ENOLIZATION OF BUTANONE (I)

DISPLACEMENT REACTIONS OF α-HALOKETONES (II)

ACETATE-CATALYZED BROMINATION AND DEUTERIUM EXCHANGE OF

2-BUTANONE (I). THE MECHANISM FOR THE BIMOLECULAR

DISPLACEMENT REACTIONS OF α-HALOKETONES (II).

by

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A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Doctor of Philosophy

McMaster University

October 1971

DOCTOR OF PHILOSOPHY   McMASTER UNIVERSITY
(Chemistry)   Hamilton, Ontario.

TITLE: Acetate-Catalyzed Bromination and Deuterium Exchange of

   2-Butanone (I). The Mechanism for the Bimolecular

   Displacement Reactions of α-Haloketones (II).

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NUMBER OF PAGES: xviii, 202

SCOPE AND CONTENTS:

   The regioselectivities of bromination and deuterium exchange

of 2-butanone are shown to be the same, under identical conditions.

This work firmly establishes that enolization is the rate-determining

step for the former reaction, contrary to some recent reports in the

literature.

   The steric effects and activation parameters in the

bimolecular nucleophilic displacement reactions of a series of

α-haloketones and alkyl halides are shown to be inconsistent with

either a bridging or conjugation mechanism for the observed rate

enhancements of haloketone over alkyl halide.

   The stereoelectronic requirements of this mechanism are

tested in a system where the stereochemistry is known (cis- and

trans-chlorocyclohexanones). The activation parameters suggest

that only in the case where the geometry is correct for maximum

conjugation (*trans*-chlorocyclohexanone) is there an appreciable

difference in mechanism (stereoelectronically) from displacement

at ordinary saturated carbon.

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to
Professor John Warkentin for his keen interest and encouragement
throughout the course of this work and especially for his
advice in the preparation of this manuscript.

The assistance of Dr. R. A. Cox, who provided pure
samples of bromoketones (obtained by a very tedious gas chromato-
graphic procedure), was greatly appreciated. Several compounds
were donated for the successful completion of this work; these
gifts are gratefully acknowledged: a sample of 2,2-dimethyl-
cyclopropanone from Dr. N. J. Turro, Columbia University, prepared
by Mr. R. B. Cagosian; pure samples of *cis*- and *trans*-3-*t*-
butylcyclohexyl chloride and *cis*-3-*t*-butylcyclohexanol from
Dr. E. L. Eliel, Notre Dame University; and pure samples of
cis- and *trans*-2-chloro-4-*t*-butylcyclohexanone and a detailed
procedure for their preparation and purification from Dr. E. W.
Warnhoff, University of Western Ontario, which were prepared by
Mr. K. E. Teo.

In addition, the author is indebted to Mrs. M. Pritchard,
Department of Chemistry, Dalhousie University, for her skill in
typing this manuscript.

Above all, the author would like to thank his wife

for bearing the hardships of a graduate student's wife and

for her patience and encouragement during the preparation

of this manuscript.

TO JOAN

TABLE OF CONTENTS

TABLE OF CONTENTS contd.

TABLE OF CONTENTS contd.

TABLE OF CONTENTS contd.

LIST OF TABLES

(xiii)

(xiv)

TABLE   Page

LIST OF FIGURES

LIST OF CHARTS

HISTORICAL INTRODUCTION

Base-Catalyzed Enolization of Ketones

The enolization of ketones is generally considered in terms of (a) acid catalysis and (b) base catalysis. The most common methods for following the course of this reaction are: halogenation, racemization of optically active ketones, or by hydrogen-deuterium exchange experiments. The older literature (prior to 1965) on this subject has been reviewed[1], while a comprehensive review of more recent work on the enolization of ketones is available[2]. Because of this, only the areas relating directly to the present author's work will be discussed here.

In 1904, Lapworth proposed[3] that the rate-determining step in the acid-catalyzed halogenation of ketones is the enolization of the ketone. Later, he reported[4] that the same step is rate-determining in the base-catalyzed reaction. The reaction rate was shown by Bartlett[5] and Bell and Longuet-Higgins[6] to be dependent on the ketone and base concentrations, but independent of the halogen concentration. The following mechanism was proposed[7] for the base-catalyzed reaction between ketones and halogens (the haloform reaction):

$$CH_3COCH_3 \xrightarrow[slow]{OH^-} [^-CH_2-\overset{O}{\overset{\|}{C}}CH_3 \longleftrightarrow CH_2=\overset{O^-}{\overset{|}{C}}CH_3] \xrightarrow[fast]{X_2} XCH_2COCH_3 \xrightarrow{fast} \text{Product}$$
$$I$$
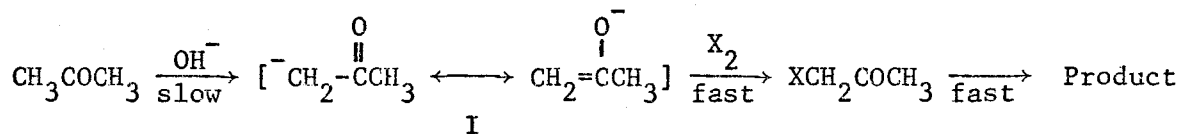
This mechanism is different from the acid-catalyzed mechanism in that here a proton is removed from the ketone itself rather than its conjugate acid, forming an enolate anion (I), rather than an enol (II).

$$CH_2 = \overset{\overset{\displaystyle OH}{|}}{C}-CH_3$$

II
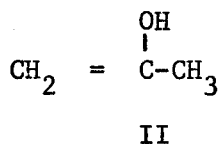
If the rate-determining step in the racemization[8,9], deuterium exchange, and halogenation[10] of ketones is enolization, all these reactions should occur at the same rate. This has been demonstrated by Hsü, Wilson, and Ingold[11,12].

Base-catalyzed enolization of unsymmetrical ketones in water was first thought to occur at the least-substituted α-position[7,13]. However, as discussed by Cox[14], evidence gathered by studies of the haloform reaction indicates that enolization at the more-substituted site may be competitive with enolization at the less-substituted site of dialkyl ketones. A study of the acetate-catalyzed iodination of 2-butanone by Schellenberger and Huebner[15] indicates preferred enolization toward the methyl group.

It has been observed by Bell and Lidwell[16] and by Lewis *et al.*[17] that haloketones enolize faster than unsubstituted ketones under base-catalyzed conditions. The inductively-electron-withdrawing halogen removes electron density from the molecule, increasing the acidity of the remaining protons and facilitating their removal by base.

The application of nmr spectroscopy to the study of the enolization of ketones has been of importance in three main areas: direct observation of enols, identification and analysis of the products of halogenation, and

hydrogen-deuterium exchange. Rappe has studied[18-22] the products

of the bromination of 2-butanone by nmr; the bromoketones have

fairly simple nmr spectra[23]. He proposed no less than five ketone

halogenation mechanisms[22]: two acid-catalyzed, one free radical,

and two base-catalyzed, both different from the base-catalyzed

deuterium exchange mechanism[21].

The conditions used by Rappe[18] were: sodium acetate and

sodium bicarbonate in a two-phase system with water and ketone,

sodium acetate in a one-phase system of acetic acid/water (1:1),

and pure acetic acid. Polyhaloketone formation was kept to a

minimum by using less than one equivalent of bromine. After extrac-

tion of the solutions into carbon tetrachloride, the products were

identified by nmr, which, by integration, also gave relative

yields. The two-phase system gave mainly monobromoketones, while

more polybromination occurred in the one-phase system. This was

interpreted as a consequence of solubility of the initially-formed

bromoketones in the medium, or to a change in mechanism[18]. Bromoform

was not a major product in most cases.

The ratio K_{Br} is defined by Rappe[18] as the amount of product

formed from a primary 3-halogenation divided by the amount from a

primary 1-halogenation. This ratio was found to be 1.5-2 for the

one-phase system, and 5-7 for the two-phase system. Rappe inter-

preted these results as indicating that the reaction in the one-phase

system is acid-catalyzed (by acetic acid), while that in the two-phase

system is base-catalyzed. The latter reaction is, according to Rappe, mechanistically different from the haloform reaction observed with strong bases and halogens in water ($K_{Br} \approx 0$).

Rappe reported studies of the two base-catalyzed mechanisms in further papers[20,21]. The reaction operating in the pH region 5.5-7 is designated as "Hal B I" and is catalyzed by weak bases such as acetate and bicarbonate and gives predominantly 3-halogenated products. Above pH 12, the "Hal B II" mechanism operates; it is catalyzed by hydroxide and gives exclusively 1-halogenation (haloform reaction). Bromination of 2-butanone was also done in deuterium oxide, and bromination and deuteration were reported[21] to proceed independently of one another in both reactions. These results led Rappe to state that, if deuteration goes by enolization, both types of halogenation are reactions with the unenolized ketone[19,21]. This is at variance with the generally-accepted mechanisms which require zero-order reaction of the halogenating agent with the enol(ate) derived from the ketone.

Hydrogen-deuterium exchange of ketones can be studied by nmr spectroscopy. Exchange at individual sites of unsymmetrical ketones can be followed by monitoring the decreased integral areas of the peaks corresponding to the protons on either side of the carbonyl group. Warkentin and Lam reported[24] the first application of this method in 1964; they studied exchange of the vinylic and allylic hydrogens of 6,6-dimethylcyclohex-2-en-1-one. Several authors have studied the base-catalyzed deuterium exchange of 2-butanone[1,25-29] by this method since 1964.

Warkentin and Tee studied the hydroxide-, acetate-, and

p-nitrophenoxide-catalyzed deuterium exchange of 2-butanone[1,28,29].

For hydroxide-catalyzed exchange in water, they found the methylene

protons to be just as reactive as the methyl protons; while toward

the weaker bases, the methylene protons are more reactive than the

methyl protons (by a factor of 2 for acetate). Changes in temperature

or ionic strength did not affect the relative rates significantly[29],

but the relative methyl reactivity was found to increase with increasing

organic solvent concentration in the reaction medium. From these

results, Warkentin and Tee postulated a transition state for base-

catalyzed enolization resembling enol and not enolate[1,29].

Rappe studied the deuterium exchange of 2-butanone[26,27] and

found the relative rates at the two sites to be approximately equal for

all bases[26], in contrast to Warkentin and Tee's results[29]. Rappe

suggested that the extrapolation method used by Warkentin and Tee[1,29] to

derive catalytic constants is wrong[27]. He also found that the relative

rates of exchange (K_D) at the two sites in 2-butanone are different from

those derived from the halogenation reactions (K_{Br}), which lead to the

proposal that different mechanisms are operating for exchange and for

halogenation[22]. These results prompted part of the work described in

this thesis and will be considered in greater detail in the Discussion.

Warkentin and Cox[30] have recently repeated the acetate-catalyzed

deuterium exchange of 2-butanone[1,29], using the buffer method of Bell and

Jones[31]. The results obtained were the same as those obtained by the

extrapolation technique used previously[1,29], and deuteroxide catalysis

was found to be different in selectivity from acetate catalysis

(K_D = 0.86 for $^-$OD and 1.9 for $^-$OAc), at variance with Rappe's results.

Summary

In summary, Rappe has claimed that base-catalyzed halogenation

of ketones can occur without enolization[20,21] (Hal B I and Hal B II) and

that enolization by bases, when it occurs, has a selectivity which does

not depend on the base[21,27]. Thus, the mechanism of base-catalyzed

exchange is different from that of base-catalyzed halogenation. In

contrast, Warkentin and coworkers report[28-30] that the value of K_D does

depend on the base used to catalyze the reaction.

The work in the first part of this thesis was undertaken to try

and resolve the controversy between Warkentin and coworkers and Rappe,

with regard to the base-catalyzed bromination and deuterium exchange of

2-butanone. It was decided to determine whether, under the same conditions

of acetate catalysis, K_D is equal to K_{Br} for 2-butanone.

NUCLEOPHILIC DISPLACEMENT REACTIONS OF α-HALOKETONES

Introduction

The α-halocarbonyl compounds are among the few substrates for

bimolecular nucleophilic displacement reactions that are more reactive

than their unhindered primary aliphatic counterparts[32]. The remarkable

ease with which α-haloketones undergo S_N2 displacements was reported as early as 1909 by Slater and Twiss[33] and has been a subject of active investigation ever since (Table I, p 8).

This enhanced reactivity has been attributed to inductive electron withdrawal by the carbonyl group[37], to a mechanism involving an intermediate in which the nucleophile is covalently bonded to the carbonyl carbon[38],

$$
\begin{array}{c}
\overset{O}{\overset{\|}{>C-C-C<}} \\
\underset{H\ \ X}{}
\end{array}
+ \ B^- \longrightarrow
\begin{array}{c}
\overset{O^{\bar{\ }}}{\overset{|}{>C-C-C<}} \\
\underset{H\ B\ X}{}
\end{array}
\longrightarrow
\begin{array}{c}
\overset{O}{\overset{\|}{>C-C-C<}} \\
\underset{H\ \ B}{}
\end{array}
+ \ X^-
$$
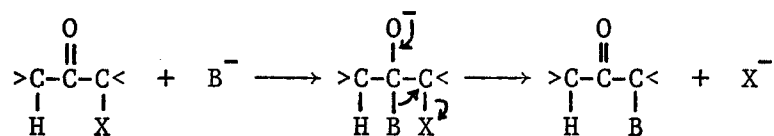
to the electrostatic effect exerted by the carbonyl group on the approaching nucleophile[34], and to orbital overlap with the nucleophile, either by the π-molecular orbital of the C-C-O system (delocalized orbital, III)[39] or the p-orbital of the carbonyl carbon (localized orbitals, IV)[40].

$$
\begin{array}{c}
\overset{O}{\overset{\|}{>C-C-C<}} \\
\underset{H\ \ X}{}
\end{array}
+ \ B^- \longrightarrow
\left[
\begin{array}{c}
\overset{O\ \ X}{\overset{\|}{>C-C-C<}} \\
\underset{H\ \ B}{}
\end{array}
\right]^-
\longrightarrow
\begin{array}{c}
\overset{O}{\overset{\|}{>C-C-C<}} \\
\underset{H\ \ B}{}
\end{array}
+ \ X^-
$$
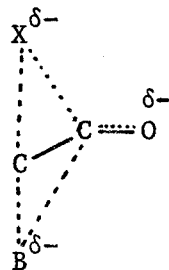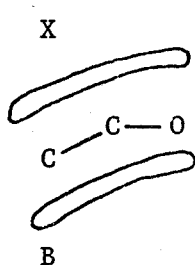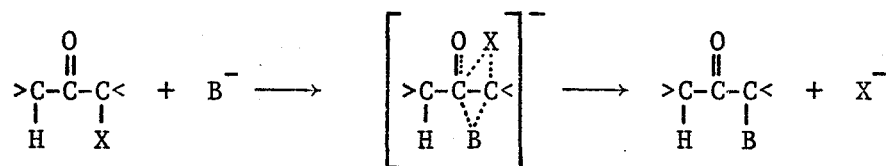
III (delocalized orbital)   IV (localized orbitals)

Table I

Relative Rates of Displacement on α-Halocarbonyl Compounds

Reaction	Relative Rates			
	C_3H_7X	XCH_2CO_2Et	$PhCOCH_2X$	CH_3COCH_2X
R-Br + pyridine in methanol at 35°[34]	1	85	450	–
R-Br + thiourea in methanol at 35°[34]	1	640	10700	–
R-Cl + potassium iodide in acetone[35] at 50°	1	1600	97000	33000
R-Cl + thiosulfate in water at 25°[33,36]	1	220	1600	1400

The stereochemical implications of the last proposal have been explored in a well-designed experiment by Bartlett and Trachtenberg[41]. Although the results strongly support the orbital overlap mechanism, they do not eliminate Pearson's[34] hypothesis. The possibility of direct substitution of halide by the nucleophile may be considered, but it gives no role to the carbonyl carbon; the large rate enhancements reported for these reactions would be difficult to explain. Evidence in support of the preceding mechanisms will be discussed in greater detail later; suffice it to say here that the orbital overlap mechanism seems to have the greatest amount of support at this time.

A mechanism which has been proposed to explain the formation of rearranged product in displacement reactions of α-haloketones involves enolization and solvolysis:

$$>\!\underset{\underset{\displaystyle H}{|}}{C}-\underset{\displaystyle \overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle X}{|}}{C}\!< \;+\; B^{-} \;\rightleftharpoons\; >\!C\!=\!\underset{\displaystyle \overset{\displaystyle O^{-}}{|}}{C}-\underset{\underset{\displaystyle X}{|}}{C}\!< \;\longrightarrow\; \underset{\underset{\displaystyle X^{-}}{+}}{\overset{\displaystyle \overset{\displaystyle O^{-}}{|}}{\underset{\displaystyle C\cdots C}{C}}} \;\longrightarrow\; \text{Products}$$

A very important area of α-haloketone chemistry involving displacement of the halide is the Favorskii rearrangement. It involves the skeletal rearrangement of α-haloketones in the presence of certain nucleophilic bases, such as hydroxide, alkoxides, or amines, to give carboxylic acid salts, esters, or amides, respectively. Monohaloketones undergo the reaction to yield derivatives of saturated acids having the same number of carbon atoms. An example is the following:

$$(CH_3)_2CBrCOCH_3 + {}^{-}OCH_3 \longrightarrow (CH_3)_3CCO_2CH_3 + Br^{-}$$

The rearrangement was first described by Favorskii[42] in 1894; since that time hundreds of papers clarifying its scope, mechanism, and stereochemistry have appeared. This survey will be concerned mainly with the more recent work (since 1955) in this area, because two excellent reviews on the Favorskii rearrangement have appeared[43,44].

The mechanisms that have been considered for the Favorskii rearrangement are as follows. One is a variation of covalent participation between the nucleophile and the carbonyl carbon in which formation of an epoxide occurs in a subsequent step:

$$>\underset{\underset{H}{|}}{C}-\underset{}{\overset{\overset{O}{||}}{C}}-\underset{\underset{X}{|}}{C}< \; + \; B^- \; \underset{\longleftarrow}{\longrightarrow} \; >\underset{\underset{H}{|}}{C}-\underset{\underset{B}{|}}{\overset{\overset{O^-}{|}}{C}}-\underset{\underset{X}{|}}{C}< \; \longrightarrow \; >-\underset{\underset{H}{|}}{C}-\underset{\underset{B}{|}}{\overset{\overset{O}{\triangle}}{C}}-C< \; + \; X^- \; \longrightarrow \; \text{Products}$$
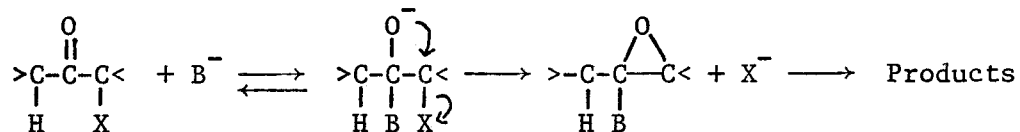
A mechanism analogous to the benzilic acid rearrangement, the semi-benzilic mechanism, features addition of the nucleophile to the carbonyl carbon, followed by a concerted displacement of halide ion by the 1,2-shift of an alkyl group with its electron pair:

$$>\underset{\underset{H}{|}}{C}-\underset{}{\overset{\overset{O}{||}}{C}}-\underset{\underset{X}{|}}{C}< \; + \; B^- \; \underset{\longleftarrow}{\longrightarrow} \; >\underset{\underset{H}{|}}{C}-\underset{\underset{B}{|}}{\overset{\overset{O^-}{|}}{C}}-\underset{\underset{X}{|}}{C}< \; \longrightarrow \; B-\underset{}{\overset{\overset{O}{||}}{C}}-\underset{\underset{CH}{|}}{C}< \; + \; X^-$$
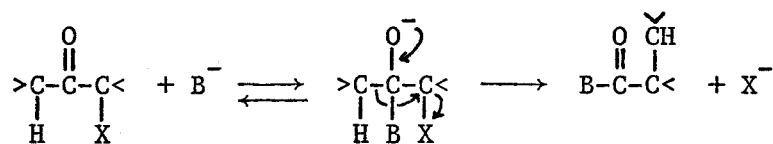
Another mechanism involves formation of a cyclopropanone intermediate (formed either in a concerted or step-wise manner) by removal of an α'-hydrogen (α-C refers to the halogen-bearing-C, α'- to the other position α- to the carbonyl group) to give the enolate anion followed by loss of halide ion. The cyclopropanone is rapidly cleaved by base to give the

rearrangement product:

$$>\underset{\underset{H}{|}}{\overset{\overset{O}{\|}}{C}}-\underset{\underset{X}{|}}{C}-C< \; + \; B^{-} \; \rightleftharpoons \; >C=\underset{\underset{X}{|}}{\overset{\overset{O^{-}}{|}}{C}}-C< \; \longleftrightarrow \; >\overset{\overset{O}{\|}}{C}-\underset{X}{\overset{|}{C}}-C< \; \longrightarrow \; \triangle \; B'^{-} \; \longrightarrow \; Products$$
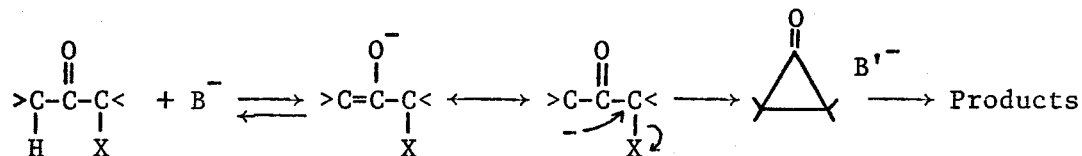
Prior isomerization of the haloketone, by migration of halogen from the

α- to the α'- carbon atom (allylic shift), has been considered:

$$>\underset{\underset{H}{|}}{\overset{\overset{O}{\|}}{C}}-\underset{\underset{X}{|}}{C}-C< \; + \; B^{-} \; \rightleftharpoons \; >C=\underset{\underset{X}{|}}{\overset{\overset{O^{-}}{|}}{C}}-C< \; \longleftrightarrow \; >\overset{\overset{O}{\|}}{C}-C-\underset{X}{\overset{|}{C}}< \; \longrightarrow \; >\overset{\overset{O}{\|}}{C}-\underset{X}{\overset{|}{C}}-C< \; \longrightarrow \; Products$$
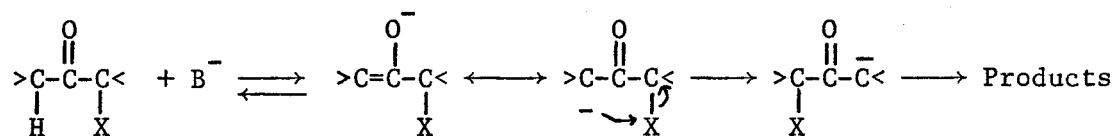
The only mechanisms which seem to have any general applicability are the

cyclopropanone and the semibenzilic mechanisms, but one has to be careful

to specify reaction conditions. The above mechanisms will be discussed

in greater detail in the following sections.

Discussion of the Mechanisms for Displacement of Halide from α-Haloketones

(a)   Covalent Bonding of the Nucleophile to the Carbonyl Carbon

The explanation for the rate enhancements of α-haloketones proposed

by Hughes[37], that electron withdrawal by the carbonyl group induces a

positive charge on the halogen-bearing carbon atom, may be criticized

because substitution of an electron-attracting group in a halide frequently

deactivates toward nucleophilic displacement reactions. Thus α-halosulfones

and α-halonitroparaffins are quite unreactive[45-47]. Also, it was pointed

out by Hinshelwood *et al.*[48] that for a neutral reagent one might predict

that an electron-withdrawing substituent would deactivate by causing the

electronegative halogen to be held more tightly.

In 1938, Baker[49] examined the bimolecular reaction between ring-

substituted phenacyl bromides and pyridine to form the pyridinium salt,

$RC_6H_4COCH_2\overset{+}{N}C_5H_5$. When the reaction was carried out at 20° in anhydrous
$\overset{}{\underset{\bar{B}r}{}}$

acetone, he observed a decrease in rate, compared to phenacyl bromide,

with *o*-substituents and electron donating *p*-substituents, and an increase

in rate with electron withdrawing *p*-substituents. The 2,4,6-trimethyl

compound was essentially unreactive. Baker interpreted these results

as supporting the formation of a covalent bond between the nucleophile

and carbonyl carbon atom, followed by rearrangement and displacement to

the product.

Baker's mechanism can be ruled out as a general one from the

results of Clark[50], who observed that phenacyl bromide is 54 times as

reactive as phenacyl chloride toward pyridine in ethanol at 55.6°; and

Pearson *et al.*[34], who observed that phenacyl bromide reacted 126 times as

fast as phenacyl chloride with thiourea in methanol at 35°. These results

are inconsistent with a rate-determining step involving addition to the

carbonyl group, but are consistent with a rate-determining step involving

displacement of the halide, where bromide is always more reactive than

chloride.

The isolation of a rearrangement product ($PhCOCHYCH_3$) as well as the normal substitution product in the displacement of bromide by acetate and benzoate ions from $PhCHBrCOCH_3$ was reported in 1938 by T.L.Temnikova[51]. The normal substitution product was obtained with $PhCOCHBrCH_3$. This work was extended by Veksler[52], who examined the reaction of α-bromodibenzylketone with the same nucleophiles to yield the normal substitution product, $PhCHYCOCH_2Ph$, in each case. In a study of S_N2 reactions of a series of α-haloketones $CH_3COCH(X)R$, $CH_3COCH(X)Ar$, $ArCH_2COCH_2X$, and $PhCOCH(X)R(X=Cl,Br)$ with acetate ion, rearrangement products were obtained with $CH_3COCH(X)Ar$ and $ArCH_2COCH_2X$. The normal substitution products were interpreted as arising from an ion-dipole interaction between the nucleophile and the carbonyl carbon atom, followed by displacement of X by a shift of the nucleophile to the α-carbon atom:

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-CHX-R' + \bar{O}COCH_3 \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle \delta-}{\underset{\underset{COCH_3}{|}}{\overset{|}{\underset{O}{\overset{|}{\underset{\delta+}{}}}}}}{\overset{X}{\underset{}{CH}}}-R' \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{OCOCH_3}{|}}{CH}-R' + X^-$$
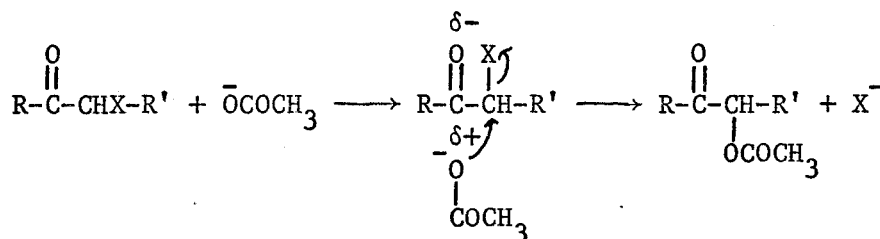
Veksler claimed[53] that the rearranged product came from formation of a covalent bond between the nucleophile and the carbonyl carbon atom, followed by rearrangement of the carbonyl oxygen and displacement of halide:

$$\text{R-C-CHXR' + }^-\text{OCOCH}_3 \longrightarrow \text{R-C-CHR''} \longrightarrow \text{R-C-C-R' + X}^- \longrightarrow \text{R-CH-C-R'}$$
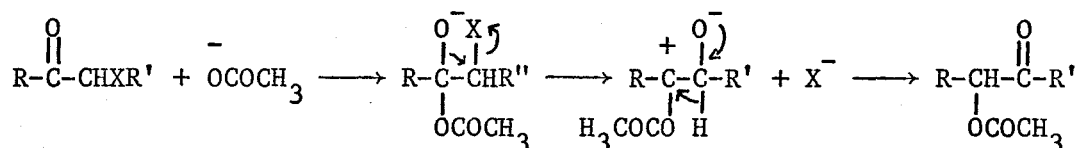
The present author feels that the evidence for the above mechanisms is not compelling; it is more probable that Veksler obtained the normal substitution products by an enol solvolysis mechansim, which would produce both products observed. Some of the normal substitution product might have come from the S_N2 mechansim, operating in competition with the enolization-solvolysis mechanism.

(b)   Epoxide Mechanism

The isolation of an epoxide in displacement reactions of α-haloketones was first reported by Kohler and Brown[54] in 1933. They examined the reaction of potassium cyanide with desyl chloride (PhCHClCOPh), in aqueous alcohol at room temperature which yields two isomeric epoxides (Ph-CH-C(CN)Ph) and no normal substitution product. A similar result was obtained by Prevost and Sommière[55], who examined the reaction of α-chlorodibenzylketone with cyanide ion and found an epoxide, PhCH-C(CN)CH$_2$Ph. The isolation of a moderately stable epoxide in the reaction of an α-haloketone with sodium methoxide in methanol was reported by Temnikova and Kropacheva[56] and by Stevens et al.[57]. They also showed that the epoxide was an intermediate in the formation of one of the products, a ketal, as did Ward[58] in the reaction of desyl chloride with ethoxide in ethanol; the intermediate epoxide, PhCH-C(OEt)Ph, was isolated.

The reaction of some alkyl-aromatic α-bromoketones of the type PhCOCBrRR' with phenoxide ion was examined by Temnikova *et al.*[59]. They observed the formation of the normal substitution product, PhCOC(OPh)RR' and of the ketal, PhC(OPh)C(OH)RR', in methanol. With less nucleophilic
                    |
                   OCH$_3$
phenoxides, they observed more substitution product and less ketal, as shown in Table II, p 16.

The action of *p*-nitrophenoxide on PhCOCBr(CH$_3$)$_2$ gave only the normal substitution product. These results were interpreted in terms of formation of an ion-dipole intermediate (see pp 13-14) with the more acidic nucleophiles, which lead to normal substitution; with the more nucleophilic reagents addition of the nucleophile to the carbonyl carbon, followed by epoxide formation, occurred. Attack by solvent (CH$_3$OH) at the benzilic position was envisaged[59], but an acid-catalyzed epoxide opening to the ketal is more probable:
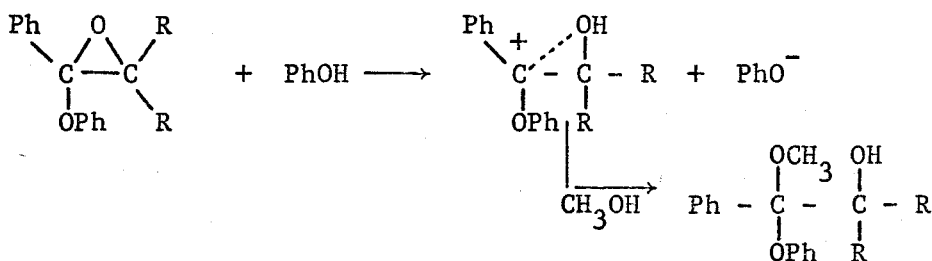
The importance of the reaction conditions was shown by Temnikova and Oshueva[60], who reported that reaction of α-bromocyclohexanone with

Table II

Product Distribution in Reaction of PhCOCBrRR' with Various Phenoxides

Nucleophile	% Ketal	% Substitution Product
Phenoxide	60	20
β-Naphthoxide	15	40
α-Naphthoxide	-	50
p-Chlorophenoxide	-	66

phenoxide ion yielded the normal substitution product in petroleum

ether, but the ketal (V) in methanol.

$$\text{V}$$
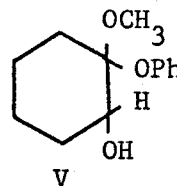
More detailed work on these reactions of α-haloketones has been

published recently by Temnikova $et\ al.$[61-66]. They have found[61-64]

that, with methoxide ion and α-haloketones of the type $p\text{-XC}_6\text{H}_4\text{COCH(Hal)R}$,

a change in X from CH_3O to Cl increases the rate 25-fold; for $R = CH_3$ or

CH_2CH_3, changing from Br to Cl reduces the rate 25-fold; and $\rho = 2.82$,

indicating a large sensitivity of the reaction to the change in electron

density at the carbonyl carbon atom caused by the polar substituents.

