll. Czech. Chem. Commun., 34, 1875 (1969).

69. A. I. Popov and W. A. Deskin, J. Amer. Chem. Soc., 80, 2976 (1958).

70. A. I. Popov and N. E. Skelly, J. Amer. Chem. Soc., 77, 3722 (1955).

71. O. Sinanoglu, in Molecular Associations in Biology, B. Pullman Ed., Academic Press 1968, p. 427.

72. A. Nakajima, Bull. Chem. Soc. Japan, 44, 3272 (1971).

73. A. Nakajima, Spectrochim. Acta, Part A, 30, 860 (1974).

74. A. Nakajima, J. Mol. Spectrosc., 61, 467 (1976).

75. A. Nakajima, J. Lumin., 11, 429 (1976).

76. N. Mataga, Y. Torihashi, and K. Ezumi, Theoret. Chim. Acta (Berl.), 2, 158 (1964).

77. M. S. Walker, T. W. Bender, and R. Lumry, J. Chem. Phys., 47, 1020 (1967).

78. K. Kalyanasundaram and J. K. Thomas, J. Amer. Chem. Soc., 99, 2039 (1977).

79. P. Suppan, J. Chem. Soc. (A), 3125 (1968).

80. M. E. Berg, W. M. Grauer, R. W. Helton, and E. P. Rack, J. Phys. Chem., 79, 1327 (1975).

81. M. D. Loberg, K. A. Krohn, and M. J. Welch, J. Amer. Chem. Soc., 95, 5596 (1973).

82. K. C. To, M. E. Gerg, W. M. Grauer, and E. P. Rack, J. Phys. Chem., 80, 1411 (1976).

83. R. G. Manning and J. W. Root, J. Phys. Chem., 79, 1478 (1975).

84. R. G. Manning and J. W. Root, J. Chem. Phys., 64, 4926 (1976).

85. G. Stöcklin, Hot Atom Chemistry Status Report, IAEA, Vienna, 1975, p. 161.

86. P. S. Fredericks and J. M. Tedder, J. Chem. Soc., 3520 (1961).

87. J. H. Root, Ph.D. Dissertation, University of Kansas, Lawrence, Kansas, 1964.

88. R. C. Weast, Handbook of Chemistry and Physics, The Chemical Rubber Co., 51st Ed., 1971.

89. D. L. Bunker and B. S. Jacobson, J. Amer. Chem. Soc., 94, 1843 (1972).

90. W. A. Cowdrey, E. D. Hughes, T. P. Nevell, and C. L. Wilson, J. Chem. Soc., 209 (1938).

91. H. J. Machulla, Ph.D. Dissertation, Institut für Radiochemie der Kernforschungsanlage Jülich GmbH, Jülich, West Germany, 1972.

ON THE STEREOCHEMICAL COURSE OF THE CHLORINE-38 FOR CHLORINE SUBSTITUTION IN DIASTEREOMERIC AND ENANTIOMERIC COMPOUNDS

by

Jiann-long Wu

(ABSTRACT)

The stereochemistry of the energetic ^{38}Cl for Cl substitution was studied in diastereomeric 2,4-dichloropentane and 2,3-dichlorobutane as well as in enantiomeric 2-chloro-1-propanol in solution. It was found that the stereochemical course of the substitution reaction exhibits a strong dependence on the concentration and nature of the solvent added when the diastereomeric compounds were used as substrate. Similar results with a lesser degree of solvent dependence were observed in the 2-chloro-1-propanol system.

A conformational analysis of 2,4-dichloropentane was made. It showed that the relative conformer population is not affected to any significant degree by the nature of the solvent. Furthermore, an examination was made of the physical and chemical properities of the solvent which could be responsible for the drastic changes

inflicted upon the stereochemistry of the ^{38}Cl for Cl substitution reaction.

The experimental results indicate that the stereochemical course of the substitution process is predominantly and directly controlled by the properties of the solvent molecules, most likely by the dielectric constant and molecular size which in turn are responsible for the magnitude of intermolecular interaction between reactants and solvents.

Although the experimental results seem to indicate that the radical-radical recombination mechanism is the most likely mechanism as compared to the hot one-step substitution process, they offer no conclusive distinction between these two mechanisms. It appears that strong intermolecular interaction favors substitution via retention of configuration, whereas in solvents having a low dielectric constant or large molecular diameter the retention/inversion ratio decreases.