The mechanism suggested was the following, with the introduction of

polar substituents having little effect on k_3:

$$\text{ArCOCHXR} + CH_3O^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Ar}-\overset{O^-}{\underset{OCH_3}{\overset{|}{\underset{|}{C}}}}-\text{CHXR} \overset{k_3}{\longrightarrow} \text{Ar}\overset{O}{\overset{\wedge}{\underset{OCH_3}{\underset{|}{C}}}}-\text{CHR} + X^-$$
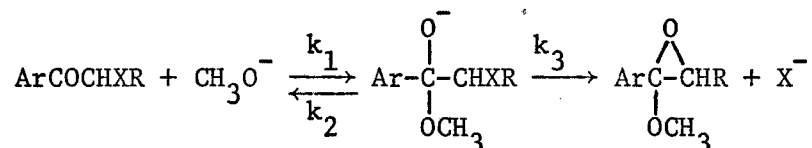
They then examined[65,66] compounds of type PhCHXCOAr and $p\text{-Y-C}_6\text{H}_4\text{-}\overset{Ph}{\overset{|}{C}}\text{XCOAr}$,

to study the effect of electronegative substituents on the amount of normal

substitution product formed. These compounds are listed in Table III, p 18.

Because methoxide ion adds to the more acidic carbon atom,

deactivating the carbonyl group and increasing the s- character of the

α-carbon atom by introducing electronegative substituents should result

in the formation of more α-methoxyketone. Compounds 1-3 gave VI, the

Table III

Displacement of Halide from Various Aromatic α-Haloketones,

Methoxide in Methanol

PhCHXCOAr

$$p\text{-Y-C}_6\text{H}_4\overset{\overset{\displaystyle \text{Ph}}{|}}{\text{C}}\text{XCOAr}$$

1) Ar = Ph, X = Br

2) Ar = Anis , X = Br

3) Ar = p-ClC$_6$H$_4$, X = Br

4) Ar = Mes, X = Cl

5) Ar = Mes, X = Br

6) Ar = Ph, Y = Cl, X = Br

7) Ar = Anis , Y = H, X = Br

8) Ar = Mes, Y = H, X = Br

9) Ar = Mes, Y = H, X = Cl

dimethyl ketal, but there was no reaction with 4 and 5. Compounds

7-9 gave the α-methoxyketone (VII), while 6 gave (VIII), the epoxide.

$$
\underset{\text{VI}}{Ar - \overset{\displaystyle OCH_3}{\underset{\displaystyle OCH_3}{\overset{|}{\underset{|}{C}}}} - CHOHPh}
\qquad
\underset{\text{VII}}{ArCO\overset{}{\underset{\displaystyle OCH_3}{\overset{|}{\underset{|}{C}}}}(Ph)_2}
\qquad
\underset{\text{VIII}}{p\text{-}Cl\text{-}C_6H_4\text{-}\overset{\displaystyle O}{\overset{/\backslash}{\underset{\displaystyle Ph}{\overset{|}{C}}}\text{---}\underset{\displaystyle OCH_3}{\overset{|}{C}}\text{-}Ph}}
$$
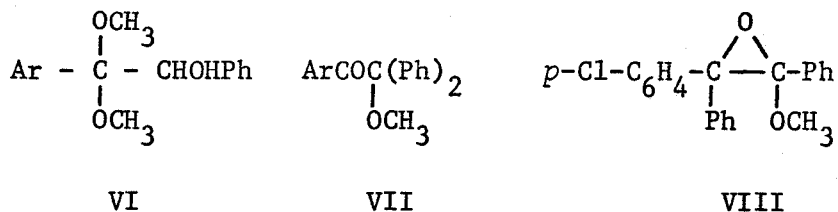
Thus the amount of normal substitution depends on the ease of dissociation

of the C-X bond.

From the above evidence, it appears that epoxides are formed in

the reactions of some α-haloketones with nucleophiles (particularly

methoxide), but, in general, epoxides do not seem to lead to normal

substitution products (*cf.* p 38) If epoxides were intermediates in

the formation of normal substitution products, then the mechanism might

be as follows:

$$
R\text{-}COCH_2X + B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R\text{-}\overset{\displaystyle O^-}{\underset{\displaystyle \overset{|}{B}^+}{\overset{|}{C}}}\text{-}CH_2X \xrightarrow{k_2} R\text{-}\overset{\displaystyle O}{\overset{/\backslash}{\underset{\displaystyle \overset{|}{B}^+}{C}}}\text{---}CH_2 + X^- \qquad (1)
$$

$$
k_3 \Big|\xrightarrow[\text{fast}]{B'} RCOCH_2B' + B \qquad (2)
$$
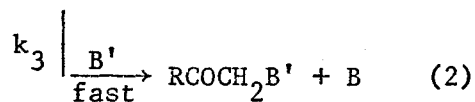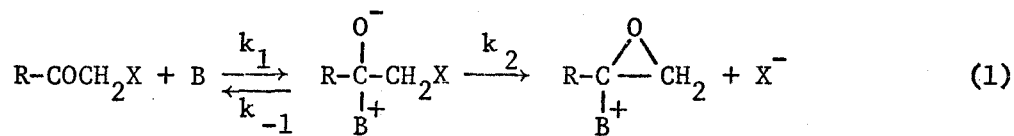
If either k_1 or k_2 is slow, then the mechanism agrees with the second-

order kinetics found for reaction of α-haloketones with nucleophiles.

An important point is that B' need not be the same as B. Pearson *et al.*[34]

investigated the above mechanism and showed first of all that displacement

of halide occurs in a rate-determining step (see p 12). They examined the

reaction of a limited amount of phenacyl bromide with excess pyridine and

aniline. The rate constants were found to be additive, and the ratio of

the products was essentially the same as the ratio of the rate constants.

Thus a mechanism involving epoxide formation (equations 1 and 2 above) is

improbable, because the relative rates for ring opening (2) would have to

be the same as for ring closing (1).

A more convincing argument against the epoxide mechanism was

reported by Lutz[67], who examined the exchange of radioactive chloride with

optically active desyl chloride. Assuming an epoxide mechanism, the reaction

would proceed as shown.

$$PhCOC\overset{H}{\underset{Cl}{\diagdown}}Ph + {}^{*}Cl^{-} \rightleftharpoons Ph-\overset{O^{-}}{\underset{{}^{*}Cl}{\overset{|}{C}}}-C\overset{H}{\underset{Cl}{\diagdown}}Ph \rightleftharpoons \underset{{}^{*}Cl}{\overset{Ph}{\diagdown}}C\overset{O}{\diagup\diagdown}C\overset{H}{\underset{Ph}{\diagdown}} + Cl^{-}$$

$$\underset{{}^{*}Cl}{\overset{Ph}{\diagdown}}C\overset{O}{\diagup\diagdown}C\overset{H}{\underset{Ph}{\diagdown}} + {}^{*}Cl^{-} \rightleftharpoons Ph\overset{O^{-}}{\underset{{}^{*}Cl}{\overset{|}{C}}}-C\overset{H}{\underset{{}^{*}Cl}{\diagdown}}Ph \rightleftharpoons PhCOC\overset{H}{\underset{{}^{*}Cl}{\diagdown}}Ph + {}^{*}Cl^{-}$$
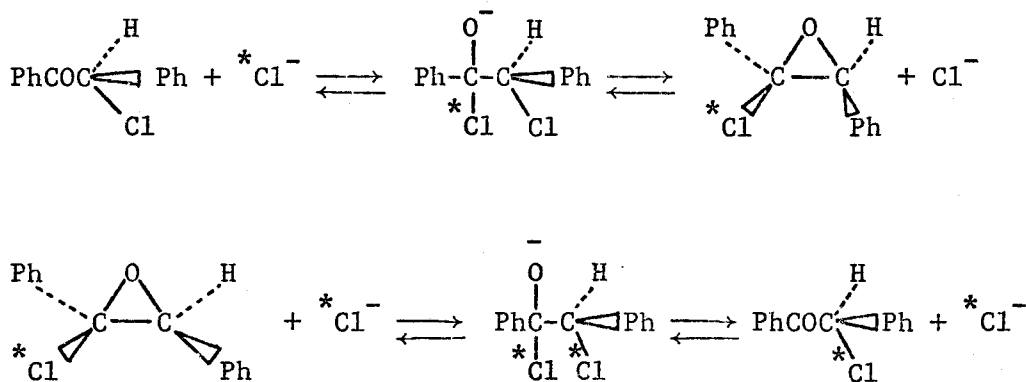
Radiochloride would be incorporated with over-all retention of configuration,

because the final product is reached by a double inversion at the asymmetric

centre. The ratio of rate constants, k_{ex}/k_{inv}, where k_{ex} represents

exchange and k_{inv} inversion, would then equal infinity. However, if the

reaction were a typical $S_N 2$ displacement, the ratio would be unity.
If the substrate happened to react by both mechanisms, the value of
K_{ex}/k_{inv} would lie somewhere between unity and infinity.

The rates of racemization and exchange were measured at 25° in
anhydrous acetone containing 0.0921 $\underline{M}$ lithium chloride. The values
obtained were 5.91 x 10^{-2} $\underline{M}^{-1}$ sec^{-1} for k_{ex} and 6.00 x 10^{-2} $\underline{M}^{-1}$ sec^{-1}
for k_{inv}, which gave 0.985 for the ratio k_{ex}/k_{inv}. The ratio suggests
strongly that desyl chloride reacts with lithium chloride in acetone
by an $S_N 2$ mechanism other than that shown above.

(c) Electrostatic Interaction Between the Carbonyl Group and the Nucleophile.

Evidence that the activating influence of the carbonyl group is
largely electrostatic in nature was presented by Pearson *et al.* in 1952[34].
To test the possibility that the nucleophile coordinates to the carbonyl
group, they measured the rate constants for the reaction of a number of
bromides with pyridine and thiourea in methanol. Pyridine is a stronger
base than thiourea by a factor of 10^5, but thiourea is a better nucleophile;
the strength of the nucleophile-carbonyl interaction should be more
dependent on base strength. Their results are given in Table IV, p 22.

From these data, the ratio k_{thio}/k_{pyr} is constant for the six
non-carbonyl bromides. The three bromoketones and the bromoester correlate
roughly with each other, but differ from the other halides in being much
more reactive toward thiourea. In view of the large polarizability of

Table IV

Second-Order Rate Constants for Organic Bromides with Pyridine and Thiourea, in Methanol at 35°

Bromide	k, Pyridine 1/mole-min	k, Thiourea 1/mole-min
Ethylene bromohydrin	1.7×10^{-5}	4.8×10^{-4}
β-Phenylethyl bromide	2.0×10^{-5}	5.3×10^{-4}
n-Propyl bromide	1.0×10^{-4}	2.8×10^{-3}
Ethyl bromide	2.3×10^{-4}	4.3×10^{-3}
2,4,6-Trimethylphenacyl bromide	2.5×10^{-4}	4.0×10^{-2}
Allyl bromide	8.3×10^{-3}	3.3×10^{-1}
Benzyl bromide	3.1×10^{-2}	8.5×10^{-1}
Ethyl bromoacetate	8.5×10^{-3}	1.8
Phenacyl bromide	4.5×10^{-2}	29.9
p-Bromophenacyl bromide	7.2×10^{-2}	46.2

thiourea, these results lead Pearson *et al.* to propose[34] that there
is an electrostatic interaction between the carbonyl group and the
nucleophile. Further evidence for and against this mechanism will be
presented in the next section.

(d)   Orbital Overlap with the Nucleophile

An attempt to gain evidence for the orbital overlap mechanism[39,40]
in which there is postulated orbital overlap between the carbonyl group
and the nucleophile was made by Bartlett and Trachtenberg[41] in 1958.
There is a stereochemical implication of this mechanism – the atoms
C-C-O(VIII and IX) of the α-haloketone determine a plane, and the
nucleophile and leaving groups must occupy positions above and below
that plane in order to find the orbitals of the two adjacent carbon
atoms with which they are to interact. Bartlett and Trachtenberg
constructed a system in which the BCCX plane is prevented from being
perpendicular to the CCO plane in the transition state for displacement.
This system was 5,7-dinitro-3-coumarone (X), where the 2,4-dinitrophenoxy
group can be displaced as an ion. If VIII or IX is a correct picture of
the reaction, then the energy of the transition state for X, should be
sharply raised in comparison with XI, where there is no such restriction.

VIII   IX   X   XI
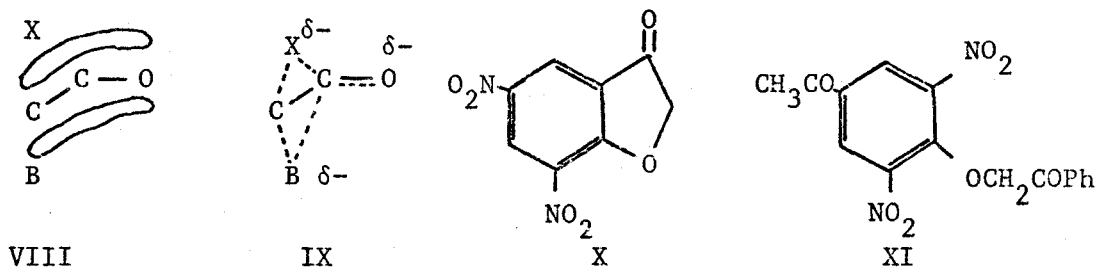
These two compounds were reacted with iodide ion in dry acetone at several temperatures. Compound X reacted 9000 times slower than compound XI at 0°. The activation parameters calculated from the rate constants are for X, $\Delta H^{\ddagger}$ = 31 kcal mol^{-1}, $\Delta S^{\ddagger}$ = 25 eu; for XI, $\Delta H^{\ddagger}$ = 10 kcal mol^{-1}, and $\Delta S^{\ddagger}$ = -30 eu. The large difference of more than 20 kcal in $\Delta H^{\ddagger}$ means that an enormous activation present in X is absent in XI. The large entropy difference was rationalized as arising from lack of phenacyl activation in X (bond breaking and bond formation may be nearly synchronous, dispersion of charge in the transition state); while in XI there is phenacyl activation (bond formation leads bond breaking, charge not dispersed). Also, in X a ring is being opened, while in XI, a highly oriented structure is being formed at the transition state.

These data are consistent with an orbital overlap mechanism. However, the lack of phenacyl activation in X is also consistent with Pearson's mechanism[34], although there are less specific geometrical requirements on the transition state. Barring steric hindrance, the electrostatically most-favoured path for the approaching nucleophile would be according to XII (where all solid bonds are in the plane of the paper), and one would expect the same results based on Pearson's model for the mechanism.
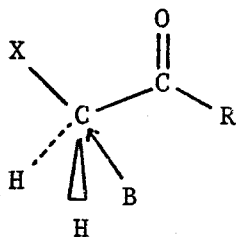
XII

Further evidence has been afforded this problem by Sisti and

Lowell[68], who examined the relative rates of the reactions of various

nucleophiles with some α-chlorocarbonyl compounds in methanol at 30°.

According to Pearson[34], the rate enhancements of α-haloketones,

relative to n-alkyl halides, are due to the charge (electrostatic) on

the nucleophile. In the Winstein-Dewar mechanism, this enhancement is

due to neighbouring group overlap, and the magnitude of the enhancement

should vary with the orbital size of the entering and leaving groups[69].

In an attempt to differentiate between the two mechanisms, Sisti and

Lowell[68] reacted a series of α-chlorocarbonyl compounds with three

charged nucleophiles with relatively small bonding orbitals ($\overline{O}COCH_3$,

N_3^-, NCO^-), and one charged nucleophile with a relatively large bonding

orbital (NCS^-). Their results are given in Table V, p 26, and the results

of Pearson and other workers are given in Table I, p 8 for comparison.

These results were interpreted[68] as evidence against the

Pearson mechanism. The observed rate enhancement with cyanate, azide,

acetate, and pyridine (charged and uncharged), is less than that of the

larger charged and uncharged nucleophiles(thiocyanate and thiourea).

A comparison of the highly polarizable nucleophiles (azide and cyanate)

shows that their response to the electrostatic activating influence of

the α-carbonyl group is essentially the same as that of the less

polarizable acetate and pyridine. It seems, therefore, that the

enhancement with all nucleophiles is due to additional covalent bonding

Table V

Relative Rates of Displacement on α-Halocarbonyl Compounds in Methanol, 30°

Compound	Acetate	Azide	Cyanate	Thiocyanate
n-Propyl chloride	1.0	1.0	1.0	1.0
Ethyl Chloroacetate	28	33	75	83
Chloroacetone	198	210	156	401
Phenacyl chloride	228	276	179	770

in the transition state with the electron-deficient carbonyl carbon,

in support of the Winstein-Dewar interpretation. The larger bonding

orbital results in more effective neighbouring group overlap and a

larger relative rate ratio.

More recent support to the orbital overlap mechanism was

given by Temnikova *et al.*[70,71] in a study of compounds XIII - XV with

methoxide and phenoxide ions in methanol. From XIII, they isolated

the dimethyl ketal XVI; while from XIV and XV, the epoxides XVII and

XVIII were isolated, respectively.

$$\begin{array}{ccc}
\overset{\displaystyle R}{\underset{\displaystyle |}{}} & \overset{\displaystyle OCH_3}{\underset{\displaystyle |}{}}\overset{\displaystyle OH}{\underset{\displaystyle |}{}} & \overset{\displaystyle O}{\diagup\!\!\!\diagdown} \\
Ph\text{-}CBrCOPh & Ph-\underset{\underset{\displaystyle OCH_3}{|}}{\overset{\overset{\displaystyle }{|}}{C}}\text{---}\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle }{|}}{C}}\text{-}Ph & Ph-\underset{\underset{\displaystyle R}{|}}{C}\text{---}\underset{\underset{\displaystyle OCH_3}{|}}{C}\text{-}Ph
\end{array}$$
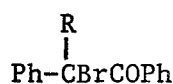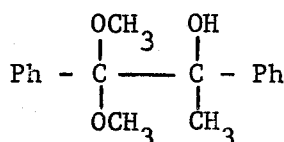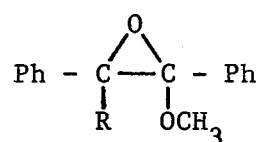
XIII - XV	XVI	XVII - XVIII
XIII R = CH_3		XVII R = CH_2Ph
XIV R = CH_2Ph		XVIII R = $p\text{-}BrC_6H_4CH_2$
XV R = $p\text{-}BrC_6H_4CH_2$		

The relative rates at 35° of XIII, XIV, and XV toward methoxide

were 1.00, 0.0049, and 0.013, respectively. With methoxide ion (highly

basic) there is a much stronger attraction to the carbonyl carbon than

in the case of weakly basic and strongly polarized nucleophiles. This

strengthens the interaction between the oxygen of the carbonyl group

and the α-carbon atom, causing inversion at the reaction centre and

forming an epoxide (XVII and XVIII). The authors claim[70] that the effect

of bulky α-substituents should be less for methoxide ion than for highly polarized and weakly basic nucleophiles such as iodide ion, because of this increased interaction. The present author does not agree with this interpretation. Their evidence is a comparison of the rates of XIII and desyl bromide (PhCOCHBrPh)[72], which shows that substitution of a methyl group into the α-position reduces the rate with methoxide by almost 9-fold; whereas for iodide[73], the ratio $k_{CH_3CHClCOPh}/k_{(CH_3)_2CClCOPh}$ has the value 2000.

When compounds XIV and XV were reacted with sodium phenoxide in methanol the products isolated were XVII and XVIII, respectively, and not phenoxy epoxides. The authors felt that because phenoxide is somewhat more polarizable than methoxide, it is more sensitive to the steric hindrance of α-substituents. Despite the much higher concentration of phenoxide ion in the medium, the reaction proceeds by interaction of the α-haloketone with the more basic nucleophile - methoxide. With 2-chloro-2-phenylacetophenone, the product isolated was the mixed methyl phenyl ketal (XIX).

$$
\begin{array}{ccc}
& OCH_3 & OH \\
& | & | \\
Ph - & C & ---- & C - Ph \\
& | & | \\
& OPh & H
\end{array}
$$

XIX

It appears that the product is determined by the conditions, *i.e.*, whether PhOH opens the first-formed epoxide or not. If there is little free PhOH (mostly PhO$^-$), it may survive.

The same authors[74] have examined the reaction of various α-bromodesoxybenzoins with *p*-anisidine in ethyl cellosolve. The overall reaction is shown in the following equation.

$$X\text{-}C_6H_4COCHBrPh + 2p\text{-}CH_3O\text{-}C_6H_4NH_2 \longrightarrow X\text{-}C_6H_4\text{-}\underset{\overset{|}{NHC_6H_4\text{-}OCH_3\text{-}p}}{COCHPh} + p\text{-}CH_3O\text{-}C_6H_4NH_2 \cdot HBr$$

The compounds used were X = Cl, Ph, H, CH$_3$, and OCH$_3$. At 60° a rate decrease from Cl to OCH$_3$ of 2.7-fold was observed. The activation parameters calculated for this series are very similar; there is less than 1 kcal difference in $\Delta H^{\ddagger}$, and less than 1 eu difference in $\Delta S^{\ddagger}$. This is shown in the small value of ρ for this reaction (0.9), which indicates that a decrease in the reactivity of the series corresponds to an increase in the electron density at the reaction centre. Because of the large values found for $\Delta S^{\ddagger}$ (-36 eu), a highly ordered polar transition state was postulated, and the transition state was pictured as a Winstein-Dewar complex. An asymmetrical transition state (XX) was pictured because the bonding of the amine to the α-carbon atom predominates.

$$X\text{-}C_6H_4COCHBrPh + p\text{-}CH_3OC_6H_4NH_2 \longrightarrow \left[X\text{-}C_6H_4\text{-}\overset{O}{\underset{}{\underset{\overset{|}{\underset{\delta+}{NH_2C_6H_4OCH_3\text{-}p}}}{\overset{\|}{C}}}}\text{-}\overset{Br^{\delta-}}{\underset{H}{\overset{}{C}}}Ph \right] \longrightarrow \text{Products}$$

$$XX$$

They also studied the same system with sodium phenoxide in dioxane[75]. Similar results were obtained, *i.e.*, a decrease in rate from X = Cl to X = OCH_3 of 4.9-fold, similar activation parameters, and a low value of ρ, indicating insensitivity to the introduction of polar substituents. Because of the low tendency of the weakly basic phenoxide ion to add to the carbonyl carbon, reaction of the nucleophile at the α-carbon atom to give the α-phenoxyketones predominated.

In summary, the evidence available at the present time seems to support the orbital overlap mechanism, but the electrostatic mechanism cannot be ruled out completely. However, the work by Sisti and Lowell[68] is quite compelling against Pearson's[34] mechanism.

(e)   Enolization and Solvolysis of α-Haloketones

The possibility that normal and isomeric substitution products from the nucleophilic displacement reactions of some α-haloketones might arise from a mechanism involving enolization, ionization, and solvolysis was considered by Richard[76] in 1938. In the reaction of $ArCHClCOCH_2R$ (XXI) and $ArCOCHClCH_2R$ (XXII) with hydroxide, cyanide, carbonate, acetate, and

phenoxide ions, he ascribed the greater reactivity of the former

chloroketone, compared with the latter chloroketone, to the fact

that XXI can form two possible enols, $ArCHCl(OH) = CHR$ and

$ArCCl = C(OH)CH_2R$, whereas XXII can form only one enol, $ArC(OH) =$

$CClCH_2R$, containing a vinylic halogen.

In 1966, Rosnati *et al.*[77] reported that reaction of

$Ph_2CHCOCH_2Cl$ with acetate ion in glacial acetic acid yielded the

normal substitution product, $Ph_2CHCOCH_2OAc$ (20%), and the isomeric

acetoxyketone, $Ph_2C(OAc)COCH_3$ (50%). The latter product was

envisaged as arising from enolization, followed by ionization and

attack by acetate to form the product.

$$Ph_2CHCOCH_2Cl \rightleftharpoons Ph_2C = \overset{\overset{\displaystyle OH}{|}}{C}-CH_2Cl \longrightarrow Ph_2\overset{+}{C}-\overset{\overset{\displaystyle OH}{|}}{C}=CH_2 \overset{\bar{O}Ac}{\longrightarrow} Ph_2\overset{\overset{\displaystyle OAc}{|}}{C}COCH_3$$
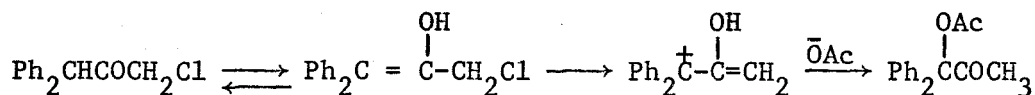
To gain further insight into the mechanism of this reaction, Rosnati

et al. studied the effect of neighbouring group participation[78-84].

They found that when a mixture of isomeric chloroketones was reacted

with acetate ion in acetic acid, only one product, the 3-acetoxyketone,

was produced. A chloroketone with no enolizable hydrogens gave

essentially no reaction under the same conditions.

$$Ph-O-CH_2COCH_2Cl + PhOCHClCOCH_3 \xrightarrow[\text{HOAc}]{\bar{O}Ac} PhO-CH(OAc)COCH_3$$

$$PhO-C(CH_3)_2COCH_2Cl \xrightarrow[\text{HOAc}]{\bar{O}Ac} \quad N.R.$$
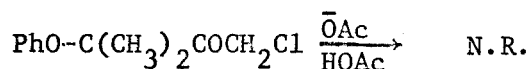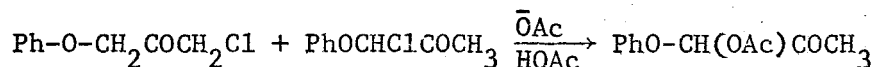
The mechanism proposed[78] is similar to that for the diphenyl system above[77], enolization, ionization, and nucleophilic attack to the product. In this case, there is the possibility of involvement of the ether oxygen lone-pairs; this was investigated in a study of a phenylmercapto- system[80,82], 1-chloro-3-phenylmercaptopropanone (XXIII). Three products were found, the amounts of which depended on the acetate concentration.

$$Ph-S-CH_2COCH_2Cl \xrightarrow[HOAc]{\overline{O}Ac} Ph-S-CH(OAc)COCH_3 + Ph-S-COCH(OAc)CH_3 + Ph-S-CH_2COCH_2OAc$$

$$\quad\text{XXIII} \qquad\qquad\qquad \text{XXIV} \qquad\qquad \text{XXV} \qquad\qquad\qquad \text{XXVI}$$
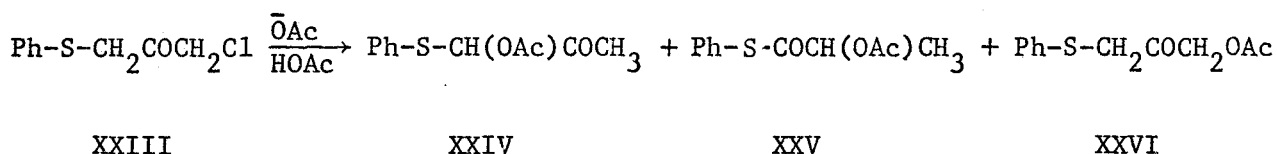
When the acetate concentration was varied from 0 to 2.2 M, the amount of XXIV decreased from 90% to only a trace, the rearranged acetate XXV increased from 0 to 80%, and XXVI remained essentially constant (Table VI, p 33).

It was first thought[80] that the rearranged acetoxyketone (XXV) came from a cyclopropanone intermediate; but it was later shown[84] that the 3-acetoxyketone (XXIV) is the precursor of the rearranged acetoxyketone (XXV).

$$Ph-S-CH(OAc)COCH_3 \xrightarrow{\overline{O}Ac}{3HOAc} \qquad\qquad \longrightarrow Ph-S-CO\overline{C}(OAc)CH_3 \xrightarrow{H^+} \quad \text{XXV}$$
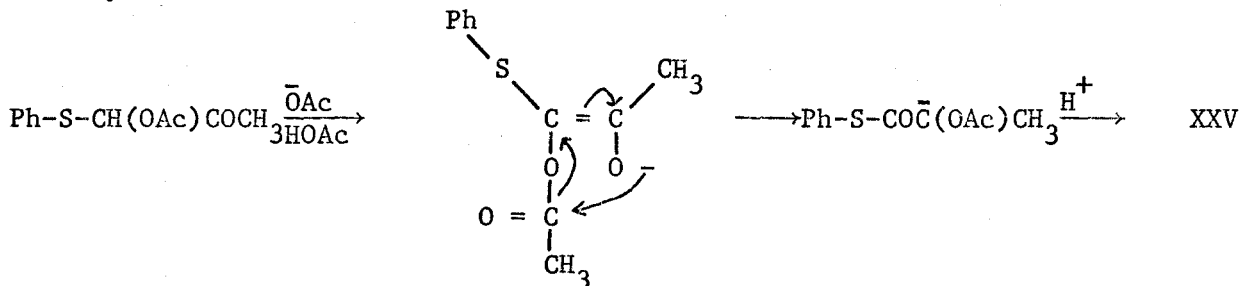
Table VI

Product Distribution in Reaction of PhSCH$_2$COCH$_2$Cl with Acetate in

Acetic Acid, 120°

	Products, %		
[⁻OAc], M	3-OAc(XXIV)	1-OAc (XXVI)	Rearranged OAc (XXV)
0	90	10	0
1.1	48	15	37
1.65	12	20	68
2.2	trace	20	80

It was shown[84] by isotopic labelling experiments that the α'-carbon atom in XXIII becomes the carbonyl carbon atom in XXV.

Bordwell and coworkers[85-88] have reported evidence for the enolization and solvolysis mechanism. They examined[85] the reaction of $ArCHClCOCH_3$ with methoxide ion in methanol to give a mixture of Favorskii ester (XXVI) and hydroxy ketal (XXVII) which arose from competing reactions.

$$ArCH_2CH_2COOCH_3 \qquad\qquad ArCH(OH)C(OCH_3)_2CH_3$$
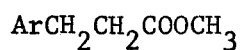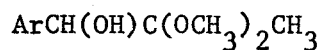
XXVI   XXVII

Proton loss from the methyl group was found to be rate-determining, and the Favorskii reaction showed a greater acceleration in rate with increased ionic strength relative to the competing reaction to form XXVII. The Hammett ρ for the latter reaction was -0.9 and for the Favorskii reaction was -2.37. Changing Ar from p-NO_2-C_6H_4 to p-CH_3O-C_6H_4 increased the yield of ester from 0 to 68%. The value of ρ found for the Favorskii reaction was interpreted as indicating a high degree of ionic character in the C-Cl bond at the transition state. It was suggested that ionization of the halogen is aided by π-bond participation from the parallel p-orbitals of the enolate ion to form either a delocalized (dipolar ion) intermediate or a cyclopropanone (see p 47).

This study was extended by these authors[86] to the $ArCH_2COCH_2Cl$ (XXVIII) system (*m*-and *p*-substituted). It was shown that the reaction of XXVIII with methoxide ion in methanol involves reversible carbanion formation, first-order in chloroketone and base, and that ρ is large and negative (-4.97). Isomerization of these chloroketones was ruled out, and the mechanism favoured by the authors[86] is analogous to that interpreted in the reaction of its isomer[85]. Because the product was the same as that from $ArCHClCOCH_3$, all unsymmetrical intermediates are ruled out. In the reaction of $ArCH_2COCHClR$ with methoxide ion in methanol, these authors have found[87] a mechanistic change on going from R = H to R = CH_3.

$$ArCH_2COCHClR + \bar{O}CH_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArCH = C\overset{\displaystyle O^-}{\underset{\displaystyle \underset{Cl}{\overset{|}{\underset{}{CHR}}}}{<}} + CH_3OH \underset{fast}{\overset{fast}{\rightleftharpoons}} ArCH = C\overset{\displaystyle OH}{\underset{\displaystyle \underset{Cl}{\overset{|}{\underset{}{CHR}}}}{<}} + \bar{O}CH_3$$

XXVIII   R = H   (E⁻)   (EH)

XXIX   R = CH_3

$$CH_3OH \downarrow k_2 \qquad\qquad CH_3OH \downarrow k_3$$

$$ArCH_2CHRCO_2CH_3 \qquad\qquad ArCH_2COCH(OCH_3)R$$

XXX   R = H   XXXII   R = CH_3

XXXI   R = CH_3
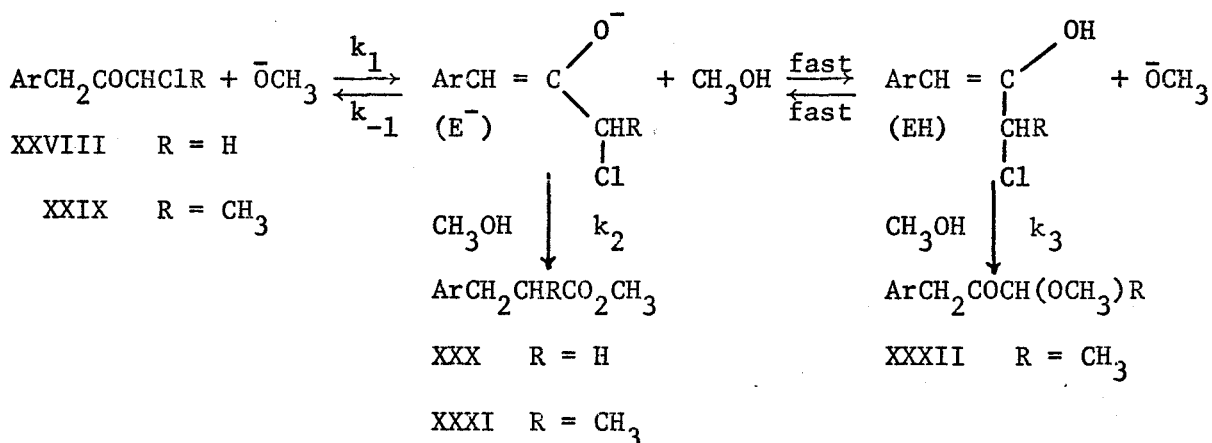
For XXVIII, formation of the enolate ion is reversible ($k_{-1} > k_2$), and k_2 is the rate-determining step. They found extensive deuterium exchange, a large Br/Cl rate ratio, and a large negative ρ (-5.0). For XXIX, formation of the enolate ion is irreversible (k_2 and $k_3 > k_{-1}$).

With XXVIII, $k_2 >> k_3$, and the ester XXX is formed both at high and low methoxide ion concentration. However, with XXIX $k_2 \simeq k_3$, and the formation of XXXII is favoured at low methoxide ion concentration, where the $E^- \rightleftharpoons EH$ equilibrium favours the enol.

In an extension of this work, Bordwell and Carlson[88] have shown that solvolysis of an enol allylic chloride is responsible for the formation of α-alkoxyketones from $PhCH_2COCHClCH_3$ (XXXIII), PhCHCl-$COCH_2CH_3$ (XXXIV), and $PhCH_2COCHClPh$ (XXXV). When XXXIII was reacted with 3 $\underline{M}$ p-toluenesulfonic acid in 75% v/v H_2O-CH_3OH, the major product (76%) was the methoxyketone; the other product was hydroxyketone (24%). The same product distribution was obtained in the same solvent system with catalysis by either 2,5-lutidine (1 $\underline{M}$) or $NaOH-NaOCH_3$ (0.02 $\underline{M}$). Compound XXXV gave similar results. It is interesting to note that this mechanism was considered by Fort[89] in 1962 as a possible route from XXXV to $PhCH_2COCH(OCH_3)Ph$, but was rejected on the grounds that lutidinium ion did not catalyze the reaction. Fort did not, however, look at the Br/Cl rate ratio. Bordwell and Carlson[88] found chloroketone XXXIV to give the same methoxyketone as XXXIII under identical conditions.

The enol solvolysis mechanism is probably responsible for the formation of α-alkoxyketone by-products from the Favorskii rearrangement carried out with dilute sodium alkoxides and alcohols in other systems[90-93]. This side reaction is avoided in aprotic media or at high alkoxide concentrations in protic media.

The formation of α-alkoxyketones from certain α-haloketones and methoxide ion in methanol has been observed to follow first-order kinetics. Temnikova *et al.*[94,95] found that α-haloketones of the type $Ph_2CXCOAr$, when treated with methoxide ion in methanol, yielded the normal substitution products, α-methoxyketones. First-order kinetics were followed, and the reaction of these compounds was rationalized by the authors as resulting from the protic solvent methanol assisting in the ionization to the carbonium ion:

$$\underset{\overset{|}{X}}{\overset{\overset{O}{\|}}{-C-C-}} + \text{solvent} \xrightarrow[\text{slow}]{-X^-} \left[\overset{\overset{O}{\|}}{-C-\overset{+}{C}\diagup} \right]_{\substack{\text{solvent} \\ CH_3OH}} \xrightarrow[CH_3OH]{\overset{-}{O}CH_3} \underset{OCH_3}{\overset{\overset{O}{\|}}{-C-C-}}$$
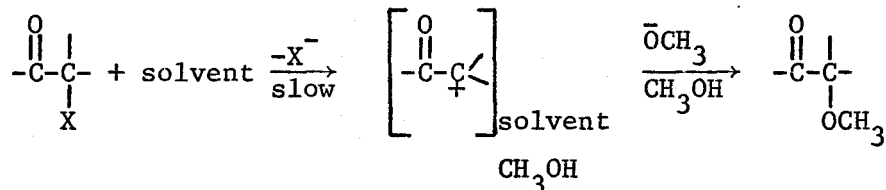
A more detailed study of this reaction was made[96] in 1969, when the results of kinetic experiments with $p\text{-}X\text{-}C_6H_4COCBrPh_2$ were reported. A 4-fold increase in rate was observed on going from p-Cl to p-OCH_3, and the slope (ρ) from a plot of log k versus $σ^+$ had the value -0.83. This was taken to indicate that the transition state for this reaction has marked carbonium ion character, in support of the above scheme.

The Favorskii Rearrangement

(a) The Epoxide Mechanism

The original mechanism proposed by Favorskii[97] involved the addition of alkoxide to the carbonyl carbon, followed by formation

of an epoxide after expulsion of halide ion, and rearrangement to the product.

$$R'-\overset{\overset{O}{\|}}{C}-CHXR'' + \bar{O}R \longrightarrow R'-\overset{\overset{\bar{O}}{}}{\underset{\underset{OR\ X}{|\ |}}{C}}-CHR'' \overset{-X^-}{\longrightarrow} R'\overset{O}{\underset{\underset{OR}{|}}{C}}-CHR'' \longrightarrow R'R''CHCO_2R$$
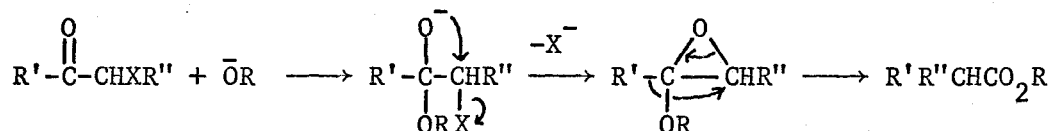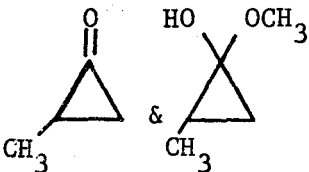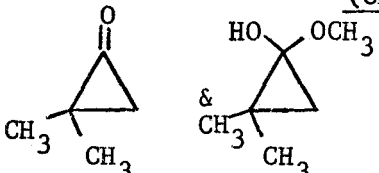
Because epoxides in general do not yield Favorskii-type products (see pp 19-20), this mechanism is probably not involved in the main course of the reaction, although it plays an important part in the formation of certain by-products (notably ketals).

There is a report in the literature that epoxides are intermediates in the formation of α-alkoxy and α-hydroxyketones. Turro, Rappe, and coworkers[98] claim that the epoxide mechanism is the major route for the formation of the α-substitution products in the reaction of 3-bromo-2-butanone, 1-bromo-2-butanone, 3-bromo-3-methyl-2-butanone, and 1-bromo-3-methyl-2-butanone with methoxide ion in methanol. Their results are given in Table VII, p 39.

The cyclopropanones and hemiketals were shown to yield 100% rearranged ester; the esters from XXXVI, XXXIX, XLII and XLV (less than 10% of the products observed) were formed via a cyclopropanone intermediate. The remainder of the products were interpreted as arising from epoxide intermediates, which decomposed to yield α-methoxy- and/or α-hydroxyketones according to the following scheme.

Table VII

Product Distribution in Reactions of Various α-Bromoketones with

Methoxide Ion in Methanol

Compound	$(CH_3)_2CHCO_2CH_3$	$CH_3COCH(OH)CH_3$	$CH_3CH_2COCH_2OCH_3$
	%	%	%
	100	-	-
$CH_3CH_2COCH_2Br$	9^a	-	43^a
$CH_3CHBrCOCH_3$	-	9^b	-

	$(CH_3)_3CCO_2CH_3$	$CH_3COC(CH_3)_2OCH_3$	$(CH_3)_2CHCOCH_2OCH_3$
	100	-	-
$(CH_3)_2CHCOCH_2Br$	9^c	-	54^c
$(CH_3)_2CBrCOCH_3$	6^d	7^d	-

^{a} Plus (45%)

^{b} Plus (89%)

^{c} Plus (35%)

^{d} Plus (56%), glpc rearrangement of

XXXVI R = H

XXXIX R = CH₃ → CH_3

XXXVII

XL
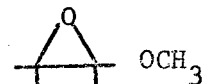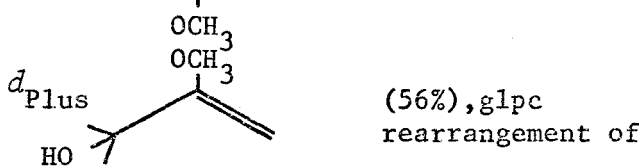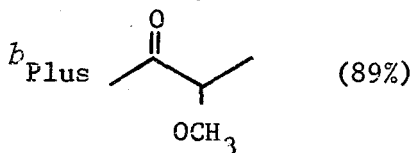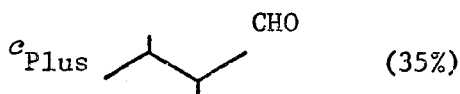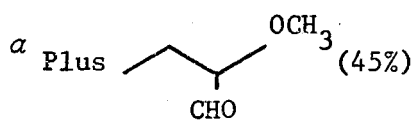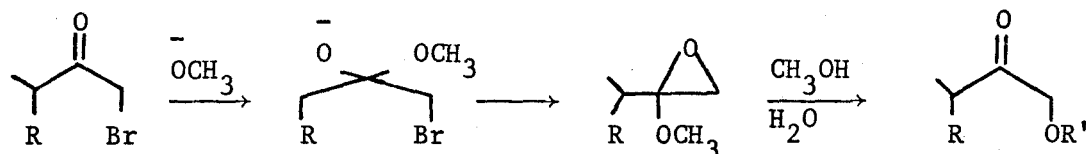
XXXVIII R' = H or CH₃(R=H)

XLI R' = H or CH₃(R=CH₃)
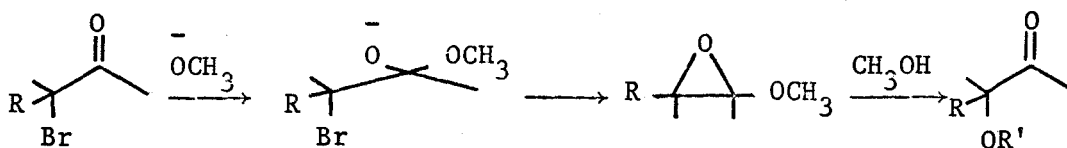
XLII R = H

XLV R = CH₃

XLIII

XLVI

XLIV R' = H or CH₃(R=H)

XLVII R' = H or CH₃(R=CH₃)

The authors observed XXXVII and XL as the major product before work-up, while XXXVIII and XLI were not formed until after work-up. Thus, it would seem that the major route for the formation of the α-substitution products was via epoxides XXXVII, XL, XLIII, and XLVI.

These results seem rather strange in view of the evidence reported by Pearson et al.[34] and by Lutz[67] against the epoxide mechanism. Turro, Rappe, et al. did not report[98] structural evidence for the epoxides they observed; it seems more likely that the epoxides they cite as intermediates would decompose to hydroxy ketals rather than α-substitution products.

(b)   The Semibenzilic Mechanism

The semibenzilic mechanism was first suggested by Tchoubar and Sackur[99] in 1939, for the reaction of 1-chlorocyclohexyl phenyl ketone with sodium hydroxide in ether. They reported the isolation of XLVIII as the major product, formed by the following mechanism:

XLVIII   XLIX
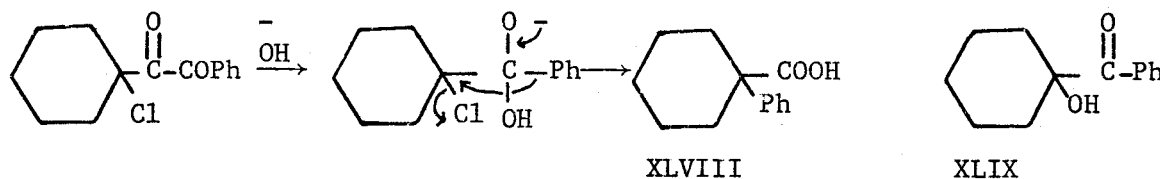
The importance of the reaction conditions for the operation of this mechanism was shown by Stevens and Farkas[100], who repeated the above work using different solvents and temperatures. In homogeneous media they found no acid (XLVIII) at all, but α-hydroxyketone (XLIX). In heterogeneous media (Tchoubar's conditions) the reaction was slow, with the formation of a small amount (9%) of XLVIII; the major product (83%) was XLIX.

An example of this mechanism operating where the α-haloketone has an α'-hydrogen atom (although it is relatively non-acidic), was reported by Cope et al.[101]. In the reaction of 1-bromobicyclo[3.3.1] nonan-9-one with sodamide in liquid ammonia, bicyclo[3.3.0]octane-1-carboxylic acid amide (L) was isolated as the major product.

L
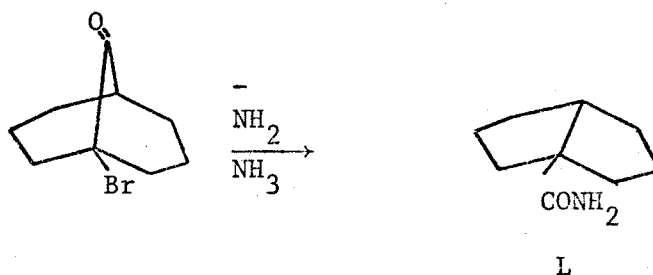
Warnhoff and coworkers[102] reported an example of an α-haloketone with an α'-hydrogen that undergoes the Favorskii rearrangement either by way of a symmetrical intermediate or by way of a semibenzilic intermediate, depending on the experimental conditions. They studied the reactions of a series of α-bromoketones LI(n), where n = 6, 7, and 8, with various bases to give the results shown in Table VIII, p 43.
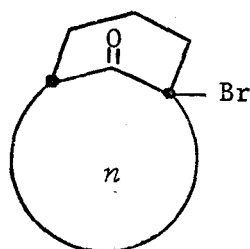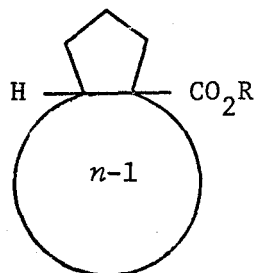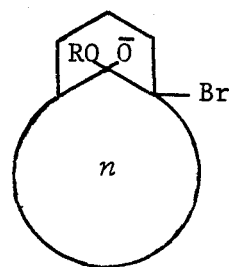
LI(*n*)   LII(*n*)   LIII(*n*)

Examination of the product for deuterium incorporation, stereochemistry, and fate of optical activity allowed an unambiguous distinction between a cyclopropanone and a semibenzilic intermediate [LIII(n)]. The semibenzilic path requires retention of optical activity and either no incorporation of carbon-bound deuterium into LII, or else deuterium exchange in LI before rearrangement. The cyclopropanone mechanism requires both incorporation of carbon-bound deuterium into LII and racemization of the optically active bromoketone; deuterium incorporation alone is sufficient provided no α'-hydrogen exchange occurs before rearrangement. All reactions gave rise to *cis*-LII, which

Table VIII

Displacement of Bromide from a Series of α-Bromoketones under Favorskii Conditions

BrK	Reagent	Solvent	Product	Atoms D	Mechanism
LI(n=6)	NaOD	EtOD-D$_2$O	LII(6) R = H	0.00	Semibenzilic
LI(n=6)	KOt-Bu	t-BuOD	LII(6) R = t-Bu	0.026	Semibenzilic
LI(n=7)	NaOD	EtOD-D$_2$O	LII(7) R = H	0.01	Semibenzilic
LI(n=7)	NaOCH$_3$	CH$_3$OD	LII(7) R = CH$_3$	0.00	Semibenzilic
LI(n=7)	KOt-Bu	t-BuOD	LII(7) R = t-Bu	0.83	Cyclopropanone
LI(n=7)	AgNO$_3$	EtOD-D$_2$O	LII(7) R = H	0.00	Semibenzilic
LI(n=8)	NaOD	EtOD-D$_2$O	LII(8) R = H	0.90	Cyclopropanone
LI(n=8)	AgNO$_3$	EtOD-D$_2$O	LII(8) R = H	0.005	Semibenzilic

is required by LIII and permitted by a cyclopropanone mechanism.
It was found that the two compounds LI(n=7) and LI(n=8) can each
rearrange to a single product by either a semibenzilic or cyclo-
propanone intermediate, showing the delicate balance between the
two mechanisms depending on the reaction conditions.

An example in which the semibenzilic mechanism operates
exclusively was reported by Conia *et al.*[103,104] in 1963 for a
compound which contains an α'-hydrogen atom, 2-bromocyclobutanone.
With strong bases, a cyclopropanecarboxylic acid derivative was
formed, while with other nucleophiles the normal substitution product
was formed[103].
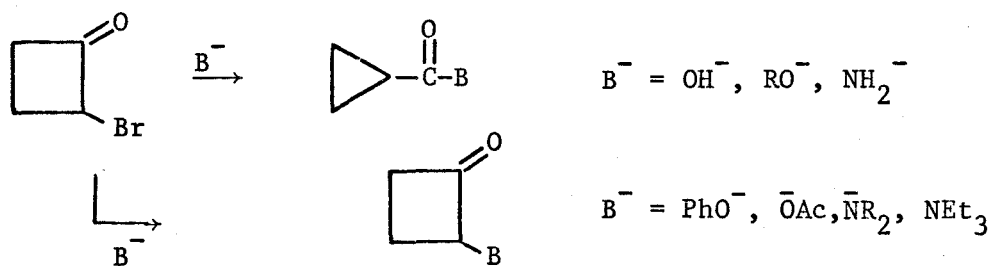
The mechanism was proved by doing the reaction in D_2O and in
Na_2CO_3/D_2O; in both cases no deuterium was incorporated into the ring.
Also, two isomeric dimethyl-substituted compounds gave the same
cyclopropanecarboxylic acid (LIV) under identical conditions:

LIV
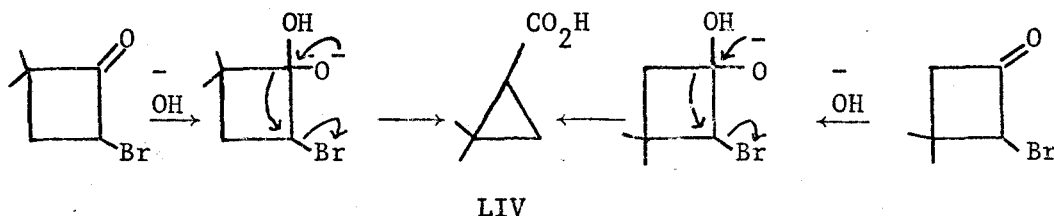
This reaction was also examined by Rappe and Knutsson[105], who confirmed that 2-bromocyclobutanone reacts via a semibenzilic mechanism under these conditions.

In conclusion, the semibenzilic mechanism appears to operate when the α-haloketone has no α'-hydrogen atom[99,100], when the α-hydrogen is relatively non-acidic[101,102], or where steric or strain factors inhibit cyclopropanone formation[103-105].

(c)   The Cyclopropanone Mechanism

From the discussion of the semibenzilic mechanism, one would predict that the rearrangement product of a given α-haloketone would be different from that of its isomer, an α'-haloketone. For example, 1-chloro-3-phenyl-2-propanone (LV) should give rise to 3-phenylpropionic acid (LVI), while 1-chloro-1-phenyl-2-propanone (LVII) should rearrange to 2-phenylpropionic acid. However, it was found by McPhee and Klingsberg[106] that both haloketones yield the same acid (LVI). Thus these compounds must rearrange by mechanisms other than those discussed in detail above.

$$PhCH_2COCH_2Cl \longrightarrow PhCH_2CH_2CO_2H$$

LV   LVI

$$PhCHClCOCH_3 \xrightarrow{\quad\times\quad} PhCH(CH_3)CO_2H$$

LVII
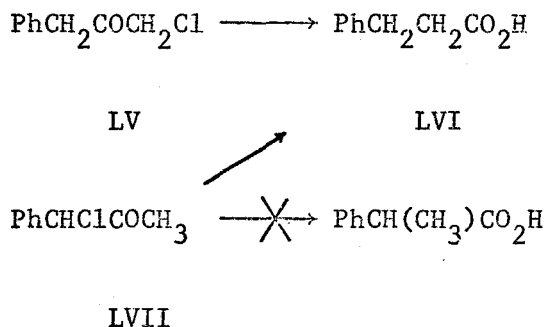
This rearrangement was rationalized by Wendler *et al.*[107] as arising
from prior isomerization of the haloketone by halogen migration from
the α- to the α'-carbon atom (p 11). However, even though this allylic
shift is analogous to the internal return of Winstein[108] (3° to a 1°
allylic halide), it is improbable because of the absence of solvolysis
products derived from the isomerized haloketone.

In 1950, Loftfield[109] proposed a symmetrical intermediate in
the rearrangement of ^{14}C- labelled 2-chlorocyclohexanone (LVIII) in
dilute ethanolic sodium ethoxide. When LVIII, in which the isotope was
equally distributed between carbon atoms 1 and 2, was treated with less
than one equivalent of sodium isoamyloxide in isoamyl alcohol, the
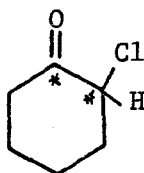
LVIII

principal product was isoamyl cyclopentanecarboxylate. The radiocarbon
in the ester fraction was distributed 50% on the carboxyl carbon atom,
25% on the ring α-carbon atom, and 25% on the two ring β-carbon atoms.
These data are compatible with a mechanism involving a cyclopropanone
intermediate. According to this mechanism, a proton is removed from
the α'-carbon atom to give the haloketone enolate anion (LIX). Concerted
or stepwise loss of halide ion leads to a cyclopropanone (LX) which is
rapidly cleaved by alkoxide to give the rearrangement product.

The stereochemical implications of this mechanism are not firmly established. Loftfield's[109] mechanism implies that cyclopropanone formation occurs via an internal S_N2-type displacement on the halogen-bearing carbon atom with consequent inversion at that centre. Burr and Dewar[110] have questioned this view on quantum mechanical grounds. They suggest that the geometry of the enolate π-orbital is not suitable for effective S_N2-type overlap with the σ-orbital of the halogen-bearing α-carbon atom. Burr and Dewar are thus in agreement with Aston and Newkirk[111], who claim that loss of halide from the enolate anion precedes cyclopropanone formation and involves the generation of a species which may be represented as a mesomeric zwitterion (LXI) or as a no-bond canonical form (LXII) of a cyclopropanone.

These mechanisms are kinetically indistinguishable if the rate-determining step is enolate formation, but there are stereochemical differences. The synchronous process would entail inversion with sp^3-hybridization at the halogen-bearing carbon atom. With LXI or LXII, one would predict racemization of the α-carbon atom.

An attempt to distinguish between the two mechanisms was made by Stork and Borowitz[112] by the reaction of two compounds epimeric at the α-carbon with sodium benzyloxide in ether. If the rearrangement occurred via a cyclopropanone mechanism, the two haloketones should give two different acids, with inversion in each case, while either of the epimeric haloketones would give the same mixture of acids by the dipolar ion mechanism. Their results with 1-chloro-*cis*-1-acetyl-2-methylcyclohexane (LXIII) and 1-chloro-*trans*-1-acetyl-2-methylcyclohexane (LXIV) are shown in the following scheme.

The rearrangement of LXIII and LXIV to different acids thus proceeds via a cyclopropanone mechanism under these reaction conditions.

That the stereochemical outcome of the above and other

Favorskii rearrangements is dependent on the polarity of the reaction

medium was shown by House and Gilmore[113] in 1961. Reaction of LXIII

with sodium methoxide in methanol yielded a mixture of LXV (inversion

at C_1, 40%) and LXVI (retention at C_1, 52%). With sodium methoxide in

1,2-dimethoxyethane, LXIII also yielded a mixture of LXV and LXVI in

which the product LXV (inversion at C_1) was the major constituent (95%).

The authors also showed[113] that there was no isomerization of LXIII to

LXIV or to LXVII. They concluded that this rearrangement is non-

stereospecific in polar media, and the dipolar ion mechanism may be

occurring. However, it appears that one should not make predictions on

the outcome of other Favorskii rearrangements, regardless of the reaction

conditions.

LXV   LXVI   LXVII
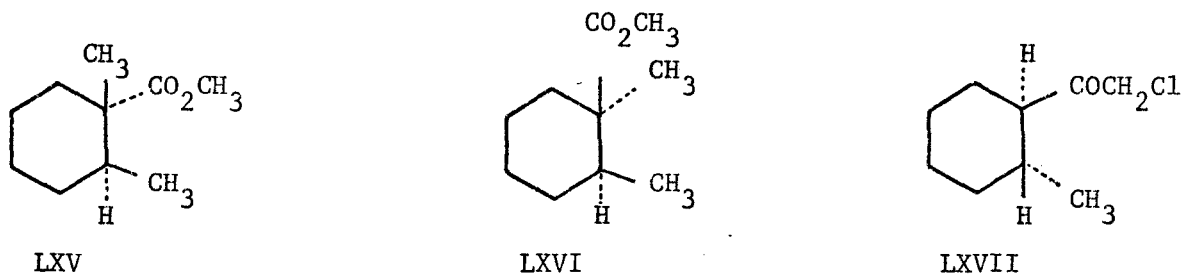
Further evidence for the dependence of the nature of the

rearrangement on the reaction conditions has been reported by Turro

and Hammond[114]. In the reaction of 2-bromo-2,4-dimethyl-3-pentanone

(LXVIII) with methoxide ion in ether at 25°, 12% of the ester (LXIX) and 88% of the α-alkoxyketone (LXX) were formed.

$$(CH_3)_2CHCOCBr(CH_3)_2 \xrightarrow[2Et_2O]{\overline{O}CH_3} (CH_3)_2CHC(CH_3)_2COOCH_3 + (CH_3)_2CHCOC(OCH_3)(CH_3)_2$$
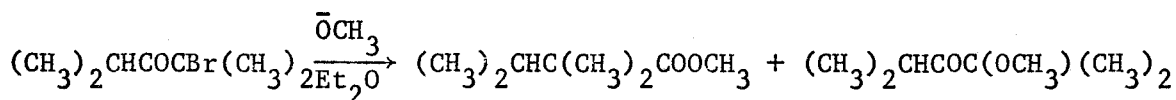
LXVIII   LXIX   LXX

They showed that both the cyclopropanone (LXXI) and the hemiketal (LXXII) went nearly quantitatively to LXIX on reaction with methoxide ion in methanol or in 1,2-dimethoxyethane. These results indicate that if LXXI is formed and carbonyl addition occurs, the zwitterion LXXIII is in equilibrium with LXXI and LXXII.
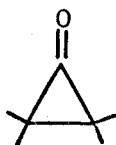
LXXI   LXXII   LXXIII
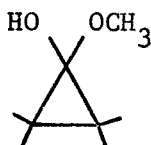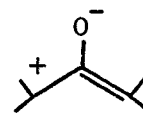
The α-alkoxyketone may also be formed by direct substitution on LXVIII because it is the major product even in nonpolar media.

House and Frank[115] have found, in a study of the same reaction, that even in methanol the ester (LXIX) is a minor product; the major product was the α-hydroxyketone formed by some mechanism other than via a cyclopropanone intermediate (the authors suggest hydrolysis of an epoxide).

One can predict that the rearrangement of unsymmetrical α-haloketones leads to the product formed through cleavage of the cyclopropanone intermediate so as to give the more stable of the

two possible transient carbanions. Thus the cyclopropanone (LXXIV)

derived from 3-bromo-3-methyl-2-butanone opens to the tertiary

trimethylacetic acid, forming a transient primary rather than

tertiary carbanion[116].

$$\left[\begin{array}{c} CH_3 \\ \overset{O}{\underset{CH_3}{\triangle}} \end{array} \right] \xrightarrow{\text{ROH}} (CH_3)_3CCO_2R$$

LXXIV
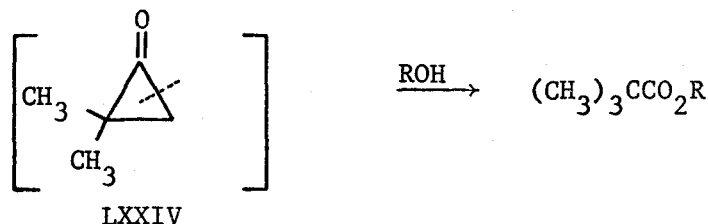
In a recent paper, Rappe, Turro and coworkers[117] have shown

that the Favorskii rearrangement of the 2- and 4-halo-2-methyl-3-

pentanones yields essentially the same ratio of esters LXXV and LXXVI

using the same base as for the ring opening of the corresponding

cyclopropanone (LXXVII) and its hemiketal (LXXVIII). This fact is

compelling evidence that LXXVII and/or LXXVIII is an intermediate in

the Favorskii rearrangement of the haloketones, since the ratio of

esters LXXV and LXXVI should be very sensitive to changes in mechanistic

pathways. The bases used were methoxide, ethoxide, and *t*-butoxide. They

also found that a larger group than methyl in the haloketone increased

the relative amount of ester derived from the less stable carbanion,

while *t*-butoxide as base yielded almost exclusively the ester

derived from the more stable carbanion. The authors suggested[117]

that these results agree with the hypothesis that steric factors

in addition to carbanion stability determine the direction of

cleavage of cyclopropanones by base.
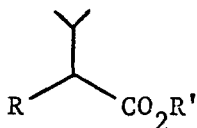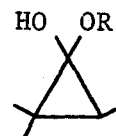
LXXV   LXXVI   LXXVII   LXXVIII

In conclusion, studies of the Favorskii rearrangement of

α-haloketones (discussed above) have demonstrated that the reaction

conditions used often influence both the stereochemical course

of the rearrangement and the nature of the products obtained. To

obtain good yields of esters in which a stereospecific rearrangement

(inversion of configuration at the α-carbon) has occurred, it appears

appropriate to use strong bases in nonpolar, aprotic solvents.

Effects of α-Substitution on the Rates of Displacement

There are very few reports in the literature on the effect of

increasing alkyl substitution α- to the reaction site in the bimolecular

displacement reactions of α-haloketones. In 1955, Fierens[118] reported

the results of kinetic experiments on a series of α-chloroketones

$CH_3COCHClR$ with potassium iodide in anhydrous acetone at 25°. Fierens'

results were compared with those of Dostovsky and Hughes[119] for the

reaction of the corresponding alkyl bromides with ethoxide ion in methanol at 55°. These data are given in Table IX, p 54.

Fierens reports[118] that the steric effect is shown in an analogous manner in the two reaction series. However, he does not mention the fact that there is a 30° temperature difference between the two reactions or that the leaving groups are different. Another study of α-substituent effects was made by Reeve *et al.*[73]. They found that PhCOCClRR', when reacted with sodium iodide in acetone at 0°, gave the following relative rates: R=R'=H, 1.00; R=CH_3, R'=H, 0.006; and R=R'=CH_3, 0.000003. The data obtained for the model alkyl chlorides, CH_3CClRR' were: R=R'=H, 1.00; R=CH_3, R'=H, 0.013; and R=R'=CH_3, 0.003. Thus, there is a difference of 10^3 in the relative rates of PhCOCCl$(CH_3)_2$ and $(CH_3)_3$CCl; the α-chloroketone seems to be more sensitive to steric hindrance at the reaction site than the alkyl chloride. However, in the results of Fierens[118] discussed above, the chloroketones show a smaller sensitivity to steric hindrance (the model system, although a poor choice, would probably show even a greater sensitivity if the temperature were lowered to 25°). Any conclusions with regard to the effect of substituents α- to the reaction site in displacement reactions of α-haloketones based upon the above information would certainly be questionable.

Table IX

Comparison of Relative Rates of Displacement of Halide from a Series of

α-Haloketones and Alkyl Halides

R	Reaction	
	$CH_3COCHClR + I^- \xrightarrow{Me_2CO}$ Relative Rates 25°	$RCH_2Br + {}^-OEt \xrightarrow{EtOH} {}^{a}$ Relative Rates 55°
Me	1.0	1.0
Et	0.61	0.28
i-Pr	0.0057	0.030
t-Bu	0.000011	0.0000042

^{a}Relative rate constants corrected for elimination reactions

Summary

Although much of the chemistry of the displacement reactions of α-haloketones is understood, there is a definite paucity of information concerning the mechanism of nucleophilic displacement reactions leading to normal substitution products. The orbital overlap mechanism seems to have the most support among chemists working in this area, but the exact nature of the transition state is not clearly understood.

Because the overlap mechanism implies response to steric hindrance at both carbons being bonded at the transition state, a test of this mechanism would be to prepare two series of α-haloketones, one with increasing steric requirements α- to the reaction site, and the other with increasing steric requirements at the α'- carbon atom. Their rates of nucleophilic substitution might provide a better picture of the transition state. These effects of substitution could be related to the steric effects in model systems. The overlap mechanism also implies a definite stereoelectronic relationship (p 23). This relationship could be tested with a system better than that chosen by Bartlett[41]. His model system had definite disadvantages, consisting as it did of one cyclic and one acyclic compound (p 23). With the above objectives in mind, the work of this part of the thesis was undertaken.

RESULTS AND DISCUSSION

I. The Acetate-Catalyzed Bromination and Deuterium Exchange of 2-Butanone

Introduction

The main objective of this section is to show that the regio-
selectivities of bromination and exchange of butanone are the same, as
required if enolization is the rate-determining step for each. Proof
of such equality, based on product studies, is not a trivial problem.
Consequently the methods used to obtain ratios from product data are
discussed in detail here, and control experiments are also described.
Main items in this section are (1) the products from acetate-catalyzed
bromination of butanone, (2) conversion of product distribution data
into the rate ratio for monobromination, and (3) the value of the
enolization rate ratio, as determined from deuterium exchange kinetics.
The discussion includes comparisons with the results of Rappe, whose
reports[18-22,26,27] led to this work, and suggestions as to the probable
origin of error in Rappe's work.

Acetate-Catalyzed Bromination of 2-Butanone

As discussed in the Historical Introduction, Rappe has proposed
for 2-butanone no less than five ketone halogenation reactions[22], two
of which are base-catalyzed and different from the base-catalyzed
deuterium exchange reaction[21]. The first of these, "Hal B I", occurs in

the pH region 5.5-7 and is catalyzed by weak bases such as acetate and bicarbonate to give K_{Br} = 5-7 (ratio of 3-products : 1-products). He has claimed[19,21] that the halogenating agent reacts with unenolized ketone, which has the implication that there is a non-zero order term in halogenating agent. However, in a recent study, Cox[2] has shown that there is no first-order (in bromine) component in the acetate-catalyzed bromination of acetone, bromoacetone, 1,1-dibromoacetone, 1,1,1-tribromo-acetone, and pinacolone under conditions similar to those used by Rappe[18-22]. This disproves Rappe's mechanism and requires some prior reaction of the ketone, presumably enolization. Thus a non-enolic mechanism is most improbable for the acetate-catalyzed bromination of 2-butanone.

In view of the claims by Rappe[18-22,26,27] that the mechanisms for acetate-catalyzed bromination and deuterium exchange of 2-butanone are different and involve different regioselectivities under the same conditions, it was decided to investigate the bromination of this ketone in detail. Base-catalyzed halogenation of a ketone consumes one equivalent of base; therefore, the reaction is not strictly catalyzed, unlike exchange. Because we are comparing halogenation and exchange, it is convenient to waive the distinction.

The first experiments on the base-catalyzed bromination of 2-butanone were performed using hydroxide as base. However, the conditions used were too severe -- a large number of components other than the two

monobromoketones were observed by glpc. A blank run, with no bromine,

yielded the same results except for the absence of the bromoketones.

Most of the components probably resulted from condensation reactions

between 2-butanone and enolates; they were not identified. Because of

these results, the use of hydroxide as catalyst was abandoned in favour

of acetate.

It was decided to study the acetate-catalyzed bromination of 2-

butanone in a 1:1 acetic acid/acetate buffer at 54.8°. Rappe has shown[27]

that in this buffer, contribution to the observed rate constant k^{obsd}

by terms involving acid catalysis is essentially zero,

$$k^{obsd} = k_o + k_{\bar{O}Ac} [\bar{O}Ac] + k_{\bar{O}D} [\bar{O}D] + k_{D_3O^+} [D_3O^+] +$$

$$k_{HOAc} [HOAc] + k_{HOAc, \bar{O}Ac} [HOAc] [\bar{O}Ac]$$

and terms involving hydroxide catalysis are approximately 10^5-fold

lower in rate than those for total base catalysis. Bromination of

2-butanone under these conditions leads to a complex mixture of bromo-

ketones, bromoform, and two products of substitution, 3-acetoxy-2-butanone

and 1-acetoxy-2-butanone. The following compounds were isolated by

preparative glpc: 3-bromo-2-butanone (3-BrK), 1-bromo-2-butanone (1-BrK),

3-acetoxy-2-butanone (3-OAc), 1-acetoxy-2-butanone (1-OAc), 3,3-dibromo-

2-butanone (3,3-BrK), 1,1-dibromo-2-butanone (1,1-BrK), 1,1,1-tribromo-2-

butanone (1,1,1-BrK), 1,1,1,3-tetrabromo-2-butanone (1,1,1,3-BrK), and

bromoform. These nine compounds were identified by their nmr and mass spectra; all are reported in the literature.

Chart 1, p 60, contains the possible reaction products, with 2-butanone at the upper left. Reactions are indicated by arrows; those inside the large box consume bromine, while reactions leading outside do not. The compounds inside the boxes in full outline have been observed by the present author; those in dashed outline have not. It should be noted here that Rappe[18] reported observation of the former compounds with the exception of the two acetoxyketones (3-acetoxy-2-butanone was observed by Rappe in one experiment, bromination of 3-bromo-2-butanone[18]). It is strange indeed that these acetoxyketones were not observed by Rappe in the bromination experiments catalyzed by acetate. They were found by the present author in significant amounts (10-50%) in the acetate-catalyzed bromination of 2-butanone, 3-bromo-2-butanone, and 1-bromo-2-butanone.

The method used to follow the acetate-catalyzed bromination of 2-butanone was glpc. A detailed procedure is given in the Experimental section; it involved adding bromine to a flask containing the buffer solution and ketone at 54.8±0.04°, with stirring. When decolourization occurred, the reaction was quenched by adding the solution to ice water and extracting with carbon tetrachloride. After concentration of the solution, an analysis was performed on both an SE-30 and QF-1 column for relative yields. The retention times of all compounds were compared

THE ACETATE-CATALYZED BROMINATION OF 2-BUTANONE, POSSIBLE PRODUCTS
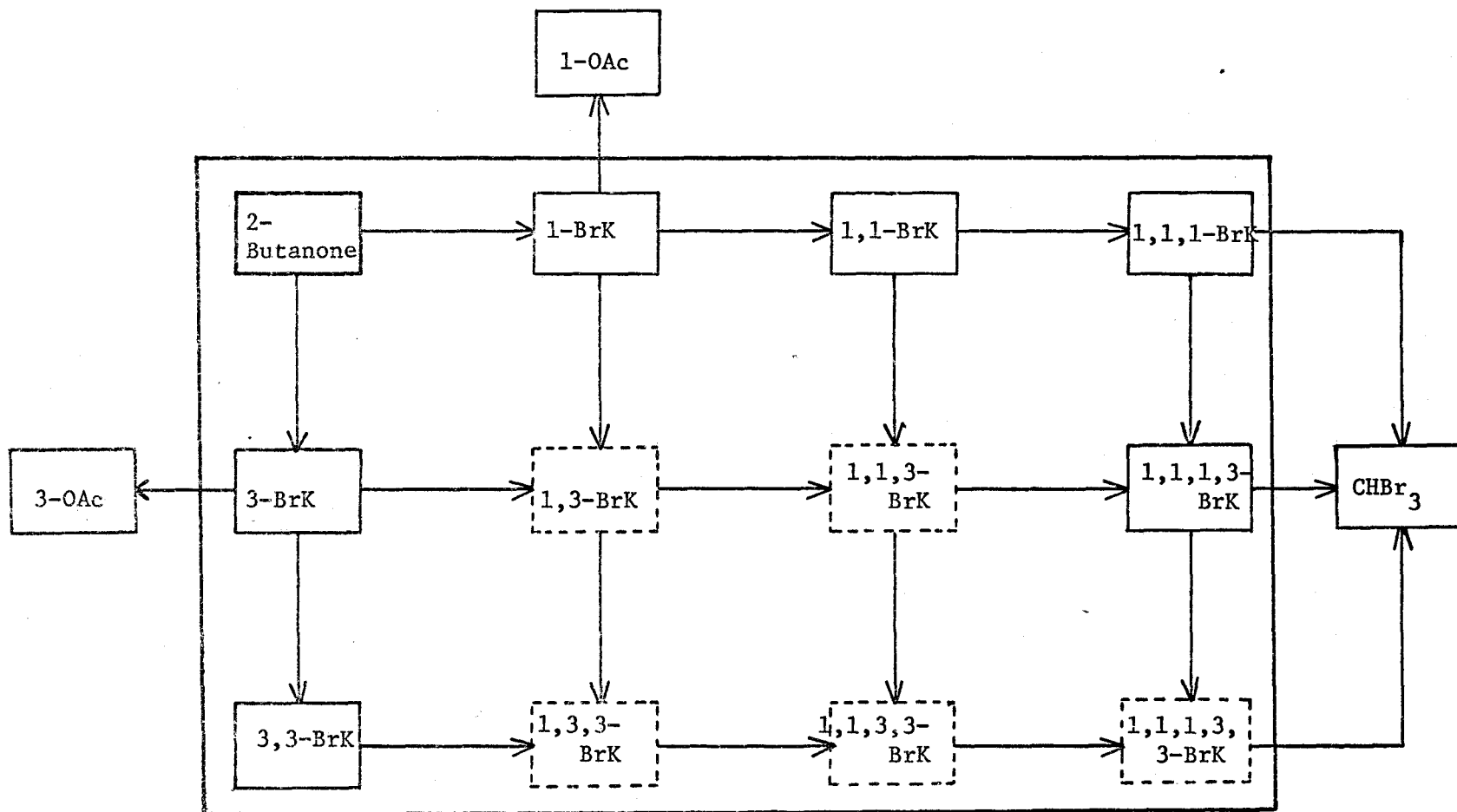
CHART 1

with those of the authentic samples. An electronic digital integrator was used to determine peak areas. Several injections were made for each sample, and the results were averaged. In all cases, the reproducibility of the integral areas was within 5%.

A rough materials balance was obtained as follows. A calibration constant for a given component was obtained by injecting different known volumes of a solution of known concentration, prepared by dissolving a weighed sample of the component in carbon tetrachloride. The constant related the integral peak area observed to the known molar quantity of material injected, for the different volumes injected showed that the calibration number was independent of sample size in the size range that was used. The peaks corresponding to the monobromoketones, the acetoxyketones, and bromoform were calibrated in this manner. Isomers gave the same detector response (same calibration constant), and the difference between the constants for acetoxyketones and bromocompounds was only 14%. The higher bromoketones were assigned the same factors as the monobromoketones. Knowledge of the volume of the solution containing the products from a bromination experiment permitted calculation of approximate concentration and yields. The material balance was based on bromine by assuming Avogadro's number of C-Br bonds in the reactions. Thus acetoxyketones were weighted as one because they arise from bromoketones, dibromoketones were weighted as two, and bromoform was given a weight of three. In a typical run the balance on Br was 90%. The small fraction of bromine

unaccounted for was probably in the form of bromoacids from the haloform reaction.

The relative yields in one run were (mole percent): 1-BrK, 10.7; 1-OAc, 12.9; 3-BrK, 15.8; 3-OAc, 14.2; 1,1-BrK, 5.7; 1,1,1-BrK, 17.1; 3,3-BrK, 1.4; 1,1,1,3-BrK, 5.9; and $CHBr_3$, 16.1

Because product composition was used to infer relative rates which were compared with deuterium exchange rates, it was necessary to be sure that the mechanisms were the same and that the method of analysis was not changing the product distribution in the mixture. To check for this, the following control experiments were performed.

First of all, samples of each bromoketone (six in all), the two acetoxyketones, and bromoform were injected separately onto an SE-30 column under the conditions used for analysis (see Experimental section). In each case a single peak was observed; it was collected in a capillary tube and subjected to mass spectral analysis. The isomeric compounds, *i.e.*, 3- and 1-BrK, 3,3- and 1,1-BrK, and the two acetoxyketones have the same parent peak but there are differences in their fragmentation patterns. Mass spectral analysis was thus used to check for isomerization, *e.g.*, 1-BrK $\longrightarrow$ 3-BrK and decomposition such as 2(1-BrK) $\longrightarrow$ MEK + 1,1-BrK. For example, 3-BrK has a characteristic doublet at m/e = 108 ($CHBrCH_3$), while 1-BrK has a characteristic doublet at m/e = 94 ($BrCH_2$). For 3,3-BrK and 1,1-BrK, characteristic triplets occur at m/e = 187 and 173, respectively. In each case the mass spectrum

was identical with that of an authentic sample, meaning that the chromatogram of the mixture from bromination gave a direct indication of the composition of the mixture.

Since the bromination results are to be compared directly with the exchange ratio under the same conditions, it was necessary to check for the major pathway followed by the reaction under these conditions, and that the mechanism did not change during the course of the reaction. First of all, a mixture of 2-butanone, water, and bromine was stirred at $54.8°$; the bromine colour disappeared only after several hours. The ratio of 3-bromination products : 1-bromination products was calculated (by glpc analysis) to be 2.9, which is similar to the value 2.7 reported[120] for the acid-catalyzed bromination of 2-butanone. Then the change in pH of the buffer solution during a bromination run was measured, where $[HOAc] = [\bar{O}Ac] = 0.610$ $\underline{M}$. The initial pH was 4.72; after the addition of 1.0×10^{-2} mole of bromine (0.10 $\underline{M}$) and decolourization, the pH had fallen to 4.60. This small change of 0.1 pH unit during the formation of 0.10 $\underline{M}$ HBr indicates that a change in mechanism during a bromination run in this medium is unlikely.

To ensure that the acetoxyketones could be used as indicators of their structurally-related bromoketones; *i.e.*, there is no isomerization or decomposition during the reaction, the following experiments were performed. A 50:50 mixture of 3-BrK and 1-BrK was refluxed in the

acetic acid/acetate buffer until 95% of the bromoketones had disappeared

By glpc and nmr, the only products observed were the two acetoxyketones,

in the same ratio as the starting materials. Another experiment showed

that these acetoxyketones were stable in the buffer solution - samples

of 3-OAc and 1-OAc were refluxed separately in the buffer solution for

several days, and no change occurred. It was also shown that only a

trace (<5%) of reaction products were left in the buffer solution after

the usual work-up, from an analysis of the aqueous layer. Because of

the problem in partitioning the polybromoketones into their initial sites

of bromination (see next section), both 1,1,1-BrK and 1,1,1,3-BrK were

placed in the buffer separately and stirred at 54.8° for 24 hours. It was

found that each was cleaved by acetate to bromoform within that time.

These results are contrary to those of Rappe[18], who found that 1,1,1-BrK

was not cleaved by acetate.

It should be mentioned that in the bromination of 3-BrK and 1-BrK,

1,2-dimethoxyethane (DME) was added to the buffer solution to keep the

organic level constant, and to ensure that the reaction medium was

homogeneous. Finally, several carbon tetrachloride solutions containing

the products from the bromination of 2-butanone, 3-BrK, and 1-BrK, were

analyzed several months after the initial analyses, and the results were

essentially the same by glpc. Thus the rates of decomposition of the

reaction products are very slow in carbon tetrachloride. The solutions

were normally kept at approximately 5° after work-up, and therefore

analyses did not require any adjustments for decomposition.

Calculation of the Rate Constant Ratio for the Acetate-Catalyzed Bromination of 2-Butanone

From an analysis of the product distribution from the acetate-catalyzed bromination of 2-butanone, it should be possible to calculate the ratio of the rate constants for initial bromination at the methylene group and initial attack at the methyl group. This selectivity of bromination would follow directly from the ratio of monobromoketones found, if these were the only products. It is not possible to keep the product mixture so simple, however. Even with a large ketone:bromine ratio (200:1), acetate-catalyzed bromination leads to a mixture of bromoketones, bromoform, and acetoxyketones, as described above. A rigorous determination of the regiochemistry of monobromination requires division of the haloform and the 1,1,1,3-tetrabromo-2-butanone yields into fractions arising from initial 3-bromination and 1-bromination. Rappe[18,20] attempted such division, somewhat arbitrarily, after examining the product distribution from separate bromination of the two monobromoketones. He estimated that 2/3 of the bromoform and 1,1,1,3-tetrabromo-2-butanone in his acetate-catalyzed reaction came from 3-bromo-2-butanone and 1/3 from 1-bromo-2-butanone.

Although Rappe did not use an equimolar acetic acid/sodium acetate buffer in any of his experiments, he did use buffer ratios of 0.028 and 0.28[20]. Reactions in these buffers are reported[27] to have no contributions

from acid catalysis. Some of Rappe's results[20] are given in Table X, p 67.

The ratio of 3-bromination:1-bromination was calculated on the basis

of his assumptions concerning the bromoform and 1,1,1,3-BrK partitioning.

This estimate may be seriously in error, at least if the ketone is present

in large excess. Under the conditions used by the present author (see

Experimental section), the two monobromoketones are formed at rates that

are nearly equal. The 1-bromo isomer, however, consumes an equivalent

of bromine about 5 times as fast as the 3-isomer under the conditions used

and must, therefore, be the major source of bromoform from 2-butanone itself

under similar conditions (if the latter is in excess). The fraction of

bromoform from each of the monobromoketones is very likely dependent on

the actual ketone:bromine ratio employed.

If the results in Table X, p 67, are re-evaluated by assigning

all the bromoform to an initial 1-bromination, the following values for

the 3-bromination:1-bromination ratio are obtained for experiments 3,6,7,8,

respectively: 3.4, 4.0, 5.4, and 3.4. This tends to support the hypothesis

that most of the bromoform arises from initial 1-halogenation; the values

are more precise and are closer to those observed by the present author

(*vide infra*) than those reported by Rappe[18,20].

In the present work, the ratio of monobromination rates of

2-butanone have been determined by two separate methods, one approximate

and one rigorous. If the ketone:bromine ratio is high, the yields of bromo-

form and of the polybromoketones can be kept relatively low. The approximate

TABLE X

Acetate-Catalyzed Bromination of 2-Butanone, Rappe's Results

Experiment[a]	[ŌAc],M	[HOAc],M	[HOAc]/[ŌAc]	[2-Butanone],M	[Br$_2$],M	3-Bromination/1-Bromination[b]	
3	0.87	0.024	0.028	0.58	0.072	6.8	(6.7)[c]
6	1.3	-	-	2.9	0.36	4.8	(5.2)
7	0.84	-	-	0.59	0.072	7.4	(7.0)
8	0.84	0.24	0.28	0.58	0.072	3.8	(3.8)

[a]Numbers refer to Rappe's experiments; concentrations calculated from his data.

[b]Calculated by Rappe, assuming 2/3 CHBr$_3$ from initial 3-halogenation, 1/3 from 1-halogenation.

[c]Numbers in parentheses calculated from Rappe's data; cause of discrepancy unknown.

method consists of determining the relative yields of monosubstitution

products 3-BrK, 3-OAc, 1-BrK, and 1-OAc, as described previously. The

rate constant ratio for the acetate-catalyzed bromination of 2-butanone

will be given approximately by the ratio (X) of the sum of the 3-mono-

products to the sum of the 1-monoproducts (equation 3). If X is near

unity and if the additional products constitute a minor fraction of the

$$X = \frac{3\text{-BrK} + 3\text{-OAc}}{1\text{-BrK} + 1\text{-OAc}} \qquad\qquad 3)$$

total, then X can not be very different from the ratio $2k_3/3k_1$ (equation

4), in which Y' and Y represent the yields of all other products arising

from 3-bromo-2-butanone and 1-bromo-2-butanone, respectively.

$$2k_3/3k_1 = \frac{3\text{-BrK} + 3\text{-OAc} + Y'}{1\text{-BrK} + 1\text{-OAc} + Y} \qquad\qquad 4)$$

The rate constants k_3 and k_1 refer to enolization rates to give

the 3-enol and the 1-enol, respectively, in 2-butanone. They are defined

on the *per hydrogen* basis as was done previously by Warkentin and

Barnett[121]. If one wished to estimate the initial ratio of the two

monobromoketones one would need to multiply the intrinsic (per H) reactivity

at a given site by the number of hydrogens at that site. Such concentration-

corrected values measure reactivity *prt group* and contain the sum of

chemical and statistical factors. If k_R^H is defined as the rate constant

per hydrogen in a group R containing n hydrogen atoms and if k_R is defined

as the rate constant *per group* then the relationship between the two measures of reactivity is given by the equation $k_R = nk_R^H$. Thus in equation 4, k_3 and k, are multiplied by the appropriate statistical factors.

Application of the approximations of equation 3 yielded the results in Table XI, p 70. The two columns shown for X are the ratios determined from two different glpc columns (see Experimental section). There is good agreement between the two sets of results, indicating that the peaks in the glpc traces are well resolved and are not composites from two or more unresolved components. From these data, the average value of X was calculated to be 1.26, and from equations 3 and 4, 3/2 X_{ave} = 1.89, which is approximately equal to k_3/k_1.

The second method is based on the kinetic model shown as Chart 2, p 71. As long as bromine is present, the reactions of Chart 2 are all possible, and the fraction of 1-BrK that goes on to 1-OAc is dependent only on the rate constants k_1', k_{11}, and k_{13}. By reacting 1-BrK with bromine under the conditions described previously, this fraction can be determined experimentally (eq. 5).

$$\frac{1\text{-OAc}}{\text{Initial 1-BrK}} = \frac{\text{Initial 1-BrK} - \text{Final 1-BrK}}{\text{Initial 1-BrK}} \quad X \quad \frac{k_1'}{k_1' + 2k_{13} + 2k_{11}} \qquad 5)$$

Thus by knowing the 1-OAc yield and the final amount of 1-BrK, the ratio of rate constants may be calculated. In 3-BrK, eq.6 is obtained by the same procedure.

TABLE XI

Ratio of Monosubstitution Products from 2-Butanone[a]

$[Br_2]$, M	Glpc	Column
	QF-1	SE-30
0.010	1.27	1.18
0.010	1.26	1.23
0.030	1.41	1.44
0.046	1.21	1.19
0.050	1.19	1.28
0.050	1.32	1.17
0.080	1.22	1.32
0.100	1.20	1.24

Average   1.26

$3/2 \ X_{ave.} = 1.89 \approx k_3/k_1$

[a] 2-Butanone (2M) in aqueous HOAc (1M) containing AcO^- (1M).

Chart 2

Acetate-Catalyzed Bromination of 2-Butanone, Kinetic Scheme

$$CH_3COCH_2CH_3 + \overset{-}{O}Ac$$

$$\xrightarrow{3k_1} \underset{OH}{CH_2 = \overset{|}{C}CH_2CH_3} \xrightarrow[\text{(fast)}]{Br_2} BrCH_2COCH_2CH_3$$

$$BrCH_2COCH_2CH_3 \xrightarrow[k_1']{\overset{-}{O}Ac} AcOCH_2COCH_2CH_3$$

$$BrCH_2COCH_2CH_3 \xrightarrow[\overset{-}{O}Ac]{2k_{11}} \underset{OH}{BrCH = \overset{|}{C}CH_2CH_3} \xrightarrow[\text{(fast)}]{Br_2} Br_2CHCOCH_2CH_3$$

$$BrCH_2COCH_2CH_3 \xrightarrow[2k_{13}]{\overset{-}{O}Ac} \underset{OH}{BrCH_2\overset{|}{C} = CHCH_3} \xrightarrow[\text{(fast)}]{Br_2} BrCH_2COCH(Br)CH_3$$

$$CH_3COCH_2CH_3 + \overset{-}{O}Ac \xrightarrow{2k_3} \underset{OH}{CH_3\overset{|}{C} = CHCH_3} \xrightarrow[\text{(fast)}]{Br_2} CH_3COCH(Br)CH_3$$

$$CH_3COCH(Br)CH_3 \xrightarrow[k_3']{\overset{-}{O}Ac} CH_3COCH(OAc)CH_3$$

$$CH_3COCH(Br)CH_3 \xrightarrow[\overset{-}{O}Ac]{3k_{31}} \underset{OH}{CH_2 = \overset{|}{C}-CH(Br)CH_3} \xrightarrow[\text{(fast)}]{Br_2} BrCH_2COCH(Br)CH_3$$

$$CH_3COCH(Br)CH_3 \xrightarrow[\overset{-}{O}Ac]{k_{33}} \underset{OH}{CH_3-\overset{|}{C} = C(Br)CH_3} \xrightarrow[\text{(fast)}]{Br_2} CH_3COC(Br)_2CH_3$$

$$\frac{\text{3-OAc}}{\text{Initial 3-BrK}} = \frac{\text{Initial 3-BrK} - \text{Final 3-BrK}}{\text{Initial 3-BrK}} \quad X \quad \frac{k_3'}{k_3' + 3k_{31} + k_{33}} \qquad 6)$$

By brominating the monobromoketones (either together or separately), under the same conditions as for the bromination of 2-butanone, the ratio of rate constants in equations 5 and 6 may be determined. The fractions of bromoketone reacted in these control experiments need not be the same as in the bromination of 2-butanone itself, as long as they are known. By dividing equation 5 by equation 6 and rearranging, the ratio of rate constants is given by equation 7.

$$\frac{k_3'(k_1'+2k_{13}+2k_{11})}{k_1'(k_3'+3k_{31}+k_{33})} = \frac{[\text{fraction reacted}]_1}{[\text{fraction reacted}]_3} \quad X \quad \frac{\text{3-OAc/Initial 3-BrK}}{\text{1-OAc/Initial 1-BrK}} \qquad 7)$$

When this ratio is determined, it may be applied to the bromination of 2-butanone, where the fraction reacted terms are different, and equation 8 can be used to calculate k_3/k_1 for the bromination of 2-butanone.

$$\frac{k_3}{k_1} = \frac{3[\text{3-OAc}]}{2[\text{1-OAc}]} \frac{[\text{fraction reacted}]_3}{[\text{fraction reacted}]_1} \quad X \quad \frac{k_3'(k_1'+2k_{13}+2k_{11})}{k_1'(k_3'+3k_{31}+k_{33})} \qquad 8)$$

The [fraction reacted] terms in equation 8 contain the unknowns of interest - the relative amounts of the two monobromoketones that were formed. Each is of the form T-R/T, where T stands for total formed and R stands for amount remaining at the time of analysis. The quantities T are not known but minimum values can be estimated from the yields of compounds identifiable as being derived from a given monobromoketone. Then for

conditions such that T>>R, the [fraction reacted] terms are essentially

unity and their ratio is unity also. It was possible to make this

approximation a very good one, with associated error smaller than 5%

(*vide infra*).

Experimentally, the ratio of rate constants in equation 7, p 72,

was determined by brominating a solution of 3-BrK and 1-BrK, in a 1:1

ratio, under conditions similar to those for the bromination of 2-butanone.

The conditions used were not identical, because 2-butanone had to be left

out to avoid changing the ratio of monobromoketones by synthesis. To

minimize the change in medium, 1,2-dimethoxyethane was added instead of

the ketone (see Experimental section). Two experiments were performed for

the bromination of the monobromoketones, and the results were used to

calculate $\dfrac{k_3'(k_1'+2k_{13}+2k_{11})}{k_1'(k_3'+3k_{31}+k_{33})}$ in the following manner.

The terms in equation 7, p 72, were determined by analyzing the

solutions, after decolorization of the bromine, on a calibrated glpc

column, where the peak integral areas are related to the number of moles

present by a constant (see Experimental section). This allows the

calculation of absolute percentage yields from the glpc traces. Thus for

one experiment, the yields were as follows: 3-BrK, 42.4; 3,3-BrK, 1.2;

3-OAc, 11.2; 1-BrK, 10.7; 1,1-BrK, 1.4; 1,1,1-BrK, 1.9; 1-OAc, 11.3; and

$CHBr_3$, 19.8. The fraction reacted for 3-BrK is then $\dfrac{100-42.4}{100} = 0.576$, and

for 1-BrK, $\dfrac{100-10.7}{100} = 0.893$. The yields of acetoxyketones (mole fractions)

were, for 3-OAc and 1-OAc, 0.112 and 0.113, respectively. When applied to

eq. 7, p 72, these factors gave 1.54 for $\dfrac{k_3'(k_1'+2k_{13}+2k_{11})}{k_1'(k_3'+3k_{31}+k_{33})}$.

In addition, the monobromoketones were brominated separately, to

determine the ratio of rate constants in eq. 7, p 72, by the same

procedure. However, the agreement was not good; the ratio was calculated

to be 3.24. The reason for the lack of agreement is not clear, but the

value obtained by brominating the monobromoketones together is probably

the better one, since the dilution factors are the same.

Fraction reacted terms can be determined in the same manner for

the bromination of 2-butanone. Thus in one experiment, 1.23% 1-BrK and

1.05% 3-BrK were left after decolorization of the bromine. Assigning

all of the $CHBr_3$ and 1,1,1,3-BrK to 1-BrK, the [fraction reacted]$_1$ term

is $\dfrac{77.2-1.23}{77.2}$ = 0.984 and the [fraction reacted]$_3$ term is $\dfrac{22.8-1.05}{22.8}$ =

0.954. If the 1,1,1,3-BrK is assigned to 3-BrK and the $CHBr_3$ to 1-BrK,

the factors become

$$\dfrac{68.1-1.23}{68.1} = 0.982 \text{ and } \dfrac{31.9-1.05}{31.9} = 0.970, \text{respectively.}$$

Thus when the amount of monobromoketone remaining is low, it does not

matter how the $CHBr_3$ and 1,1,1,3-BrK are assigned. In addition, these

results imply a precision that is probably outside the capability of the

method. It appears therefore that the [fraction reacted] terms for both

bromoketones are close to one and thus their ratio is very close to unity. The probable deviation of this ratio from unity is about 7 per cent, from these results. This error is indicative of the errors associated with this method of analysis, involving glpc areas and calibrations.

A 100% materials balance is not necessary for this approach if the amount of monobromoketone left after the bromine has disappeared in the bromination of 2-butanone is small. In these experiments the mono-bromoketones represent less than 5% of the identified products from them. Thus if they are less than 5% of the identified products, then they must be an even smaller fraction of the total products from the monobromoketones.

These results are summarized in Table XII, p 76, and were used to calculate k_3/k_1 for the acetate-catalyzed bromination of 2-butanone, according to equation 8, p 72. From two determinations of k_3/k_1, the average value was calculated to be 1.69 ± 0.05. The actual error is probably of the order of 10%.

In conclusion, the rate constant ratio for the acetate-catalyzed bromination of 2-butanone, based on an assumed enolization mechanism and product analysis, is about 1.9 and 1.7, respectively, by the approximate and rigorous methods described above. It is important to note that the higher value of k_3/k_1 from the approximate method means that Y>Y' in equation 4, p 68. That is, more of the bromoform and 1,3-polybromoketones came from 1-BrK than from 3-BrK. This confirms the evidence discussed on p 66 concerning the rate of consumption of bromine by the two monobromoketones.

TABLE XII

Acetate-Catalyzed Bromination of 2-Butanone at 54.8°

| Reactants | [Fraction Reacted]$_3$ | [Fraction Reacted]$_1$ | Mole Fractions | | $\dfrac{k_3'(k_1'+2k_{13}+2k_{11})}{k_1'(k_3'+3k_{31}+k_{33})}$ [a] | k_3/k_1 [b] |
			3-OAc	1-OAc		(bromination)
3-BrK, 1-BrK	0.576	0.893	0.112	0.113	1.54	
3-BrK, 1-BrK	0.683	0.920	0.264	0.232	1.53	
2-Butanone	1.0	1.0	0.140	0.185		1.74
2-Butanone	1.0	1.0	0.136	0.191		1.64

[a] Calculated from eq. 7, obtained by brominating the monobromoketones

[b] Calculated from eq. 8, using the average value of the ratio of rate constants in a.

The Relative Rates of Acetate-Catalyzed Deuterium Exchange of 2-Butanone

In order to compare the results obtained in the acetate-catalyzed bromination of 2-butanone (k_3/k_1 = 1.7-1.9, previous section) with the relative rates of deuterium exchange at the two sites in 2-butanone, it was necessary to repeat the exchange work of Warkentin and coworkers[1,29,30], using the conditions that were used for the bromination work. Rates of hydrogen isotope exchange in 2-butanone can be estimated readily by nmr analysis, to yield the reactivity ratios, $k^H_{CH_2}/k^H_{CH_3}$, defined on the *per hydrogen* basis[121]. This ratio for acetate catalysis has been determined by Warkentin and Tee[1,29] to be 2.16 ± 0.36 at 59.2° and by Warkentin and Cox[30] to be 1.90 ± 0.17 at 54.8°; numbers which are in agreement within experimental error. Rappe, on the other hand, reported[122] a value of 1.2 at 54.8°.

The experimental techniques for using nmr spectroscopy to determine the ratio $k^H_{CH_2}/k^H_{CH_3}$ are described in the Experimental section. Briefly, a buffer solution of acetic acid and sodium acetate (0.832 $\underline{M}$ in each) in D_2O was made up, in which the ketone concentration was 2.00 $\underline{M}$. Samples of this buffer were sealed into nmr tubes and placed in a bath kept at 54.8 ± 0.04°, along with a tube containing 2-butanone in D_2O without catalyzing species. The initial ratio of deuterium to exchangeable hydrogen was approximately 8:1. Analyses were performed on a Varian A-60 nmr instrument at appropriate intervals, integrating the signals from the

1- and 3- positions of 2-butanone, relative to that of the non-exchanging

β-methyl group as internal standard. This procedure was repeated using a

buffer in which the acetic acid and acetate concentrations were each

0.610 $\underline{M}$. In this case, the analyses were performed on a Varian T-60

instrument.

Rappe has criticized[122] the use of undeuterated acetic acid and

sodium acetate as a buffer medium for these exchange studies by nmr. He

claims[122] that the methyl signals from the buffer components are very

close to the methyl singlet of 2-butanone, resulting in overlap as

exchange progresses and difficulty in estimating the rate of methyl

deuteration. However, the present author has found that there is no such

interference from the buffer components under the conditions used, namely,

a 1:1 acetic acid/acetate buffer. The following data, for exchange in a

0.610 $\underline{M}$ buffer, obtained with a Varian T-60 nmr spectrometer support this

statement.

The nmr data for a sample kept at 0°C (t=0) were the following:

δ 2.48 (q, 2, J=7.35 Hz[28], C$\underline{H}_2$CH$_3$), 2.12 (s, 3, C$\underline{H}_3$CO), 1.92 (s, C$\underline{H}_3$CO,

buffer components), and 0.98 (t, 3, J=7.35 Hz[28], CH$_2$C$\underline{H}_3$). As the α- and

α'- protons in 2-butanone are replaced by deuterium, the nmr spectrum

changes in several ways. First of all, the lines are broadened as exchange

progresses; the methylene envelope was widened by 7 Hz at 50% exchange (~12

days), while the α'-CH$_3$ signal was broadened by 5 Hz at 50% deuteration

(~20 days). At 50% deuteration, there are two superimposed spectra for

the β-CH$_3$ protons – the original triplet from molecules still possessing

–CH$_2$CH$_3$, and a pair of triplets arising from an adjacent –CHD group.

Tee and Warkentin reported[28] $J_{H\alpha H\beta}$ = 7.25 Hz and $J_{D\alpha H\beta}$ = 1.0-1.1 Hz. At

50% exchange, the α'-CH$_3$ spectrum shows a triplet of –CH$_2$D and a quintet

of –CHD$_2$, superimposed. The methylene spectrum at 50% deuteration shows

each absorption of the original quartet split into a triplet, due to the

presence of –CHD in the molecule.

Another phenomenon caused by exchange is a shift of each signal

upfield from its position at t = 0. The methylene envelope was observed

to have shifted 1.0 Hz upfield at 50% exchange, the α'-CH$_3$ absorption

shifted 1.5 Hz, while the β-CH$_3$ envelope moved approximately 0.5 Hz upfield

at 50% deuteration.

The original signal widths measured from a spectrum recorded at

250 Hz sweep width, where 1 mm (chart) = 1 Hz were :CH$_2$ envelope, 26 Hz;

separated by 5.5 Hz from the α'-CH$_3$ signal, 6 Hz; in turn separated by

6Hz from the CH$_3$ signal from the buffer components, 5.5 Hz. At 50%

exchange for the CH$_2$ group, the following signal widths were recorded:

CH$_2$ envelope 33 Hz; separation of 2.5 Hz; α'-CH$_3$ signal, width 8 Hz;

separation of 4.5 Hz; buffer signal 5.5 Hz. After 50% exchange of the

α'-CH$_3$ group, the widths were: CH$_2$ envelope 34 Hz; separation of 2 Hz;

α'-CH$_3$ signal, width 11 Hz; separation of 2 Hz; buffer signal 5.5 Hz.

The β-CH$_3$ signal used as internal standard was removed from the other

signals,being at 0.98 δ.

From the line widths given above, it can be seen that there was no overlap between the α'-CH_3 signal and the CH_3 signal from the buffer components observed at any time during the exchange process. The minimum separation observed was 2 Hz, which was equal to 2 mm on the chart paper; the corresponding integral traces had good inflection points. Also, a further precaution was taken - three integrations were performed in each direction, and an average value was taken. Thus the integral areas recorded for the α'-CH_3 signal were, at least to one half-life, indicative of the number of protons remaining in that group per molecule, after correction by the internal standard. Rappe's assertion[122] that the use of undeuterated acetic acid and sodium acetate leads to an erroneous value of the rate of methyl deuteration in 2-butanone is not correct, at least for the conditions used by the present author. Overlap may occur under some conditions; the position of the methyl signals from the buffer components is surely dependent on the buffer ratio.

Observed rate constants were obtained from pseudo first-order plots of log I_t against time, where I_t is the normalized integral of a given signal at time t. Straight lines were obtained, the slopes of which agreed with computer-fitted values to 3% or better (see Appendix I, p 189). An example of a rate plot with buffer concentration 0.610 $\underline{M}$ is given in Figure 1, p 81. Pseudo first-order rate constants and their standard deviations obtained were: $k_{CH_3}^{obsd}$ = 6.85 ± 0.16 x 10^{-7} sec^{-1}, $k_{CH_2}^{obsd}$ =

FIGURE 1

Deuterium Exchange of 2-Butanone, Buffer Concentration 0.610 M.
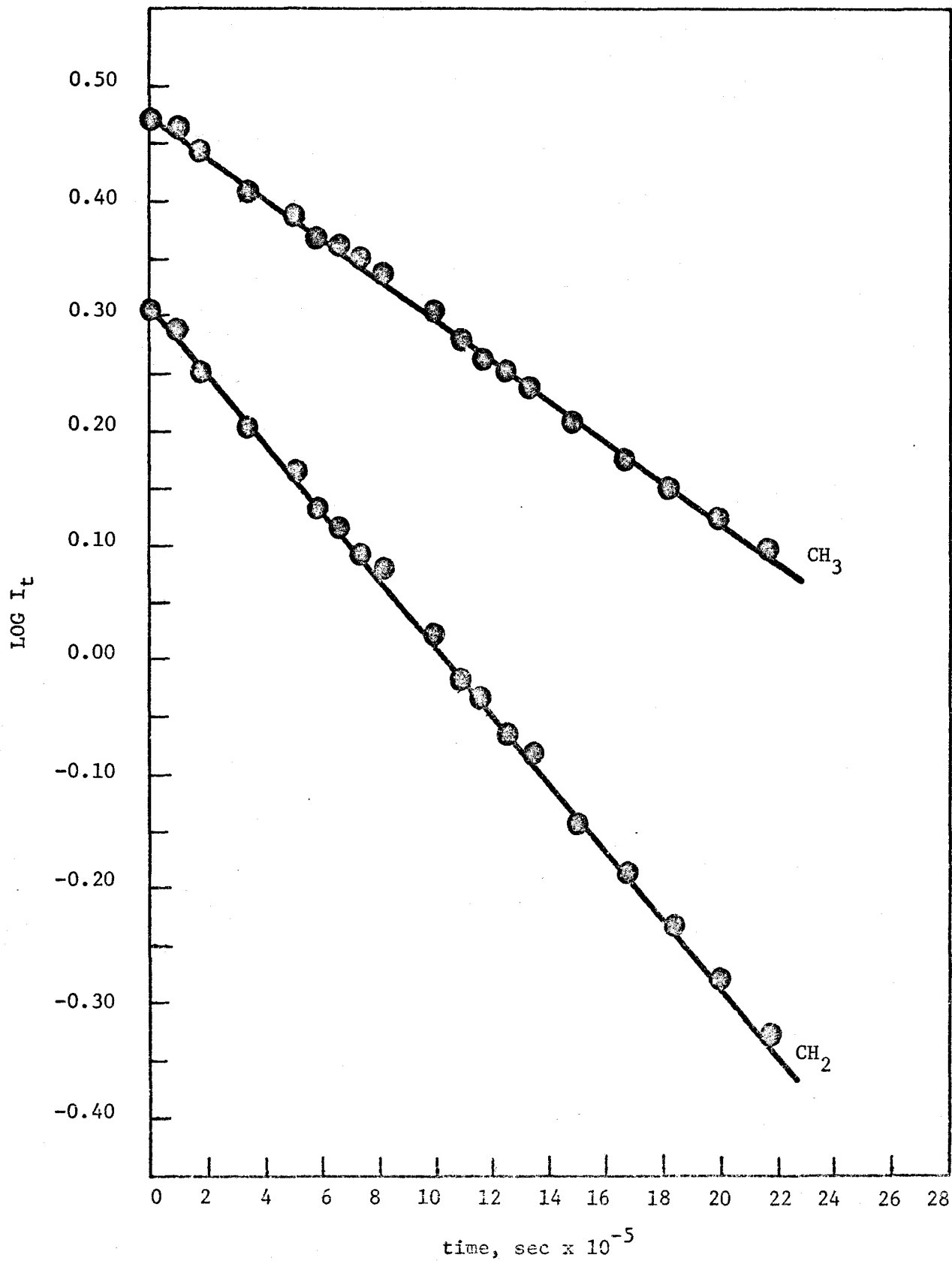
$11.64 \pm 0.44 \times 10^{-7}$ sec^{-1} for a buffer concentration of 0.832 $\underline{M}$; $k_{CH_3}^{obsd} = 4.10 \pm 0.13 \times 10^{-7}$ sec^{-1}, $k_{CH_2}^{obsd} = 6.89 \pm 0.28 \times 10^{-7}$ sec^{-1} for a buffer concentration of 0.610 $\underline{M}$. These rate constants give $k_{CH_2}^{H}/k_{CH_3}^{H} =$ 1.70 $\pm$ 0.11 and 1.68 $\pm$ 0.12, respectively. The errors given are indicative only of the quality of the fit to pseudo first-order kinetics and of the probable reliability of rate ratios from a given run. Absolute values of rate constants are much less certain; errors in concentration and temperature would cancel out in the ratio. In these two experiments, the second-order rate constants are 8.23 $\times 10^{-7}$ $\underline{M}^{-1}$ sec^{-1} and 6.73 $\times 10^{-7}$ $\underline{M}^{-1}$ sec^{-1} for exchange at the methyl group, and 14.0 $\times 10^{-7}$ $\underline{M}^{-1}$ sec^{-1} and 11.3 $\times 10^{-7}$ $\underline{M}^{-1}$ sec^{-1} for exchange at the methylene group. These rate constants for a given site differ by approximately 20%.

In conclusion, the values of $k_{CH_2}^{H}/k_{CH_3}^{H}$ (K_D) determined from this work (1.70, 1.68) are in good agreement with the results of Warkentin and Cox[30], who found K_D = 1.90 at 54.8°. The value reported by Warkentin and Tee[29] at 59.2° was 2.2, indicating either that 4.4° makes a large difference in K_D, or that the value of 2.2 is in error. The temperature dependence for deuteroxide catalysis was shown to be small[2], less than the average experimental error and is probably small for acetate catalysis as well. Thus the value of 2.2 seems too large until the error limits are considered. The actual value reported[29] was 2.16 $\pm$ 0.36, which has an error 2-3 times that of Warkentin and Cox[30] and the present author. Taking the error limits into account, these four values of K_D are in agreement, and that a

temperature difference of 4° can probably be neglected. The excellent

agreement found by the present author using two different nmr spectro-

meters seems to indicate that there are no large errors associated with

a particular nmr instrument.

It seems that the dependence of the rate ratio on buffer ratio

is also small. The four values reported above are for widely different

buffer systems, ranging from no acetic acid in the experiments of

Warkentin and Tee[29] to a 1:1 buffer in the present work.

Rappe performed deuteration experiments on 2-butanone in an

acetic acid/acetate buffer near 55°[20,122] and obtained an average value

of 1.13 for K_D. His average rate ratios are much smaller than those

reported by Warkentin and coworkers[29.30,123], and the present author

cannot explain this discrepancy.

General Conclusions

The average of the ratio of observed rate constants, $k_{CH_2}^{obsd}/k_{CH_3}^{obsd}$,

which is equal to the ratio of the rate constants, k_3/k_1 (for exchange)

defined on the *per hydrogen* basis, was 1.69 at 54.8°. It appears that

the rate ratio for deuterium exchange of 2-butanone can be equated with

the rate ratio for enolization. Although Rappe has claimed[20,122] that

the ratio does not depend on the base employed and that its magnitude

(on the *per hydrogen* basis)is near unity, he has not challenged the long-

accepted mechanism of exchange. The mechanism appears to have universal

acceptance as involving an enol or enolate intermediate. It has been shown[30,123], in fact, that direct reaction between D_2O and 2-butanone is immeasurably slow. It is very probable then that the ratio of enolization rate constants, k_3/k_1, for the acetate-catalyzed reaction of 2-butanone is near 1.7 at $54.8°$.

The rate constant ratio for acetate-catalyzed bromination has been found to be between 1.7 and 1.9 from the work discussed above, under conditions identical to those for the exchange work. This excellent agreement means that, contrary to the claims of Rappe[18-21], the product composition in the bromination of 2-butanone is completely compatible with an enolization mechanism. Although direct reaction between bromine and ketone may occur under other conditions, it seems preferable to retain the enolization mechanism generally, unless there is compelling evidence against its applicability.

II. Nucleophilic Displacement Reactions of α-Haloketones

Introduction

The α-halocarbonyl compounds are among the few substrates for bimolecular nucleophilic displacement reactions that are more reactive than their unhindered primary aliphatic counterparts[32]. This enhanced reactivity is dramatically illustrated by α-chloroacetophenone, which reacts with potassium iodide in acetone at 50° some 97,000 times faster than n-propyl chloride[35]. Compounds containing the PhCO group and its ring-substituted analogs exhibit the largest accelerations (relative to n-propyl chloride) reported for any S_N2 reaction[35, 124], with compounds containing electron-withdrawing substituents reacting faster than unsubstituted compounds. For example, p-$O_2NC_6H_4COCH_2Cl$ reacts nearly 11 times faster than $PhCOCH_2Cl$ with iodide in acetone at 0°[35].

The source of the increased reactivity of these compounds is still a matter of debate, as can be seen from the Historical Introduction. A stabilizing interaction between the nucleophile, the leaving group, and the carbonyl group in the transition state can be justified by molecular orbital calculations[32(a)] and on stereochemical grounds[41], although steric effects may be important[124].

One mechanism that has received some consideration[34] is based on the assumption that the reaction is not a typical $S_N 2$ reaction, but that it is actually a multistep process in which the nucleophile first adds to the carbonyl group. The resulting ion then undergoes an internal displacement to yield an intermediate epoxide which reacts with a nucleophile from the medium to give the observed product. This mechanism has been shown not to be a general one by Pearson and coworkers[34] and by Lutz[67].

The mechanism that has gained the most support is the neighbouring group orbital overlap mechanism of Winstein and Dewar[39-41]. This mechanism is discussed in detail in the Historical Introduction. Pearson stated[34] that the available evidence was accommodated by an electrostatic model, provided that the orientation of the carbonyl dipole with respect to the direction of approach of the nucleophile is given consideration. He suggested[34] that if the nucleophilic reagent approaches from the direction of the positive end of the carbonyl dipole, displacement will be assisted most effectively. However, it is the present author's opinion that the results of Sisti and Lowell[68] do not support Pearson's mechanism, in that the rate enhancements observed in displacement of halide by various charged nucleophiles from chloroacetone and chloroacetophenone depended more on the orbital size of the nucleophiles than on their charge or polarizability.

The enhancements observed[68] with all the nucleophiles are probably
due to additional covalent bonding with the carbonyl carbon in the
transition state.

Although there are many reports in the literature on the
displacement reactions of α-haloketones, there is very little data
on the effects of increasing substitution at the α- and α'-positions
on the rates of halide displacement. This is an important point,
since the orbital overlap mechanism predicts that substitution at
both sites would affect the bonding between the nucleophile, carbonyl
carbon and α-carbon atoms at the transition state. Reeve and coworkers
reported[73] that replacing the α-hydrogen by methyl in $PhCOCHClCH_3$ caused
a 2000-fold reduction in rate on reaction with iodide ion, whereas
Karavan and Temnikova[70] found that a similar structural change in
PhCOCHBrPh reduced the rate of reaction with methoxide by only 9-fold.
Fierens[118] found that in the displacement of chloride by iodide ion
in acetone from the series $CH_3COCHClR$, where R = Me, Et, i-Pr, and t-Bu,
a rate retardation of approximately 10^5-fold was observed on going from
R = Me to R = t-Bu.

Since the above literature data is somewhat sketchy with regard
to the effects of substitution on both sides of the carbonyl group in
displacement reactions of α-haloketones, it was decided to study the
displacement reactions of a series of α-bromo- and α-chloroketones with
varying steric requirements at the α- and α'- positions. The effect of

substitution at each position might shed more light on the nature of the transition state for the displacement reactions of α-haloketones. In addition to this probe for the steric requirements, it was necessary to construct a model system to probe for the stereoelectronic requirements of this reaction. The model system chosen was better than that of Bartlett and Trachtenberg[41], whose system suffered from the disadvantage of containing one cyclic and one acyclic compound.

Definition of the System

Two series of α-haloketones were prepared, one substituted at the α'-position (1-haloketones), and the other substituted at the α-position (3-haloketones). They are listed in Table XIII, p 89. These compounds have all been reported in the literature and were prepared by standard methods (see Experimental section). They were purified by preparative-scale gas chromatography. Although this procedure was very time-consuming (some compounds had to be chromatographed twice), the purity achieved in all cases was greater than 98%, by nmr analysis. It was observed that the stability of the pure haloketones was much improved by the addition of a trace of magnesium oxide to the sealed sample kept in a refrigerator.

The solvent system employed in the kinetic experiments on these haloketones was the following: 1.00 M in acetic acid and sodium acetate, 24.0 ml of 1,2-dimethoxyethane (DME), and water to 100 ml.

TABLE XIII

α-Haloketones Prepared for Study of Substituent Effects on

Displacement of Halide. X = Br and Cl

3-Haloketones	1-Haloketones
$CH_3CHXCOCH_3$	CH_3COCH_2X
$(CH_3)_2CXCOCH_3$	$CH_3CH_2COCH_2X$
$CH_3CH_2CHXCOCH_3$	$(CH_3)_2CHCOCH_2X$
$(CH_3)_2CHCHXCOCH_3$	$(CH_3)_3CCOCH_2X$
$(CH_3)_3CCHXCOCH_3$	$CH_3CH_2CH_2COCH_2X$
	$(CH_3)_2CHCH_2COCH_2X$
	$(CH_3)_3CCH_2COCH_2X$
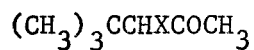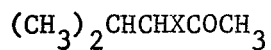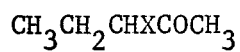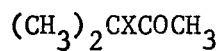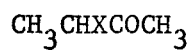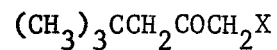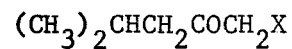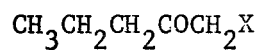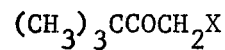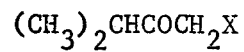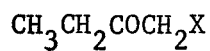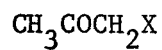
The DME was added to increase the solubility of the haloketone in the buffer solution. Since the maximum concentration of haloketone used in these experiments was 1 g/l, it is very unlikely that the system was non-homogeneous. However, to ensure that the haloketones were indeed soluble, each experiment was repeated, changing the haloketone concentration. The concentration of haloketone was reduced by a factor of four to ensure that the rate-determining step of halide ion formation is displacement by acetate rather than dissolution of haloketone in the medium. If the haloketone was not soluble in the medium, the rate of displacement of halide might be determined by the rate constant k_1 rather than by k_2:

$$\text{Haloketone (globule)} \xrightarrow{\ k_1\ } \text{Haloketone (solution)} \xrightarrow[\text{fast}]{\ k_2\ } X^-$$
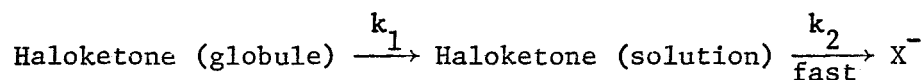
The rate of solution of the haloketone (given by k_1) would be a function of the surface area of the undissolved globule, which is a function of the quantity of α-haloketone present. Even though the halide ion electrode would be measuring the rate of displacement of halide by acetate, this rate would be determined by the rate of dissolution of haloketone in the medium. Thus, if the concentration of haloketone were reduced, the rate constant obtained for the displacement of halide would be lower. In this work, the rates of displacement did not depend on the concentration of haloketone, as required if the haloketone is soluble in the medium. Another piece of evidence for solubility of the haloketones is a visual one - it was found that a very few milligrams of haloketone insoluble in

water are visible as globules at the bottom of the flask; the refractive indices are different enough to permit this observation. This phenomenon was not observed in any of the kinetic experiments.

As described in the Experimental section, each kinetic run was analyzed for products by glpc. The aqueous solution was extracted with carbon tetrachloride, and the combined extracts were subjected to glpc analysis, collecting each component. At least two different stationary phases were used to detect any components that might not have been resolved on a given stationary phase. Each component was then analyzed by nmr to determine its identity and/or purity. For the displacement of bromide with acetate from the α-bromoketones, only one product was observed, namely, the α-acetoxyketone, in all cases except for two compounds. These exceptions were 3-bromo-3-methyl-2-butanone, and 1-bromo-3-methyl-2-butanone. The results obtained from these two compounds will be discussed in the last section of the Discussion. With azide as nucleophile, only one product was observed and was identified from its nmr spectrum in each case to be the α-azidoketone. The only difference in the nmr of the product compared to the starting material was in the chemical shifts caused by the presence of a different α-substituent. The cyclohexyl chlorides went cleanly - one product was found in each case corresponding to inversion at the reaction site. Products from elimination reactions were not observed by nmr. Similar results were obtained with the chlorocyclohexanones; the product in each

case was the α-acetoxyketone with inverted configuration at the α-
position compared with starting material. This is discussed in more
detail in the Experimental section.

The Method Used to Follow the Displacement of Halide

The rates of displacement of halide from these haloketones
by acetate were originally determined by monitoring the reaction by
glpc. Aliquots were taken at appropriate intervals, chilled in ice
water to stop the reaction, and extracted with carbon tetrachloride.
The combined extracts were then dried, and most of the solvent was
removed. Analysis of the residue by glpc was used to follow the
disappearance of starting material. However, the results were not
satisfactory; the reproducibility was poor, and there were losses
during work-up as evidenced by yields which were less than quantitative
by glpc. Thus, a better method of analysis was sought; the method
adopted was based on the specific ion electrode.

These electrodes, which are similar in characteristics to the
glass electrode, are commercially available (see Experimental section
and Appendix II). Electrodes specific to several anions are available,
including fluoride, chloride, bromide, iodide, cyanide, and nitrate.
They may be used to measure the activity of the ion in solution and the
concentration if a calibration curve is determined in the solvent
system employed. Thus, in this work bromide and chloride ion electrodes

were used to follow the displacement of the halide from the bromo- and chloroketones, respectively. The electrodes were shown to be compatible with the acetic acid/acetate buffer in control experiments.

Each electrode was calibrated by measuring the potentials of solutions containing known amounts of halide ion in the buffer solution. The bromide ion electrode was used in conjunction with a saturated calomel electrode and was used in the range 1.0×10^{-5} to 3.5×10^{-3} $\underline{M}$ in Br^-. The chloride ion electrode could not be used with the calomel electrode, since chloride ion leaking from this electrode would contaminate the solution. Instead, a double-junction reference electrode was used, which has a KNO_3 solution in contact with the solution whose potential is to be measured. The chloride ion electrode was used in the range 1.0×10^{-4} to 1.0×10^{-2} $\underline{M}$ in Cl^-. Calibration curves for the bromide ion and chloride ion electrodes are given in Figure 2, p 94, and Figure 3, p 95 , respectively. In addition, a 1mV recorder was calibrated for bromide ion concentration; this was used with some of the kinetic experiments with short half-lives (<20 min). This curve is shown in Figure 4, p 96. It was observed that the characteristics of the bromide ion electrode did not change appreciably with time; the calibration curve obtained after 6 months was almost identical to the original one. However, the chloride ion electrode was not as stable; it had to be re-calibrated every month or so.

FIGURE 2

94

Calibration Curve for the Bromide Ion Electrode

$[Br^-]_t$, $\underline{M}$

Electrode Potential, mV

FIGURE 3

95
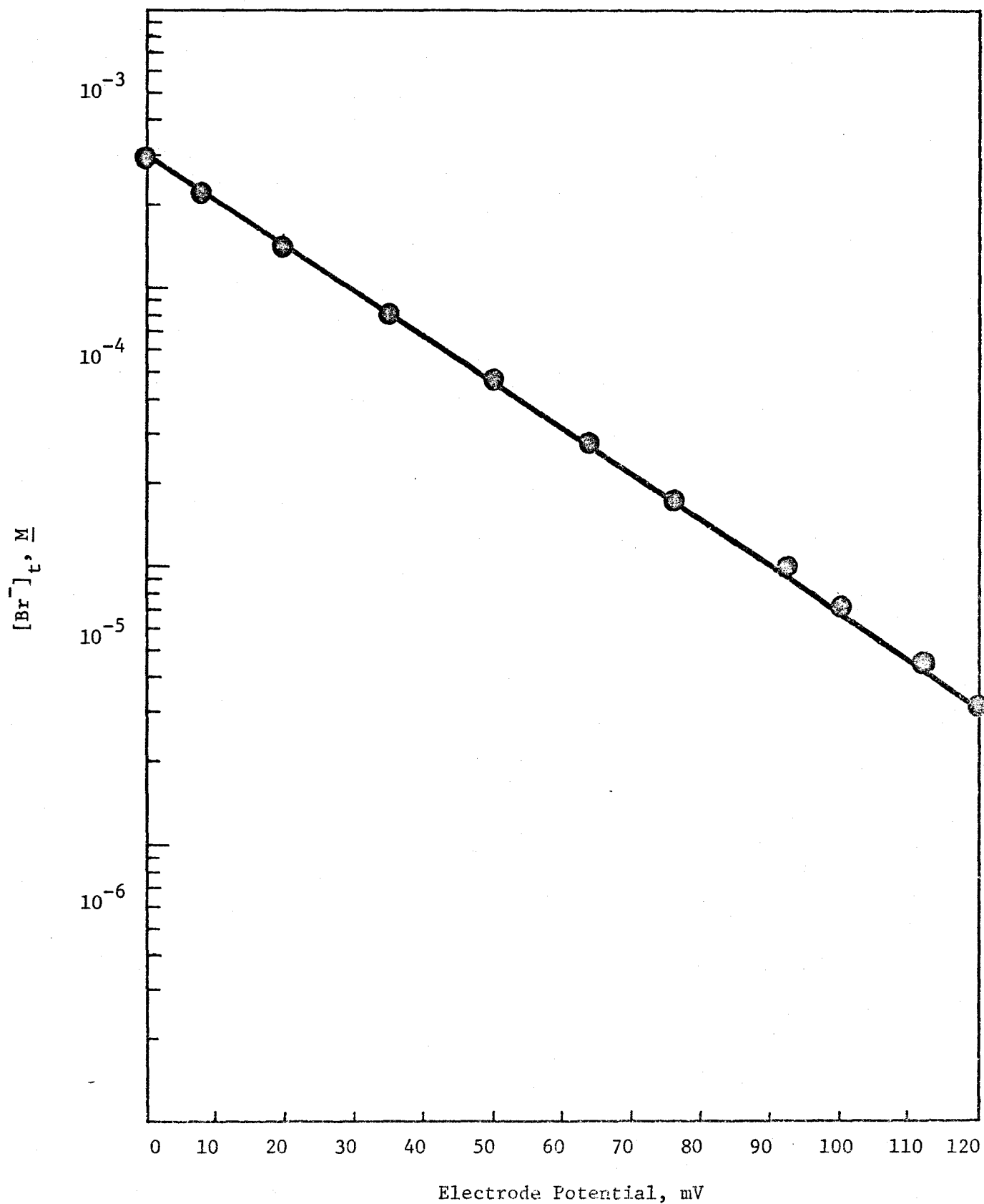
Calibration Curve for the Chloride Ion Electrode

Electrode Potential, mV

FIGURE 4

Calibration Curve for the Glpc Recorder

Recorder Reading, Chart Divisions
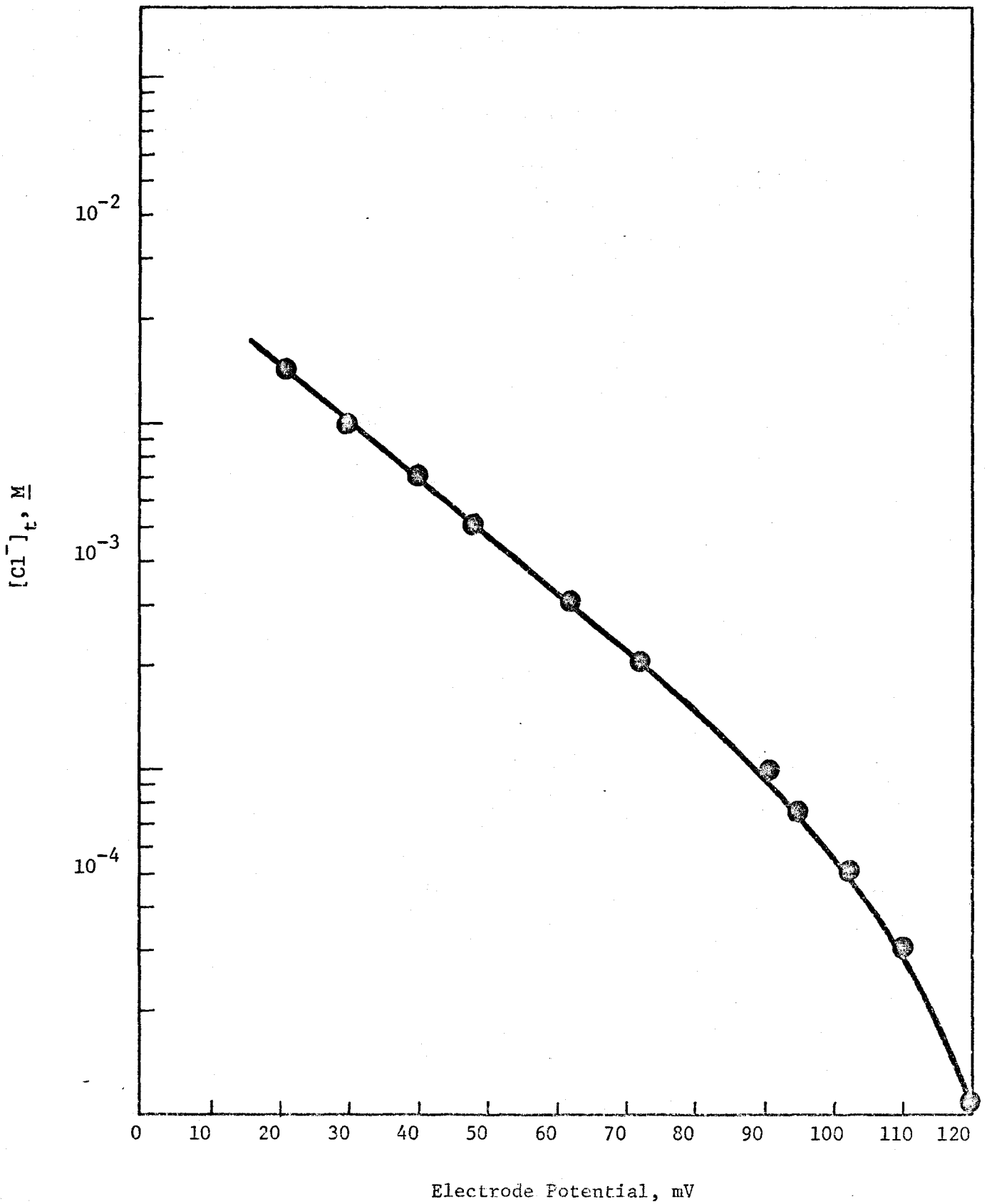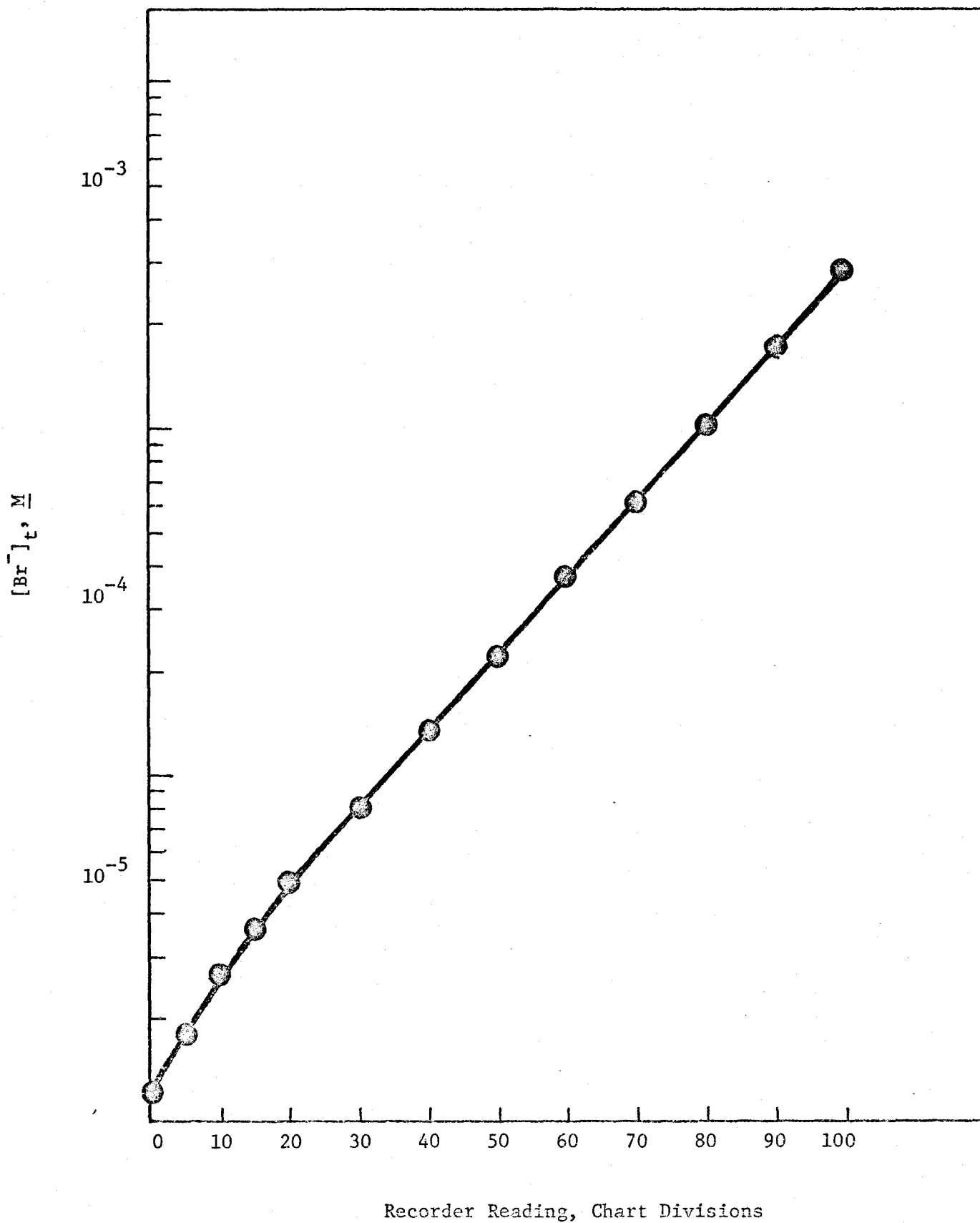
Briefly, the kinetic procedure used is as follows. The buffer solution was placed in a water bath kept at 54.8 ± 0.04° and stirred. After the electrodes were placed in the flask, the system was allowed to equilibrate for 20 min. Then the expanded scale pH meter, used to read the potential of the solution, was switched to the expanded scale millivolt position (140-0mV), and the recorder was started if necessary. The haloketone (previously weighed out in a 100 μl syringe) was added to the solution as a stop-watch was started. Potential readings were then taken at appropriate intervals until 2-3 half-lives of the reaction had elapsed. An infinity point was usually obtained by allowing the reaction to proceed until 7-8 half-lives (>99%) had elapsed. The solution was analyzed for products as described in the Experimental section.

As was mentioned above, each experiment was repeated at least once and usually twice, to ensure that the haloketone was soluble in the medium and that the reaction was first-order in acetate. In all cases, the second-order rate constants calculated for displacement of halide from the α-haloketones agreed to within 5%, including experiments where the acetate concentration was changed to 0.5 $\underline{M}$.

Since the acetate concentration in these experiments changes by a maximum of 1% during the run, the reaction may be treated as following pseudo first-order kinetics. As described in detail in the Experimental section, the following relationship applies:

$$\log \left\{ [X^-]_\infty - [X^-]_t \right\} = - \frac{k}{2.303} t + \log [X^-]_\infty$$

Thus a plot of log $\left\{ [X^-]_\infty - [X^-]_t \right\}$ against time should yield a straight line of slope $-\dfrac{k}{2.303}$ and intercept log $[X^-]_\infty$. The first-order rate constant obtained can then be converted into a second-order rate constant by dividing by the acetate concentration, which was 1.00 $\underline{M}$ in these experiments. Typical plots for the reaction of 1-bromo-4-methyl-2-pentanone and for chloroacetone with acetate, are shown in Figures 5, p 99, and 6, p 100, respectively. These plots show the degree of scatter that was observed in most of the experiments.

A number that is very critical to the slope of each graph is the value of $[X^-]_\infty$, the concentration of halide ion at infinity, which should be equal to the initial concentration of haloketone. In most cases it was possible to obtain a value which was very close to $[X^-]_\infty$ (after 8 half-lives). The agreement between the measured infinity value of the halide ion concentration and the amount of haloketone weighed into the reaction flask was in all cases better than 4%. However, some of the haloketones, such as $(CH_3)_3CCHXCOCH_3$, had such long half-lives that it was not possible to follow the reaction beyond 2 half-lives. In these cases, the value of $[X^-]_\infty$ was calculated from the amount of haloketone weighed in.

Results of the Kinetic Experiments with Acetate

The rates of bimolecular nucleophilic substitution of halide by acetate from the twelve bromoketones and twelve chloroketones at 54.8° are given in Tables XIV and XV, pp 101 and 102, respectively. These

FIGURE 5   99

Substitution of 1-Bromo-4-methyl-2-pentanone, 1.00 $\underline{M}$

Acetate in 24% Aqueous DME, 54.8°

time, sec x 10^{-2}

FIGURE 6
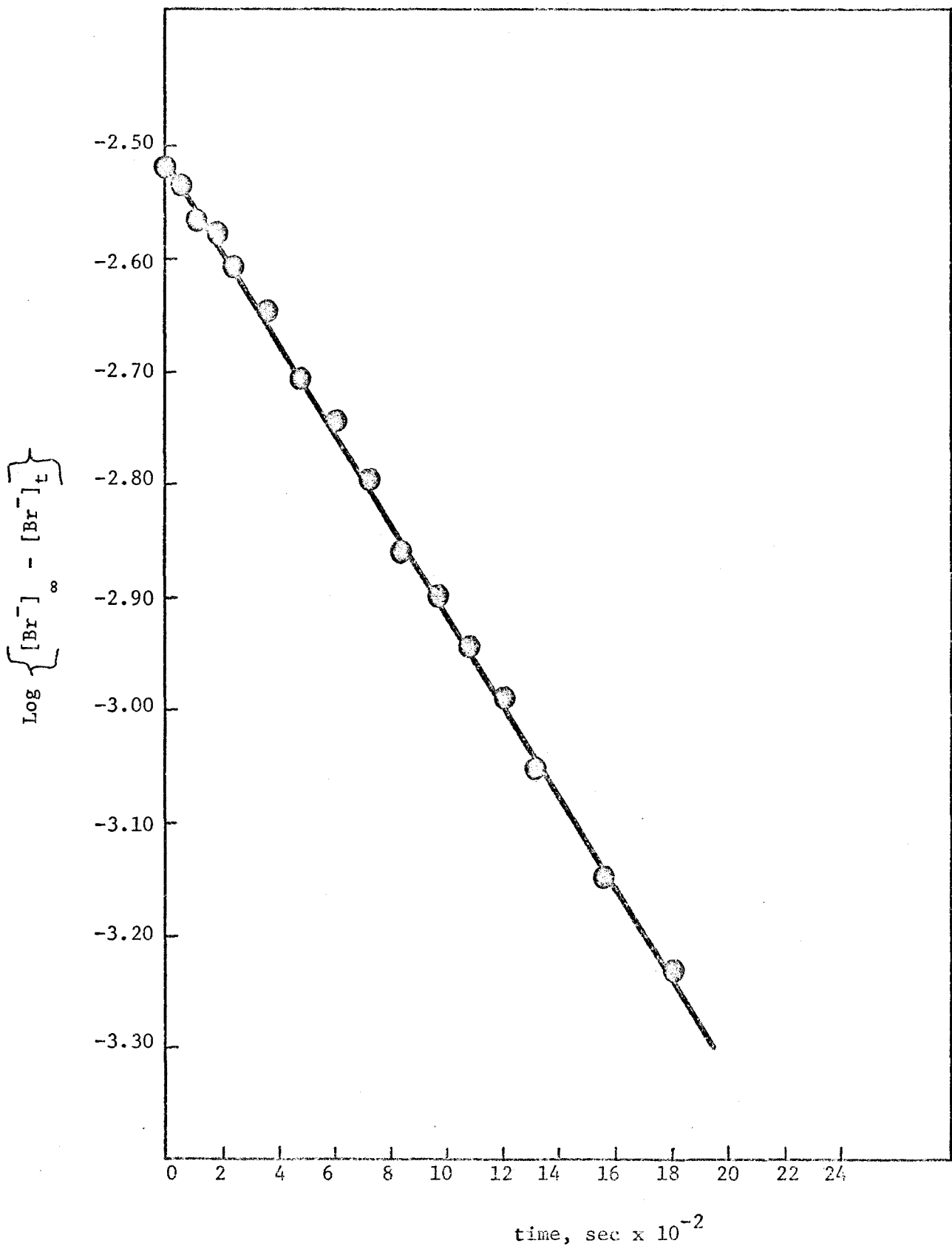
Substitution of Chloroacetone, 1.00 M Acetate in 24%

Aqueous DME, 54.8°

time, sec x 10^{-2}
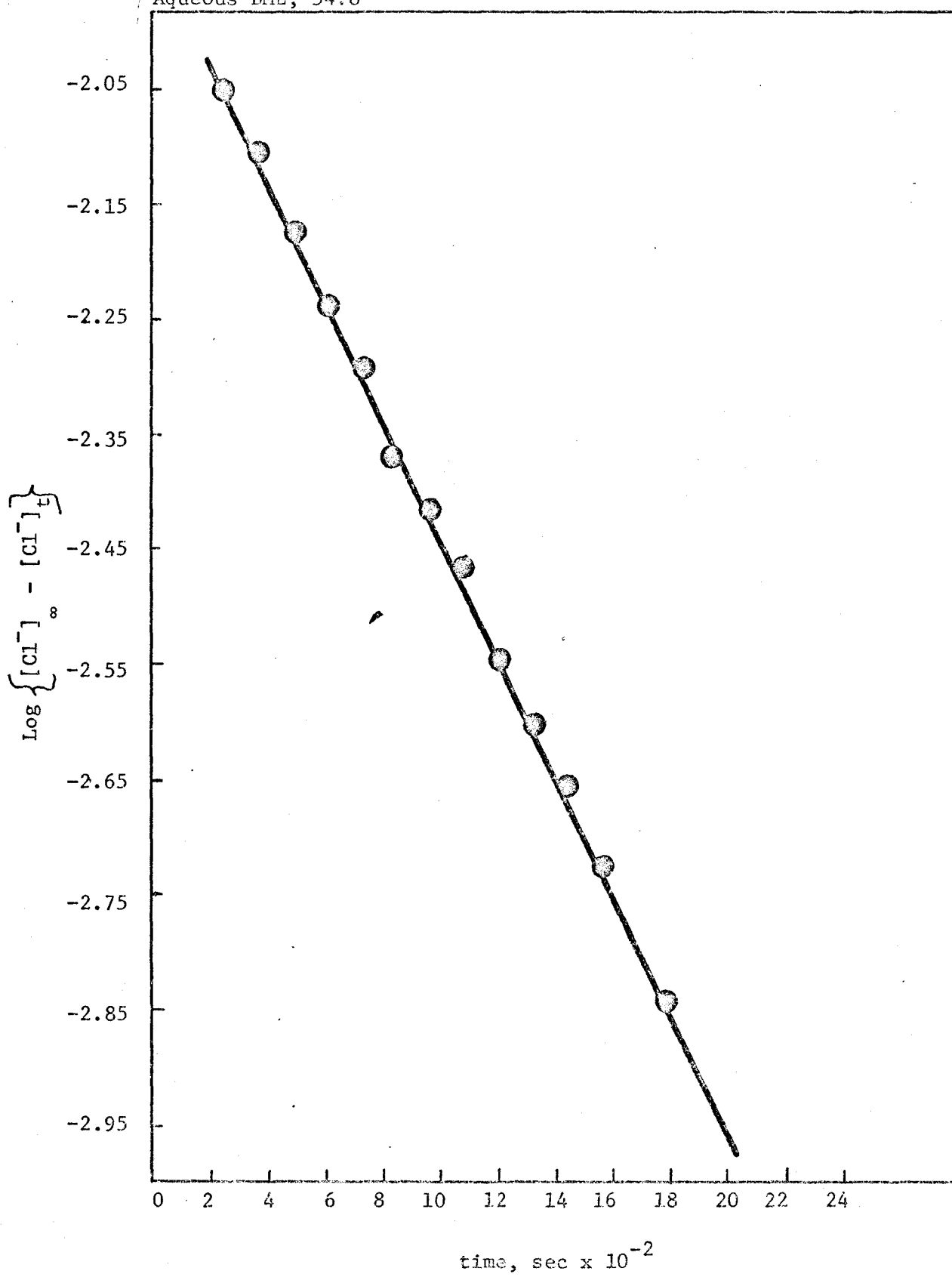
TABLE XIV

Rates of Bimolecular Nucleophilic Substitution by Acetate in

24% Aqueous DME, 54.8°

	Bromoketone	$k, M^{-1} sec^{-1}$	Relative Rate
A	$CH_3COCH_2Br^{a}$	$1.46\pm0.02 \times 10^{-3}$	1.00
	$CH_3CH_2COCH_2Br$	$1.46\pm0.015 \times 10^{-3}$	1.00
	$(CH_3)_2CHCOCH_2Br$	$1.05\pm0.02 \times 10^{-3}$	0.720
	$(CH_3)_3CCOCH_2Br^{a}$	$5.92\pm0.05 \times 10^{-4}$	0.405
B	$CH_3CH_2COCH_2Br$	$1.46\pm0.015 \times 10^{-3}$	1.00
	$CH_3CH_2CH_2COCH_2Br$	$1.78\pm0.015 \times 10^{-3}$	0.810
	$(CH_3)_2CHCH_2COCH_2Br$	$9.22\pm0.095 \times 10^{-4}$	0.631
	$(CH_3)_3CCH_2COCH_2Br$	$6.01\pm0.055 \times 10^{-4}$	0.412
C	$CH_2BrCOCH_3$	$1.46\pm0.02 \times 10^{-3}$	1.00
	$CH_3CHBrCOCH_3$	$6.12\pm0.65 \times 10^{-4}$	0.418
	$(CH_3)_2CBrCOCH_3$	$2.28\pm0.035 \times 10^{-5}$	0.0156
D	$CH_3CHBrCOCH_3$	$6.12\pm0.065 \times 10^{-4}$	1.00
	$CH_3CH_2CHBrCOCH_3$	$2.00\pm0.025 \times 10^{-4}$	0.327
	$(CH_3)_2CHCHBrCOCH_3$	$1.26\pm0.015 \times 10^{-5}$	0.0206
	$(CH_3)_3CCHBrCOCH_3$	$8.23\pm0.15 \times 10^{-7}$	0.00134

^{a}Rate ratio of bromoacetone to bromopinacolone was found to be 6.0

at 0.2°.

TABLE XV

Rates of Bimolecular Nucleophilic Substitution by Acetate in

24% Aqueous DME, 54.8°.

Chloroketone	$k, \underline{M}^{-1} sec^{-1}$	Relative Rate
A CH_3COCH_2Cl	$1.14\pm0.02 \times 10^{-3}$	1.00
$CH_3CH_2COCH_2Cl$	$1.05\pm0.02 \times 10^{-3}$	0.922
$(CH_3)_2CHCOCH_2Cl$	$7.10\pm0.125 \times 10^{-4}$	0.623
$(CH_3)_3CCOCH_2Cl$	$3.35\pm0.05 \times 10^{-4}$	0.294
B $CH_3CH_2COCH_2Cl$	$1.05\pm0.02 \times 10^{-3}$	1.00
$CH_3CH_2CH_2COCH_2Cl$	$6.20\pm0.09 \times 10^{-4}$	0.590
$(CH_3)_2CHCH_2COCH_2Cl$	$1.29\pm0.02 \times 10^{-4}$	0.123
$(CH_3)_3CCH_2COCH_2Cl$	$5.75\pm0.08 \times 10^{-5}$	0.0547
C $CH_2ClCOCH_3$	$1.14\pm0.02 \times 10^{-3}$	1.00
$CH_3CHClCOCH_3$	$4.04\pm0.055 \times 10^{-4}$	0.354
$(CH_3)_2CClCOCH_3$	$3.72\pm0.06 \times 10^{-6}$	0.00326
D $CH_3CHClCOCH_3$	$4.04\pm0.055 \times 10^{-4}$	1.00
$CH_3CH_2CHClCOCH_3$	$2.78\pm0.035 \times 10^{-5}$	0.0687
$(CH_3)_2CHCHClCOCH_3$	$8.52\pm0.135 \times 10^{-7}$	0.00211
$(CH_3)_3CCHClCOCH_3$	$5.61\pm0.11 \times 10^{-8}$	0.000139

haloketones are divided into four groups, two of which (A and B) have increasing methyl substitution on the side of the carbonyl group opposite to the halogen, while the other two (C and D) are increasingly substituted on the same side of the carbonyl group as the halogen. Group A contains compounds substituted at the α'- position with 0, 1, 2, and 3 methyl groups; group B contains compounds with the same substitution pattern at the β'- position (β' refers to the side of carbonyl opposite to X); group C shows the effects of increasing methyl substitution (from 0 to 2) at the α-position; group D shows the effects of increasing methyl substitution (from 0 to 3) at the β-position. The rate constants, which are the average of several runs, are given with the range of values observed.

Although the orbital overlap mechanism involves interaction between the orbitals of the nucleophile, carbonyl system, and leaving group at the transition state, this interaction may occur in two different ways. One way involves a direct overlap of the p-orbitals of the carbonyl carbon and the α-carbon with the nucleophile, as shown in LXXIX. This will be referred to as the bridging mechanism. An important alternative to this picture does not involve direct overlap between the orbitals of the nucleophile and the carbonyl carbon. This mechanism is shown in LXXX, where charge is able to flow into the carbonyl group without bringing the nucleophile into bonding distance of the

carbonyl carbon. If the α-carbon orbital shown is viewed as an

LXXIX   LXXX
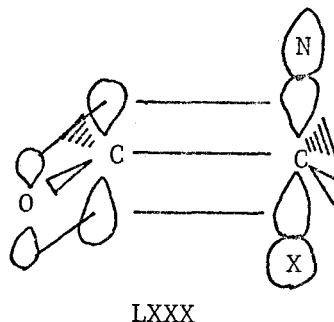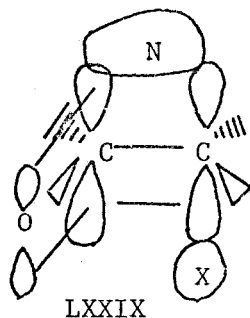
atomic orbital, then it is very p-like for a symmetric transition

state and will overlap with the carbonyl p-orbitals if the geometry

of the system permits, *i.e.*, if charge may flow into the carbonyl

group via a molecular orbital. This will be referred to as the

conjugation mechanism.

Implicit in the bridging mechanism discussed above is that

the rate of displacement of halide should depend not only on

substitution at the reaction site, *i.e.*, the α-position, but also

on substitution at the other side of the carbonyl group. The inter-

action between the nucleophile and the carbonyl group at the transition

state should be influenced by the presence of groups with large steric

requirements at both the α'- and β'- positions. On the other hand, these

effects should not be as important for the conjugation mechanism, where

the nucleophile would not be influenced as much by bulky groups at the

α'- and β'- positions. However, since the nucleophile would approach

the α-carbon atom as shown in LXXX, the effects of substitution at the

α- and β- positions should be large, larger than if the bridging

mechanism were operating. For either mechanism, the substituent

effects should be larger for the chloroketones than for the bromo-

ketones, because chloride is a poorer leaving group than bromide.

The nucleophile would have to be closer to the α-carbon atom at

the transition state for the chloroketones than for the bromoketones,

other factors being equal.

From an examination of the rate constants in Tables XIV and

XV on pp 101 and 102, respectively, it should be possible to decide

which of the two mechanisms discussed above is better supported by

the data. First of all, the overall rates of displacement are larger

for the bromoketones than for the chloroketones as predicted. In

addition, the effects of substitution in each group of the chloroketones

are much more pronounced than for the corresponding bromoketones. In

group A, where there is increasing methyl substitution at the α'- position,

a 2.5-fold reduction in rate was observed on going from bromoacetone to

bromopinacolone; a slightly larger (3.4-fold) decrease was found for the

corresponding chloroketones. Group B shows the effects of adding methyl

groups to the β'- position, where a rate retardation similar to that of

group A on going from $CH_3CH_2COCH_2Br$ to $(CH_3)_3CCH_2COCH_2Br$ was observed.

The effect was larger for the corresponding chloroketones; an 18-fold

decrease in rate was found. Thus the steric factors are more pronounced

for the chloroketones, especially where there is a t-butyl group at the

β'- position. These data are not consistent with a bridging mechanism,
as shown by the small rate retardations in groups A and B. If the
nucleophile were bridging the carbonyl and α-carbon atoms, the steric
effects would surely be larger than those observed. The results are
consistent with the conjugation mechanism described above.

A measure of the temperature effects was obtained for the
bromoketones by determining the rates of displacement of bromide from
bromoacetone and bromopinacolone at 0.2°. The pseudo first-order rate
constants observed were 4.97×10^{-6} and 8.30×10^{-7} sec^{-1}, respectively,
which gives a rate retardation of 6-fold near 0°. This factor seems
reasonable for the steric effect even if the nucleophile does not bond
to carbonyl.

In group C, where there is increasing substitution at the α-carbon,
the steric requirements of the methyl groups caused substantial decreases
in rate, 64-fold on going from bromoacetone to methyl bromoisopropyl
ketone and 307-fold for the corresponding chloroketones. The effect of
substitution at the reaction site is thus much greater where the leaving
group is chloride, in agreement with the above reasoning (p105). Group D
shows the effects of increasing substitution at the β-position; the largest
rate retardations were observed for this series. A reduction of 746-fold
was found on going from 3-bromo-2-butanone to methyl bromoneopentyl ketone,
while a much larger retardation, 7190-fold, was observed for the corresponding
chloro-compounds. Thus there is a striking effect on the rate of displacement

of halide from α-haloketones that have bulky substituents at the β-position. Indeed, in the last compound of the series, 3-halo-4,4-dimethyl-2-pentanone, the nucleophile is required to displace the halide from a neopentyl carbon. Neopentyl halides are extremely inactive toward nucleophilic reagents in bimolecular substitutions. The relative rates for exchange of RI with chloride ion in acetone at 25° are for R = Et, n-Pr, i-Bu, and neopentyl; 1.00, 0.60, 0.038, and 0.000014, respectively[7]. When there are 3 β-methyl groups, as in neopentyl iodide, there is no way that interference between the β-methyl groups and the nucleophile can be avoided; thus, the reaction is very slow because of the lack of free rotation of the carbon-carbon bonds in the transition state.

The above data, from groups C and D, seem to support the bridging mechanism as well as the conjugation mechanism. However, the large rate retardations, on closer examination, are more compatible with the latter mechanism. If a symmetric bridging mechanism were operating, then the presence of bulky substituents at the α- and β- positions should not affect the rates of displacement much more than those of α'- and β'-substituents. This is not the case, however, and the results suggest that in the transition state, the nucleophile is more in line with the p-orbital of the α-carbon atom (LXXX). A possibility would be an unsymmetric bridged transition state, but the unbridged mechanism is more probable.

Comparison of the Rate Data with some Literature Data

An important point, which should be considered, is the size of the

rate enhancements observed with the α-haloketones, relative to alkyl halides.

The rates of displacement of halide from n-butyl bromide and n-butyl chloride

by acetate were measured in the buffer system at 54.8°. Second-order rate

constants obtained were 2.06 and 10^{-5} and 1.34×10^{-6} $\underline{M}^{-1}$ sec^{-1}, respectively.

If the rate constants of n-butyl bromide and n-butyl chloride are taken as

1.00, then the rates for 1-bromo- and 1-chloro-2-butanone are 70.9 and

784, respectively. Although these rate enhancements are much lower than

most of the enhancements reported in the literature (see Historical

Introduction), in 1964 Sisti and Lowell reported[68] that chloroacetone

reacts 200 times faster than n-propyl chloride with acetate in methanol.

Thus, the results reported above are in fairly good agreement with that

of Sisti and Lowell[68] for displacement by acetate. It would seem, therefore,

that the solvent has a large effect on the rates observed in the displacement

reactions of α-haloketones. Most of the large rate enhancements reported

in the early literature were obtained with iodide in acetone, an aprotic

solvent. It is not surprising, then, that the range of rates might be

compressed in the protic solvent system employed here.

Another mechanism for displacement of halide from the α-haloketones

involves direct addition of the nucleophile to the carbonyl carbon. However,

if this mechanism were operating, the effects of methyl substitution should

be greater than observed for these compounds. This would be true especially for group A, where the nucleophile would be bonding to a pseudo neopentyl carbon atom. One would surely expect a larger rate retardation than the 2.5- to 3.4- fold reduction observed. The literature contains a substantial amount of data on the effects of alkyl substitution in reactions where carbonyl addition is known to occur, *e.g.*, acid-[125,126] and base-[126,127] catalyzed hydrolysis of aliphatic esters, acid-catalyzed esterification of aliphatic acids,[128] and acid- and base-catalyzed hydrolysis of aliphatic amides[129].

For example, Kindler[125] reported that on going from ethyl acetate to ethyl 2,2-dimethylpropionate($(CH_3)_3CCOOEt$), the rate of acid-catalyzed hydrolysis in 88% ethanol at 30° was lowered by 91-fold. The rate reduction for this same series was reported by Davies and Evans[126] to be 22-fold in 70% aqueous acetone at 44.7°. Base hydrolysis of the same compounds under similar conditions was reported[126] to cause a 155-fold reduction in rate. In 85% ethanol at 50°, base hydrolysis of these compounds yielded[127] a rate factor of 161. In the acid-catalyzed esterification of aliphatic acids, β-alkyl substituents are significantly more effective at providing steric hindrance than α-alkyl substituents[128]. Thus, in methanol at 40°, incorporation of three α-methyl groups into acetic acid lowered the esterification rate by a factor of 27, but incorporation of three β-methyl groups into propionic acid lowered the rate by 36-fold.

In contrast to these numbers, for the acid hydrolysis of amides in aqueous sulfuric acid at 65°, a rate factor of 3.8 was observed by Roo and Bruylants[129] on going from CH_3CONH_2 to $(CH_3)_3CCONH_2$; going from $CH_3CH_2CONH_2$ to $(CH_3)_3CCH_2CONH_2$, the factor was 57-fold. The factors for the same series for base hydrolysis were 10.7 and 159, respectively. Thus, β-substitution led to a 15-fold larger decrease in relative rate than α-substitution, for both acid and base hydrolysis. In general, α- or β-substitution seem to cause greater rate retardation for base hydrolysis than acid hydrolysis by a factor of approximately 3. Also, the results reported above seem to indicate rather larger steric factors for carbonyl addition (11-160) than observed here (2.4-18) for the displacement of halide from the α-haloketones in groups A and B, Tables XIV and XV, pp 101 and 102 , respectively.

There are other reactions that might be considered as models, for example, carbene addition to olefins and hydroboration of substituted olefins. It was reported by Moss and Mamantov[130] that in the addition of dichlorocarbene to $RCH=CH_2$ at -10°, a 34-fold reduction in rate was observed for R = t-butyl, compared to R = ethyl. For alkyl substitution at the β-position, the rates for R = iso-butyl and neopentyl were nearly the same as the reference compound, 0.99 and 0.97, respectively. The substituent effects are only important for α-substitution in this reaction. Brown and coworkers reported[131,132] results of the treatment of a series of substituted cis-olefins with bis(3-methyl-2-butyl)borane(disiamylborane)

in THF at 0°. They found a 30-fold reduction in rate for $(CH_3)_3CCH=$ $CHCH_3$ compared to $CH_3CH=CHCH_3$.

Although the temperature effects in these systems are not known, it is likely that the rate factors for both carbene addition and hydroboration of olefins would be much less than 30 at 54.9°. A similar temperature difference in this study caused a change in relative rate ratio of more than 2-fold for bromoacetone over bromopinacolone. Thus the steric effects for addition to olefins may well be of similar magnitude to those observed here.

In conclusion, the data reported in the literature for the rate reductions caused by alkyl substitution (α- or β-) in reactions where carbonyl addition is known to occur seem to be much larger than the relatively small effects observed in this study. Also, in a different type of reaction, addition to substituted olefins, the introduction of three methyl groups bonded to the α-carbon atom caused a 30-fold reduction in rate compared to the case where there were none. However, rate retardation might well be much smaller at 54.8°.

Thus, it would seem that the rate retardations observed in this work are too small for direct carbonyl addition and seem to indicate other involvement of the carbonyl carbon with the nucleophile at the transition state, consistent with an orbital overlap mechanism.

Displacement of Bromide by Azide Ion

Further evidence in support of the conjugation mechanism was obtained by using a different nucleophile to displace bromide from a series of bromoketones. The conditions used were very similar to those used for displacement by acetate, except that the medium was 0.5 $\underline{M}$ in HOAc and N_3^-, with no acetate present. In all, nine bromoketones were studied, with at least duplicate runs for each compound. A typical run, for methyl bromoisobutyl ketone, is plotted in Figure 7, p 113, to determine the pseudo first-order rate constant. Second-order rate constants for the nine bromoketones are given in Table XVI, p 114, along with the range of values observed and the relative rates for each group of compounds, as before. From a comparison of these results with those in Table XIV, p 101, two important points are obvious. First, the overall rates of displacement by azide are greater than by acetate by a factor of 65-410. Secondly, the rate retardations in each group are smaller than observed for acetate displacement. For example, in group A the rate reduction is 1.63, compared to 2.47 for acetate. Group B contains similar results. As with acetate as nucleophile, the steric effects are larger for the compounds in groups C and D. In group C, a rate retardation of 64-fold was observed for acetate, with azide a reduction of only 9.6 was observed. Similarly in group D, the numbers are 746-fold and 172-fold, respectively. These data support the conclusions reached on

FIGURE 7   113

Substitution of 3-Bromo-4-methyl-2-pentanone, 0.500 $\underline{M}$ Azide

in 24% Aqueous DME, 54.8°

time, sec x 10^{-2}
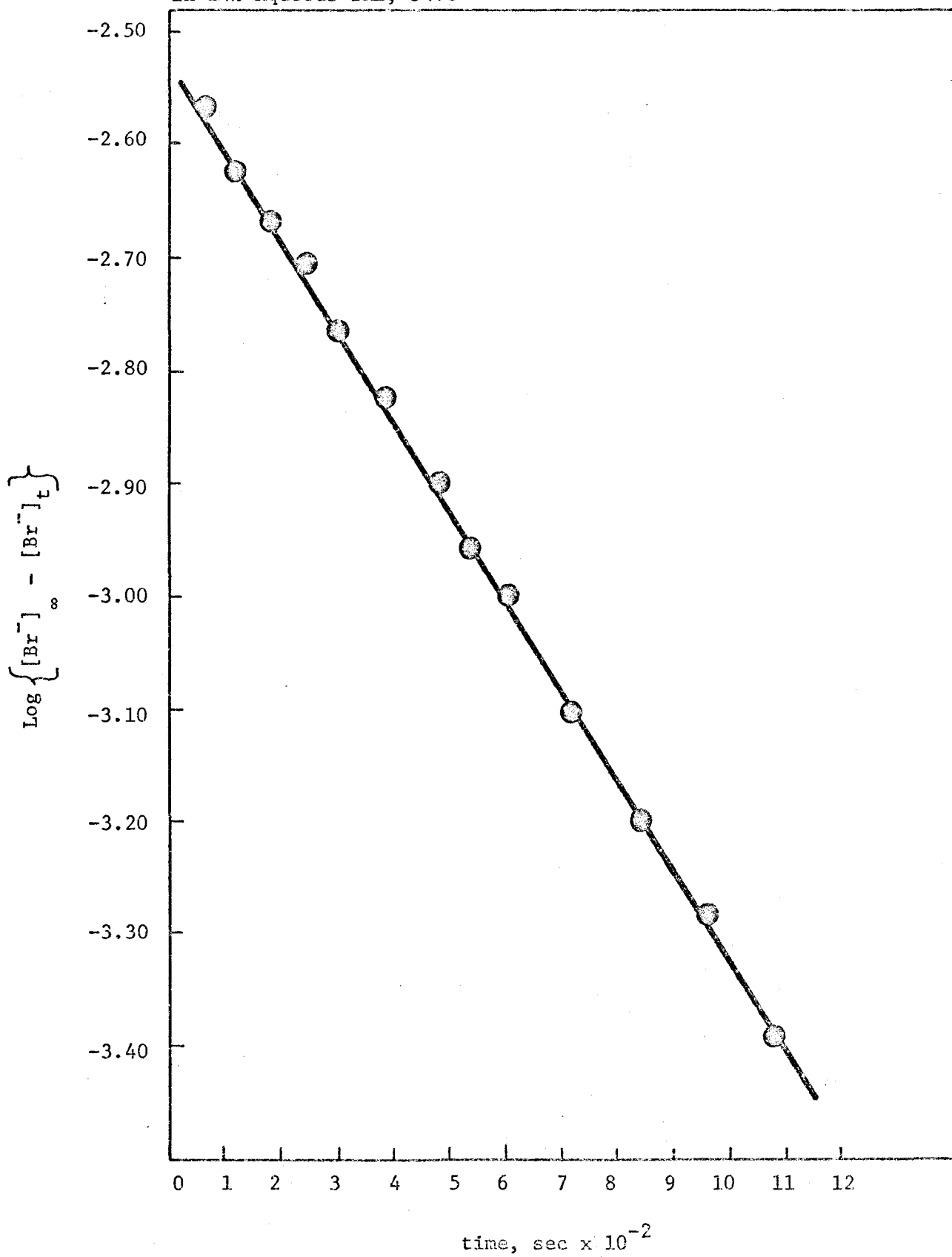
TABLE XVI

Rates of Substitution of Bromide by Azide in

24% Aqueous DME, 54.8°.

	Bromoketone	k, M^{-1} sec^{-1}	Relative Rate
A	CH_3COCH_2Br	$9.48 \pm 0.095 \times 10^{-2}$	1.00
	$CH_3CH_2COCH_2Br$	$9.24 \pm 0.105 \times 10^{-2}$	0.975
	$(CH_3)_3CCOCH_2Br$	$5.81 \pm 0.07 \times 10^{-2}$	0.614
B	$CH_3CH_2COCH_2Br$	$9.24 \pm 0.105 \times 10^{-2}$	1.00
	$CH_3CH_2CH_2COCH_2Br$	$8.68 \pm 0.085 \times 10^{-2}$	0.940
	$(CH_3)_3CCH_2COCH_2Br$	$5.93 \pm 0.07 \times 10^{-2}$	0.642
C	CH_3COCH_2Br	$9.48 \pm 0.095 \times 10^{-2}$	1.00
	$(CH_3)_2CBrCOCH_3$	$9.88 \pm 0.115 \times 10^{-3}$	0.104
D	$CH_3CHBrCOCH_3$	$5.76 \pm 0.065 \times 10^{-2}$	1.00
	$(CH_3)_2CHCHBrCOCH_3$	$3.70 \pm 0.04 \times 10^{-3}$	0.0643
	$(CH_3)_3CCHBrCOCH_3$	$3.35 \pm 0.04 \times 10^{-4}$	0.00582

p 107 for the conjugation mechanism, rather than the bridging mechanism.

Because azide is a much better nucleophile than acetate, one would expect the overall rates to be greater for the former, and this is indeed the case. Sisti and Lowell reported[68] an increase in rate of 126- and 46-fold for the displacement of chloride from $PhCOCH_2Cl$ and CH_3COCH_2Cl, respectively, by azide, compared with acetate, in methanol at 30°. These numbers are in good agreement with those reported here. In addition, the rates in Table XVI show a much smaller dependence on the steric requirements of the groups at the α- or β-positions. The fact that the steric effects at the α- and β-positions are much larger than those on the other side of the carbonyl group indicates that at the transition state the nucleophile must be closer to the reaction site than to the carbonyl carbon atom. This is consistent with either an asymmetric bridged transition state or a symmetric unbridged one but not with a symmetric bridged transition state.

Activation Parameters for *n*-Butyl Bromide and 1-Bromo-2-butanone

In order to measure the effect of the carbonyl group in the displacement reactions of α-haloketones, the obvious way would be to leave it out. However, one then has the problem of what to substitute for it without changing more than one factor. Thus, the simplest model to choose for an α-haloketone is its alkyl halide analog, where the CO group is substituted by a CH_2 group. For example, a model for 1-bromo-2-butanone would be *n*-butyl bromide.

One way of comparing the reactions of structurally different

compounds is through their activation parameters; this was done for

n-butyl bromide and 1-bromo-2-butanone. The rates of displacement of

bromide from the bromo-compounds by acetate were determined at three

different temperatures, as described in the Experimental section. At

least two determinations were made at each temperature, and the

average rate constant observed at each temperature is given in Table

XVII, p [117], along with the range of values observed. These rate

constants were used to calculate activation parameters, from a plot of

log k/T against 1/T, in the usual manner (see Experimental section)

using the standard equation derivable from transition-state theory[176]:

$$\frac{\ln k}{T} = \ln \frac{kK}{h} - \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R}$$

The plots for n-butyl bromide and 1-bromo-2-butanone are given in

Figure 8, p118, and Figure 9, p119, respectively. Values of $\Delta H^{\ddagger}$ and

$\Delta S^{\ddagger}$ were obtained from a least-squares computer calculation of the

slopes and intercepts, respectively. These values are given in

Table XVIII, p120, along with the errors calculated from maximum and

minimum slopes as determined by the range of rate constants observed.

They are probably indicative of the real errors involved in these

determinations.

It is apparent from Table XVIII that the rate differences between

these two compounds are caused by differences in the entropy term rather

TABLE XVII

Displacement of Bromide in *n*-Butyl bromide and 1-Bromo-2-butanone

by Acetate in 24% Aqueous DME, for Activation Parameters.

Compound	Temperature	$k, \underline{M}^{-1} \sec^{-1}$
$CH_3CH_2CH_2CH_2Br$	$40.0° \pm 0.025°C$	$4.82 \pm 0.045 \times 10^{-6}$
$CH_3CH_2CH_2CH_2Br$	$54.8° \pm 0.04°C$	$2.06 \pm 0.025 \times 10^{-5}$
$CH_3CH_2CH_2CH_2Br$	$70.0° \pm 0.07°C$	$8.81 \pm 0.19 \times 10^{-5}$
$CH_3CH_2COCH_2Br$	$0.20° \pm 0.01°C$	$1.52 \pm 0.02 \times 10^{-6}$
$CH_3CH_2COCH_2Br$	$30.0° \pm 0.02°C$	$8.11 \pm 0.09 \times 10^{-5}$
$CH_3CH_2COCH_2Br$	$54.8° \pm 0.04°C$	$1.46 \pm 0.015 \times 10^{-3}$

FIGURE 8   118

Activation Parameters for Substitution of *n*-Butyl Bromide

By Acetate

$1/T$, $\times 10^3$

FIGURE 9   119
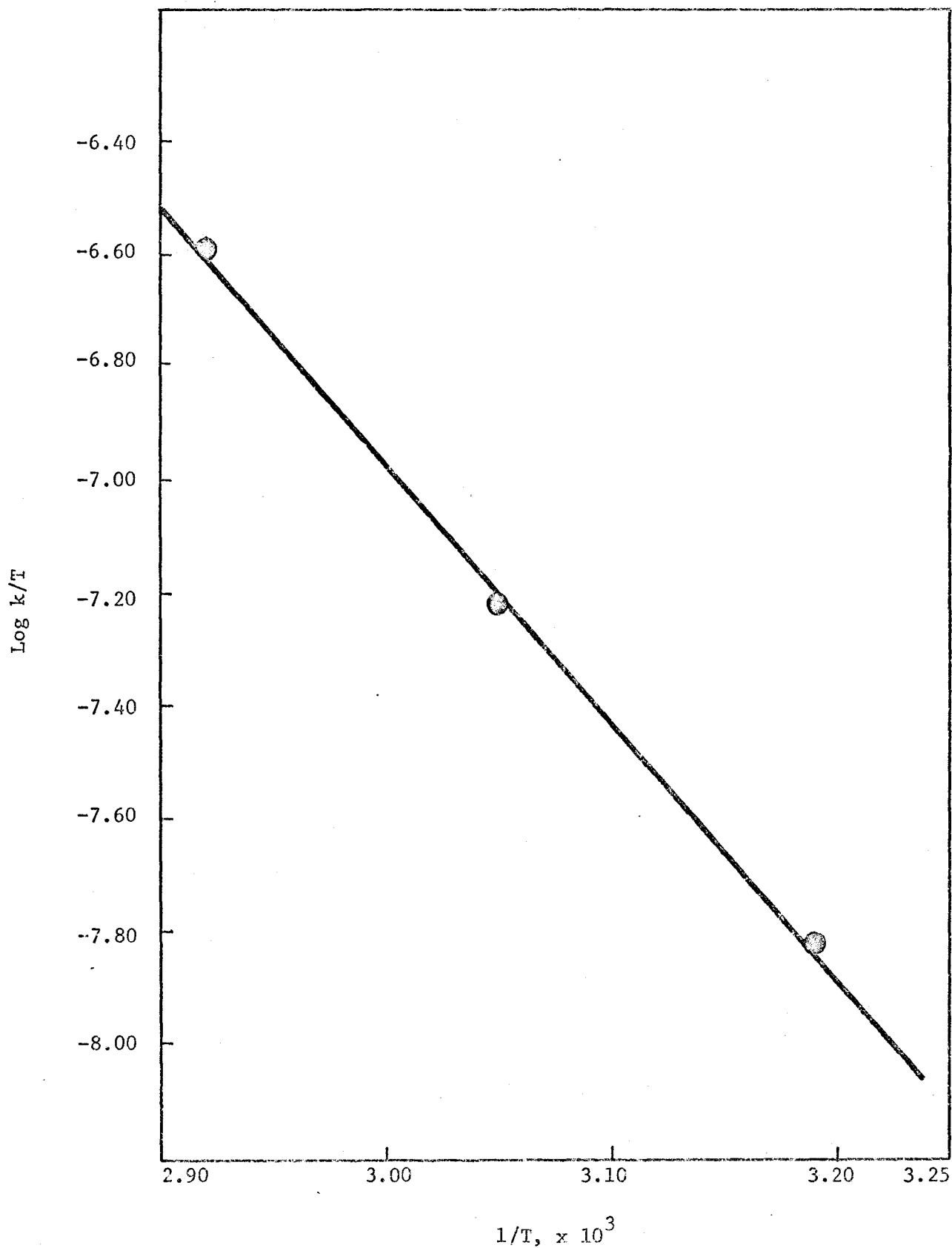
Activation Parameters for Substitution of 1-Bromo-2-butanone

by Acetate
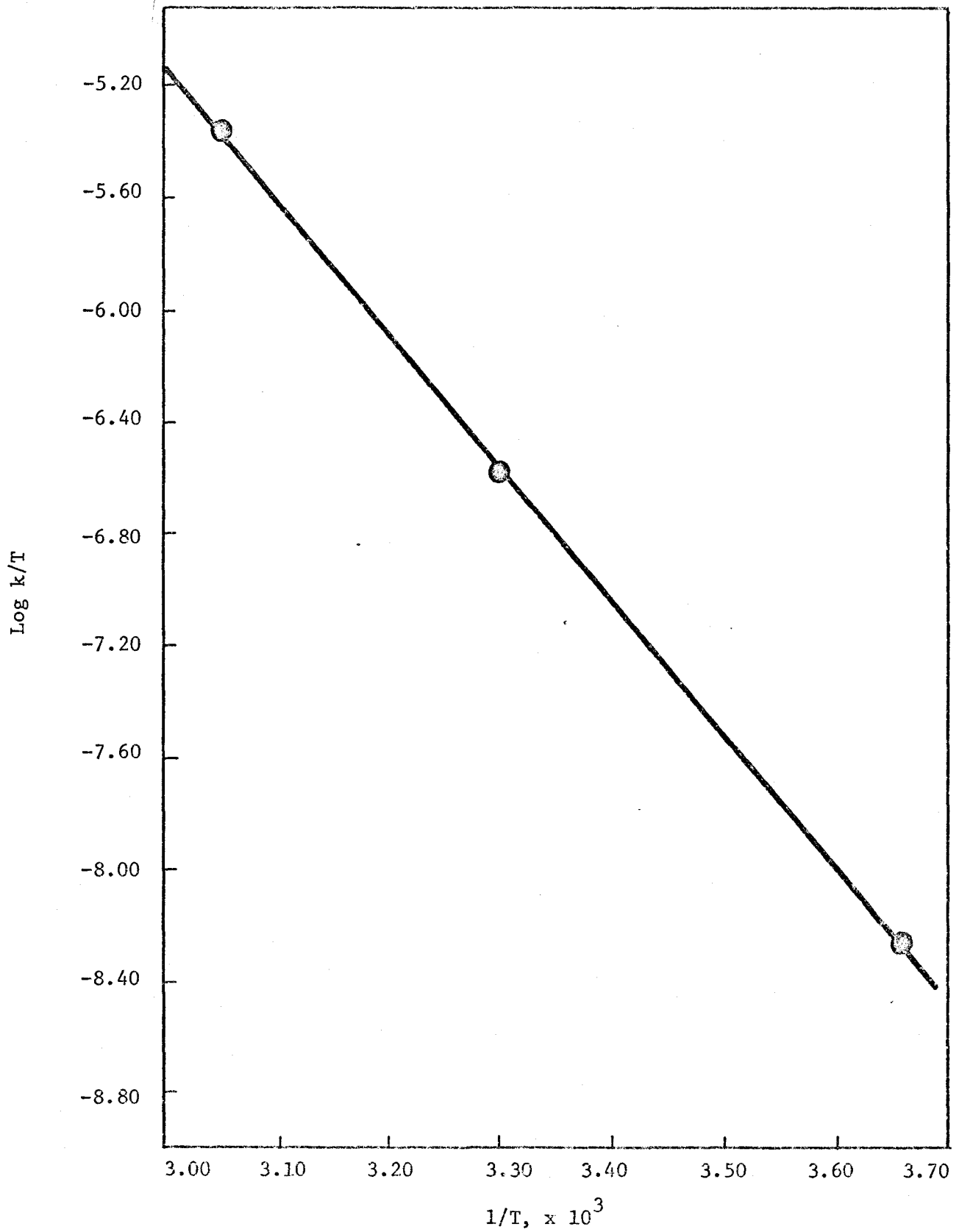
TABLE XVIII

Activation Parameters for n-Butyl Bromide and 1-Bromo-2-butanone

Compound	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
$CH_3CH_2CH_2CH_2Br$	20.7 ± 0.56	-17.0 ± 1.7
$CH_3CH_2COCH_2Br$	21.8 ± 0.31	-5.41 ± 0.96

than in the enthalpies, which are nearly the same within experimental error. The difference in free energy of activation between n-butyl bromide and 1-bromo-2-butanone at $54.8°$ (2.71 kcal mol^{-1}) has a contribution of $(-)$ 1.10 kcal mol^{-1} from $\Delta H^{\ddagger}$, and 3.81 kcal mol^{-1} from $T\Delta S^{\ddagger}$; thus it is due mostly to the $T\Delta S^{\ddagger}$ term.

Bordwell has observed[124] a similar effect in the reaction of $PhCOCH_2Cl$ and n-BuCl with iodide in acetone at $75°$. He found a rate enhancement of 32,000-fold of $PhCOCH_2Cl$ over n-BuCl under these conditions; the entropies of activation were $-8eu$ for the chloroketone and $-26eu$ for the alkyl chloride. Bordwell suggested that the rate-enhancing ability of the carbonyl group arises partly from the absence of rate-retarding steric and field effects, along with a mildly rate-enhancing inductive effect. The increase in the entropy of activation ($18eu$) for the chloroketone compared to n-butyl chloride was interpreted[124] as arising from lowered steric requirements for the chloroketone at the transition state. Bordwell implied that this low steric effect accounts for much of the rate enhancement, $i.e.$, that $\Delta\Delta S^{\ddagger}$ is the major contributor to $\Delta\Delta G^{\ddagger}$. This same effect may well be operating in the present case, where an increase in $\Delta S^{\ddagger}$ of $12eu$ was observed for 1-bromo-2-butanone over n-butyl bromide. This interpretation will be referred to again later in the Discussion.

An alternative to this interpretation involves delocalization of charge by the solvent at the transition state. A less negative entropy of

activation for the bromoketone must mean that fewer degrees of freedom

are lost by the molecule/solvent complex at the transition state. This

may be due to delocalization of negative charge into the carbonyl group;

the solvent could be less restricted since the charge would not have to

be delocalized as much by solvation. With the alkyl bromide, however,

the charge would not be as effectively delocalized internally, and more

solvent restriction at the transition state might be necessary, with a

corresponding decrease in the entropy of activation.

Test for the Stereoelectronic Requirements - Choice of a Model
System

Although the results discussed above are compatible with an

orbital overlap mechanism, they are not definitive in view of the lack

of a suitable model system with which to compare them. As discussed in

the Historical Introduction, there are stereochemical implications of

this mechanism[41]. Thus, for the achievement of maximum overlap among

the orbitals which interact at the transition state, the nucleophile

and leaving groups must be above and below the plane determined by the

atoms CCO in LXXXI. Bartlett and Trachtenberg[41] chose a model compound

$$\delta - \begin{array}{c} X \\ \diagup \diagdown \\ C ==== O \quad \delta- \\ C \diagdown \diagup \\ \delta- \\ Y \end{array}$$
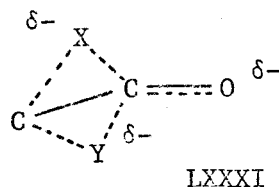
LXXXI

(LXXXII) in which the YCCX plane could not be perpendicular to the CCO

plane at the transition state for displacement of the dinitrophenoxy

group by iodide ion.   They compared the reactivity of LXXXII with that

of LXXXIII, in which such restraints were not present.   It was found

that LXXXIII was more reactive than LXXXII by a factor of 9000 at 0°,
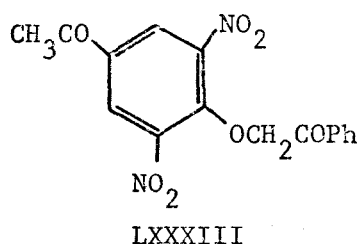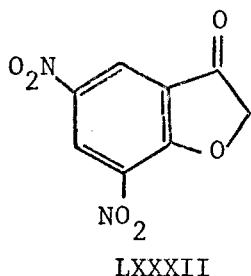
LXXXII   LXXXIII

and the activation parameters were $\Delta H^{\ddagger} = 10$ kcal mol^{-1}, $\Delta S^{\ddagger} = -30$eu for

LXXXIII, and $\Delta H^{\ddagger} = 31$ kcal mol^{-1}, $\Delta S^{\ddagger} = 25$eu for LXXXII.   Thus there

is a large difference (20 kcal mol^{-1}) in activation energy between the

two compounds; activation by the phenacyl group according to the proposed

mechanism was used to explain this difference.   The large difference in

entropy of activation was explained as arising from ring opening in the

transition state for LXXXII versus the formation of a pseudo ring in the

transition state for LXXXIII, as well as solvation effects.

Although the work by Bartlett and Trachtenberg[41] can be interpreted

as evidence for an orbital overlap mechanism, there is one serious drawback

in their choice of compounds.   This shortcoming is the use of one cyclic and

one acyclic system, LXXXII and LXXXIII, respectively.   A stronger argument

might be made if comparisons could be made in systems where the stereochemistry

is known and the structures are more similar. One such system involves

derivatives of *t*-butylcyclohexane.   It is well known[133] that conformational

equilibrium in a substituted cyclohexane favours the equatorial position

of the substituent. Comparison of the rates of displacement of halide

by acetate in halocyclohexyl ketones of known conformation with their

cyclohexyl halide analogs should provide a good picture of the stereo-

electronic requirements of the reaction.

Examination of models of *cis*- and *trans*-2-chloro-4-*t*-butyl-

cyclohexanone shows that the latter compound is structurally very favourable

for operation of an orbital overlap mechanism, while the latter is not. In

the *trans*-compound, the orbitals of the entering and leaving group are

approximately parallel to the orbitals of the carbonyl group, thus

permitting maximum overlap at the transition state. However, in the *cis*-

compound, the orbitals in question are nearly perpendicular; overlap will

be at a minimum. Since any rate differences observed might be due to

factors inherent in the structures themselves, the hydrocarbons corresponding

to the chloroketones would have to be studied under the same conditions.

Samples of *cis*- and *trans*-3-*t*-butylcyclohexyl chloride (LXXXIV and

LXXXV) were prepared from *cis*-3-*t*-butylcyclohexanol and purified by

preparative glpc as described in the Experimental section. The chloroketones,

cis- and *trans*-2-chloro-4-*t*-butylcyclohexanone (LXXXVI and LXXXVII) were

prepared by chlorination of the parent ketone and purified as described in

the Experimental section.

| LXXXIV | LXXXV | LXXXVI | LXXXVII |
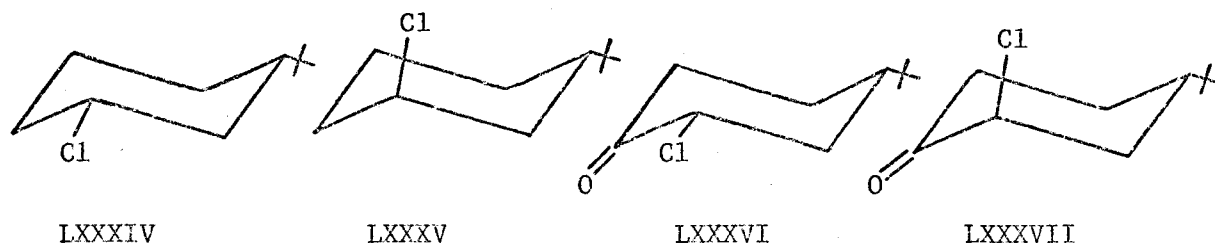
The rates of displacement of chloride by acetate ion in the acetic acid/acetate buffer were measured at 54.8° (as described in the Experimental section) for compounds LXXXIV-LXXXVII. Several determinations were made for each compound; typical rate plots for these compounds are given in Figures 10-13 pp 126-129. The concentration of chloro-compound was varied for each run to ensure, as before, that the measured rate did not depend on the rate of dissolution of the compound in the medium. In all cases the second-order rate constants were within 4%. It should be mentioned that for the cyclohexyl chlorides, the value of $[Cl^-]_\infty$ was determined from the amount of cyclohexyl chloride added to the buffer solution. Because the reactions were so slow, it was not possible to obtain good infinity values. With the chloroketones, however, the values of $[Cl^-]_\infty$ were obtained from infinity values, and these values are included in the graphs (see Figures 12 and 13, pp 128-129).

In order to calculate activation parameters for these compounds, the rates of substitution were determined at one other temperature for the cyclohexyl chlorides and two other temperatures for the chlorocyclo-hexanones. Only two temperatures were used for the former compounds because of their slow rates and shortage of pure substrate. The average second-order rate constants for the displacement of chloride by acetate at various temperatures is given in Table XIX, p130, along with the range of values calculated from several runs. From these data, the rate factor between the *cis-* and *trans-*cyclohexyl chlorides was calculated to be 2.15 (in favour

FIGURE 10 126

Substitution of *Cis*-3-*t*-Butylcyclohexyl Chloride, 1.00 $\underline{M}$ Acetate

in 24% Aqueous DME, 54.8°

time, sec x 10^{-5}

FIGURE 11
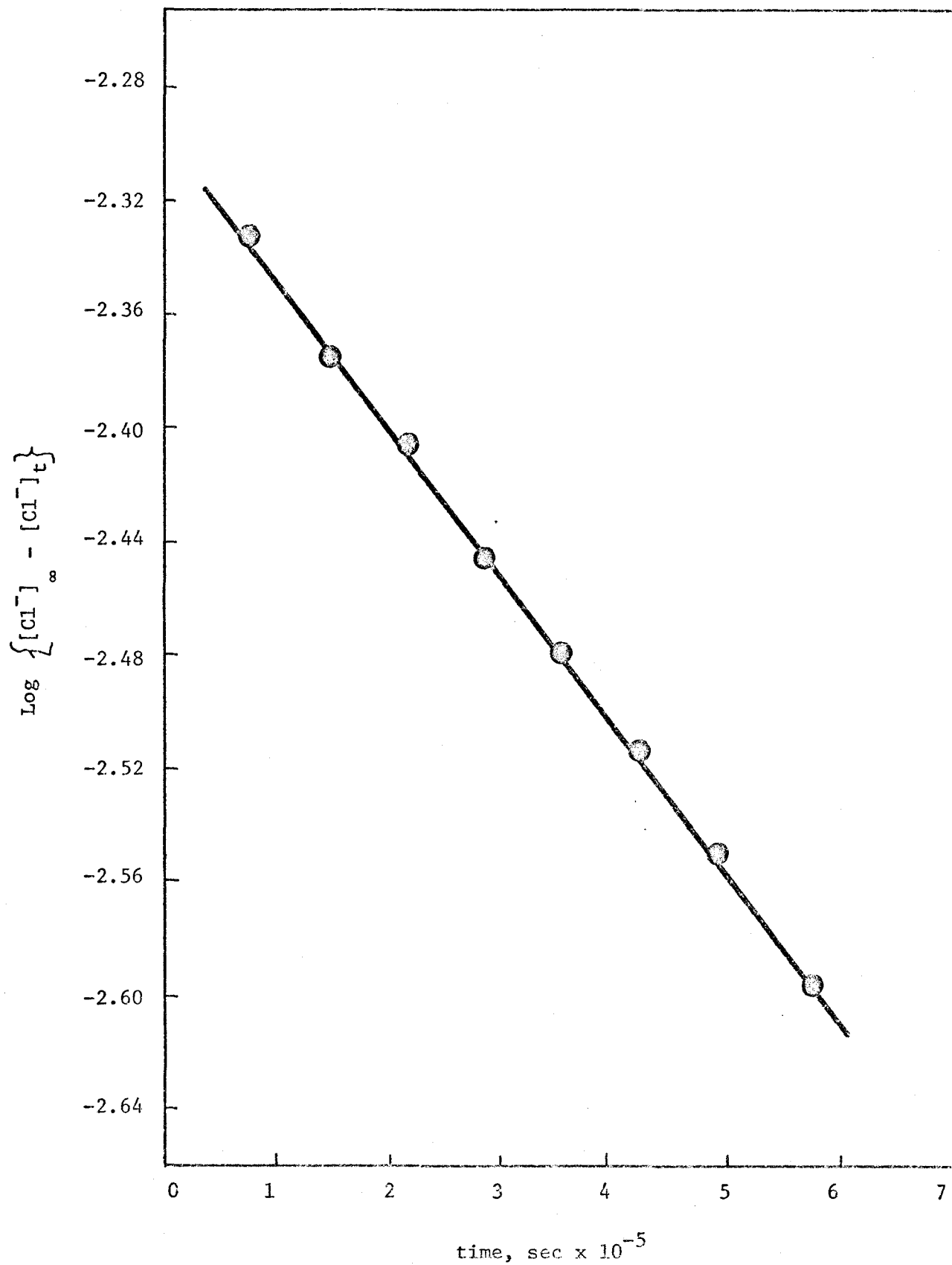
Substitution of *Trans*-3-*t*-Butylcyclohexyl Chloride, 1.00 $\underline{M}$ Acetate

in 24% Aqueous DME, 54.8°

FIGURE 12   128
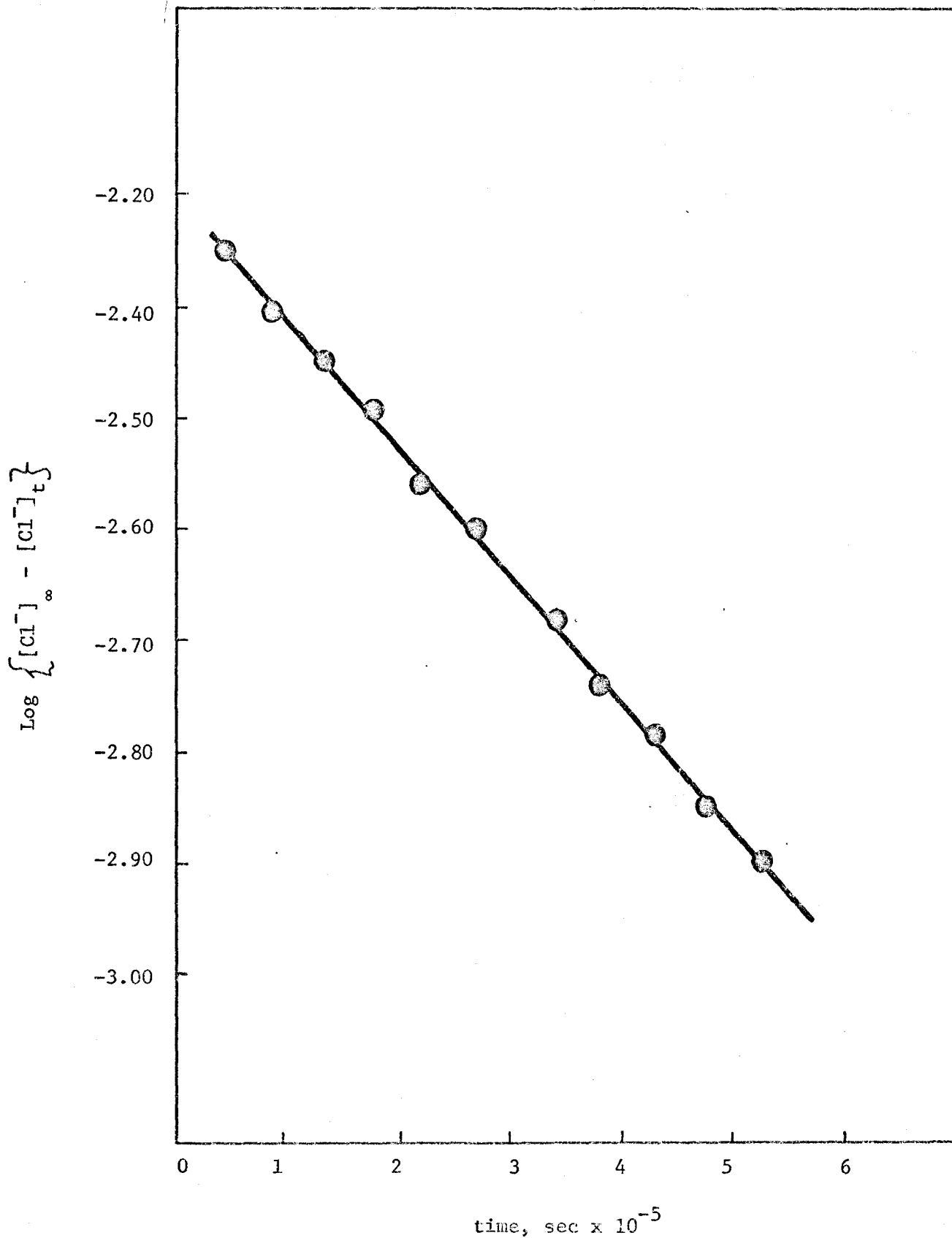
Substitution of *Cis*-2-Chloro-4-*t*-butylcyclohexanone, 1.00 $\underline{M}$

Acetate in 24% Aqueous DME, 54.8°

time, sec x 10^{-4}

FIGURE 13

129
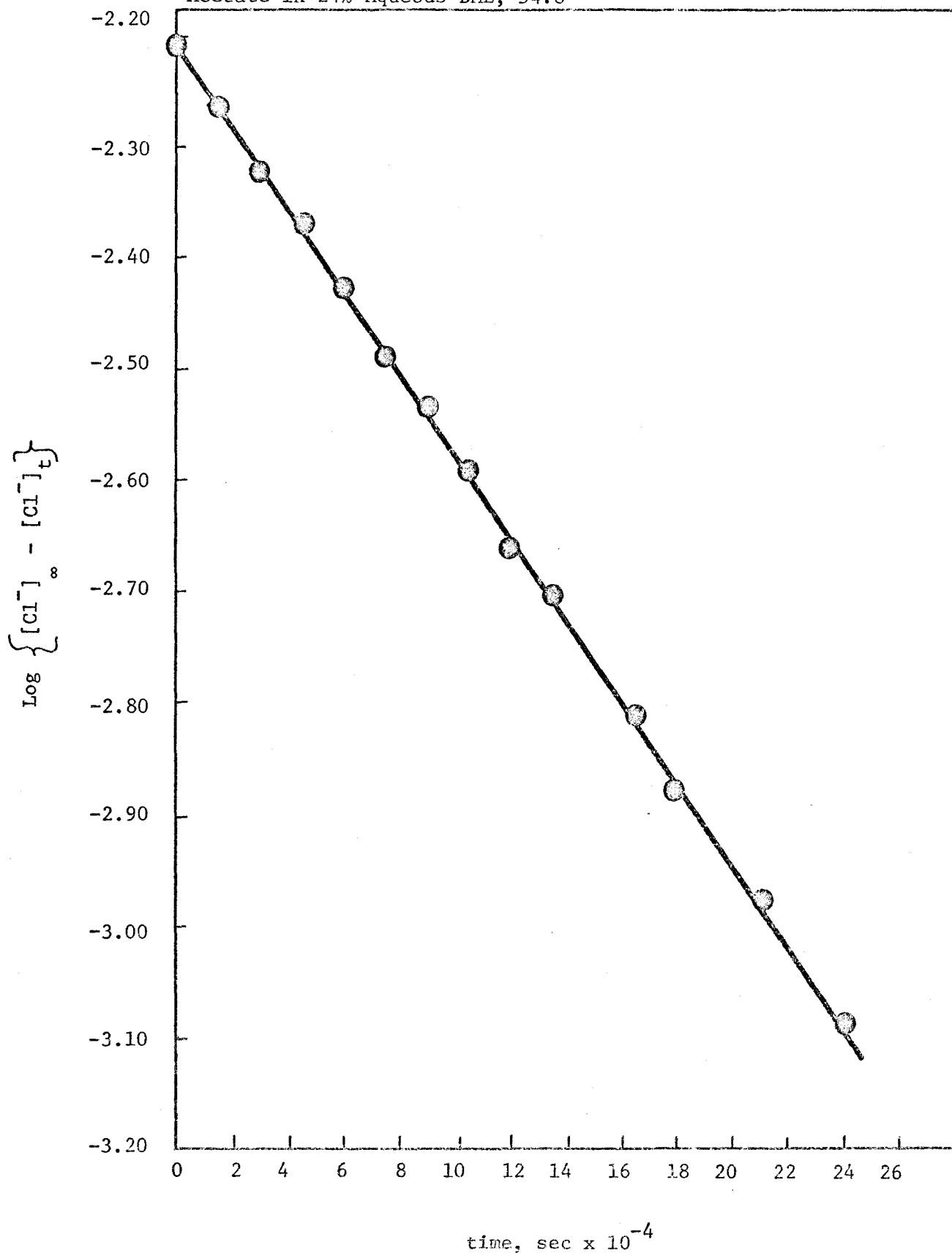
Substitution of *Trans*-2-Chloro-4-*t*-butylcyclohexanone, 1.00 M̲

Acetate in 24% Aqueous DME, 54.8°

time, sec x 10^{-2}
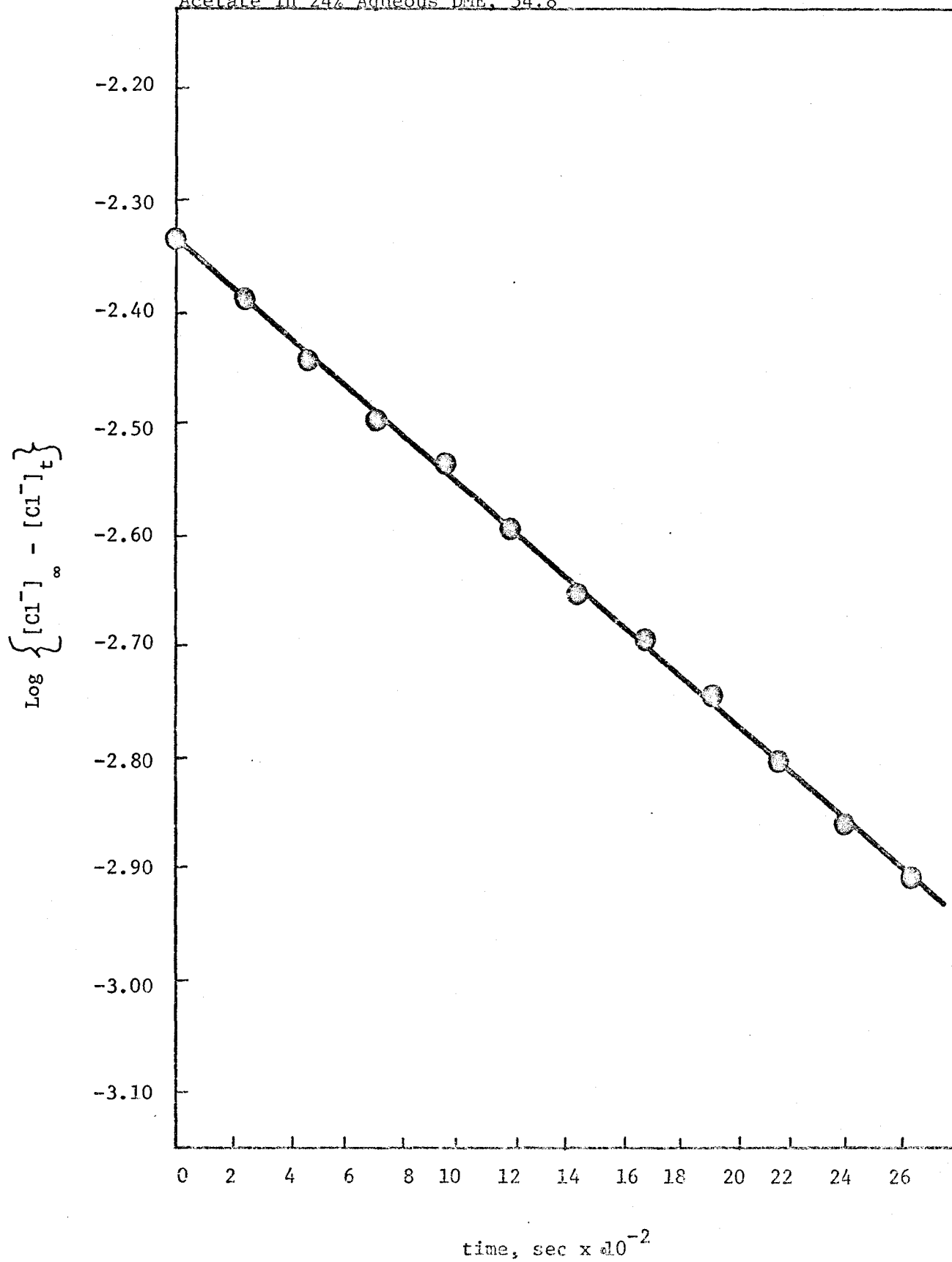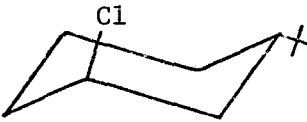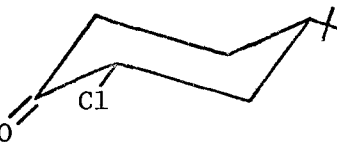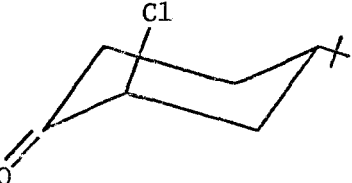
TABLE XIX

Substitution of Cyclohexyl Chlorides and Chlorocyclohexanones by Acetate in 24% Aqueous DME, for Activation Parameters

Compound	Temperature	$k, \underline{M}^{-1} sec^{-1}$
	54.8°±0.04°C	1.18±0.02 x 10^{-6}
	75.0°±0.08°C	4.90±0.085 x 10^{-6}
	54.8°±0.04°C	2.54±0.05 x 10^{-6}
	75.0°±0.08°C	9.67±0.15 x 10^{-6}
	35.0°±0.02°C	1.22±0.015 x 10^{-6}
	54.8°±0.04°C	8.32±0.12 x 10^{-6}
	75.0°±0.08°C	3.95±0.07 x 10^{-5}
	35.0°±0.02°C	1.58±0.02 x 10^{-4}
	54.8°±0.04°C	5.06±0.08 x 10^{-4}
	75.0°±0.09°C	1.19±0.02 x 10^{-3}

of the *trans*-compound) at 54.8° and 1.97 at 75°. Thus the *trans*-compound

is slightly favoured toward substitution by acetate. The rate factors

between the *cis*- and *trans*-chlorocyclohexanones are 60.7 at 54.8° and

30.2 at 75°. In addition, the *trans*-chloroketone reacts 200 times faster

than the *trans*-cyclohexyl chloride at 54.8°, while the difference in

reactivity for the *cis*-compounds is only 7.0-fold at the same temperature.

Thus, there is only a very small difference in reactivity between

the cyclohexyl chlorides, with the *trans*-chloride reacting faster than the

cis-chloride by a factor near 2.0 between 54.8° and 75°. On the other hand,

the *trans*-chloroketone reacts much faster than the *cis*-compound, by a

factor of 61 at 54.8°. There would seem to be an activation present in

the reaction of the *trans*-chloroketone with acetate which is absent in

the reaction of the *cis*-chloroketone. These effects are not apparent in

the cyclohexyl chlorides themselves. The rate enhancement observed for

the *trans*-chlorocyclohexanone over the *trans*-cyclohexyl chloride is quite

large, 200-fold, while there is a small rate enhancement of 7-fold for the

cis-chlorocyclohexanone over the *cis*-cyclohexyl chloride. This result is

rather striking, in that a rate enhancement is observed even if the geometry

is wrong for bridging or conjugation to occur, as discussed above. The

carbonyl group probably provides for a less-ordered transition state through

its lower steric requirement[124] and/or its ability to disperse charge

inductively, hence lowering the solvent restriction.

Further evidence on this point was obtained from calculation of

the activation parameters from the data in Table XIX, p 130. The enthalpies

and entropies of activation were calculated in the usual manner from plots

of log k/T against 1/T for the four compounds studied. The plots for the

chlorocyclohexanones are shown in Figure 14, p 133. Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$

for each compound were calculated from the least-squares computer values

of slope and intercept, respectively, while the errors were calculated from

the maximum and minimum slopes of the plots determined by the range of

rate constants observed. These numbers are given in Table XX, p 134.

As can be seen from Table XX, p 134, the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are

the same, within experimental error, for the two cyclohexyl chlorides. The

activation parameters for the chlorocyclohexanones, on the other hand, are

very different. The *trans*-chlorocyclohexanone has a lower enthalpy of

activation, by 7.9 kcal mol^{-1} and a more negative entropy of activation,

by 16eu, than the *cis*-chlorocyclohexanones at 54.8°, the difference in

$\Delta G^{\ddagger}$ between the *cis*- and *trans*-chloroketones (2.75 kcal mol^{-1}) contains a

contribution of 7.90 kcal mol^{-1} from the $\Delta H^{\ddagger}$ term, and (-) 5.15 kcal mol^{-1}

from the $T\Delta S^{\ddagger}$ term.

The enthalpy of activation is lower by 8 kcal mol^{-1} for the *trans*-

chlorocyclohexanone, with a concomittant decrease in the entropy of

activation of 16eu. If this effect is caused by bridging or conjugation at

the transition state, then the acyclic ketones are not taking much advantage

FIGURE 14   133

Activation Parameters for Substitution of *Cis-* and *Trans*-2-Chloro-
4-*t*-butylcyclohexanone by Acetate

$1/T$, x 10^3
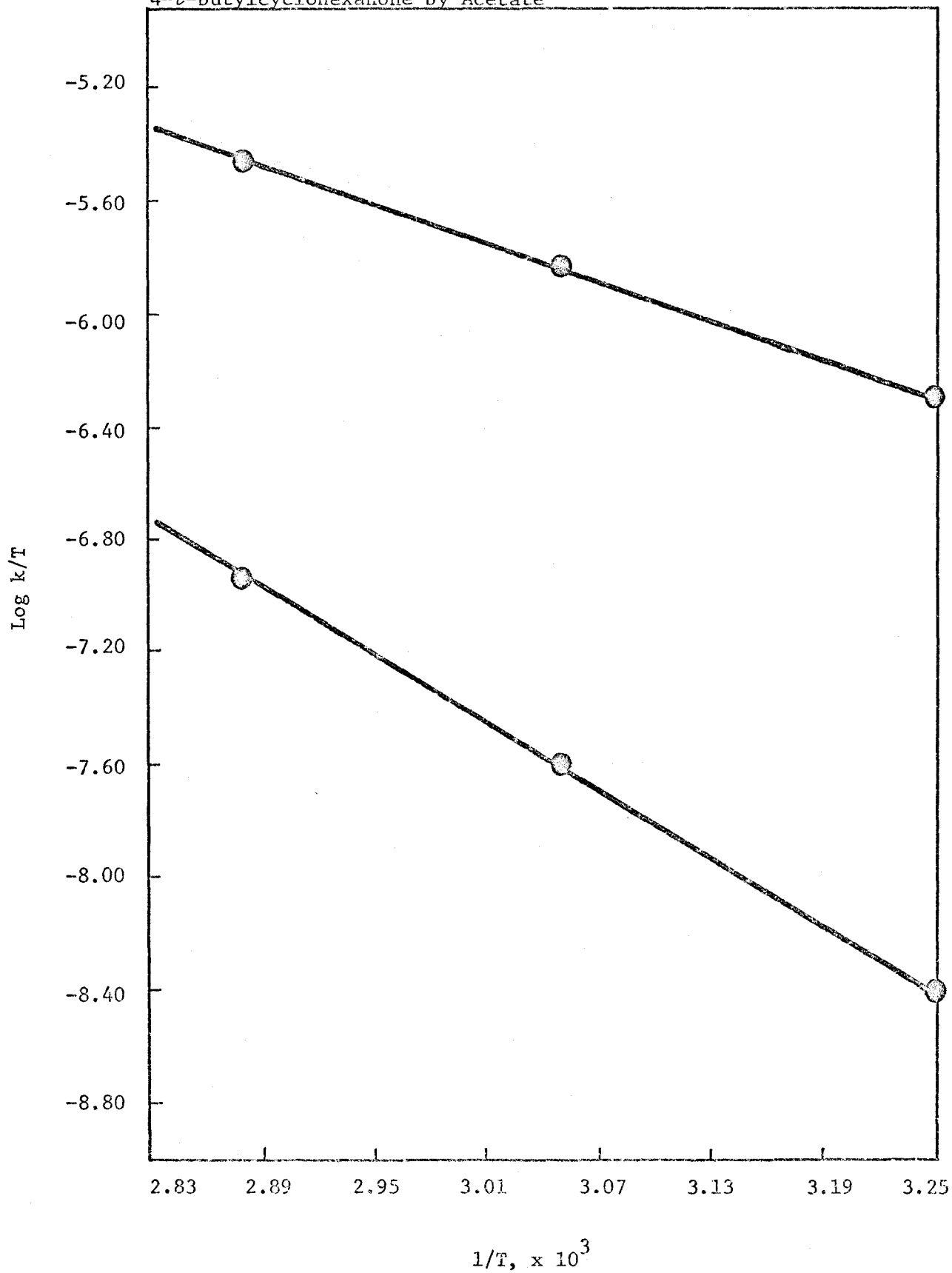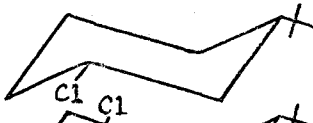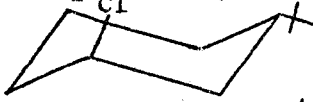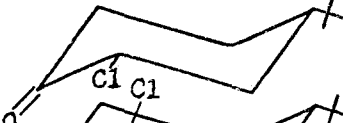
TABLE XX

Activation Parameters for the *Cis-* and *Trans*-Cyclohexyl Chlorides

and Chloro-Cyclohexanones

Compound	$\Delta H^{\ddagger}$ kcal mole^{-1}	$\Delta S^{\ddagger}$ eu
	16.0±0.79	−37.3±2.4
	15.0±0.98	−38.8±3.0
	18.1±0.33	−27.0±1.0
	10.2±0.32	−42.8±0.96

of such activation. The enthalpies of activation are the same, within experimental error, for 1-bromo-2-butanone and *n*-butyl bromide. The rate enhancement observed for the bromoketone over the alkyl bromide must be caused by entropy effects. It appears that the entropy factor comes not from charge dispersal effects on solvent constriction, but from the ability of the carbonyl group to raise $\Delta S^{\ddagger}$ because of a lower steric effect than the methylene group, as proposed by Bordwell[124]. Indeed, there is a similar entropy difference (~10eu) between the cyclohexyl chlorides and *cis*-chlorocyclohexanone. Since the geometry is wrong for conjugation or bridging in the latter, the activating influence of the carbonyl group must be to raise $\Delta S^{\ddagger}$ with a resulting increase in rate over the cyclohexyl chlorides. Thus, it is very probable that conjugation or bridging is important only in the case of the *trans*-chlorocyclohexanone. For this compound, $\Delta S^{\ddagger}$ is lowered along with $\Delta H^{\ddagger}$, as expected for a reaction in which stabilization can be gained only by putting strict geometric requirements on the transition state.

In summary, there is a very strong similarity between the activation parameters for the acyclic bromoketones and alkyl bromides on the one hand, and the cyclohexyl chlorides and *cis*-chlorocyclohexanone on the other. The obvious conclusion then, is that only the *trans*-chlorocyclohexanone is appreciably different in mechanism (stereoelectronically) from bimolecular nucleophilic displacement at ordinary saturated carbon.

In the case of the chloro-compounds, where the rate factors are much higher (*e.g.*, 780-fold (X = Cl) compared to 71-fold (X = Br) for $CH_3CH_2COCH_2X$ over $CH_3CH_2CH_2CH_2X$), there may be a greater overlap effect in the acyclic chloroketones because the transition state will be farther along the reaction coordinate toward products.

Anomalous Products

Anomalous results were obtained from the displacement of bromide by acetate from $(CH_3)_2CBrCOCH_3$ and $(CH_3)_2CHCOCH_2Br$. In addition to the acetoxyketone expected from displacement of bromide from each bromoketone, its isomeric acetoxyketone was produced, and also two α-hydroxyketones were found, as shown in the following scheme.

$$(CH_3)_2CBrCOCH_3 + \overline{OAc} \xrightarrow[H_2O]{HOAc}$$

LXXXVIII

$$(CH_3)_2C(OAc)COCH_3 + (CH_3)_2C(OH)COCH_3$$

XC   XCI

$$(CH_3)_2CHCOCH_2Br + \overline{OAc} \xrightarrow[H_2O]{HOAc}$$

LXXXIX

$$+ (CH_3)_2CHCOCH_2OAc + (CH_3)_2CHCOCH_2OH$$

XCII   XCIII
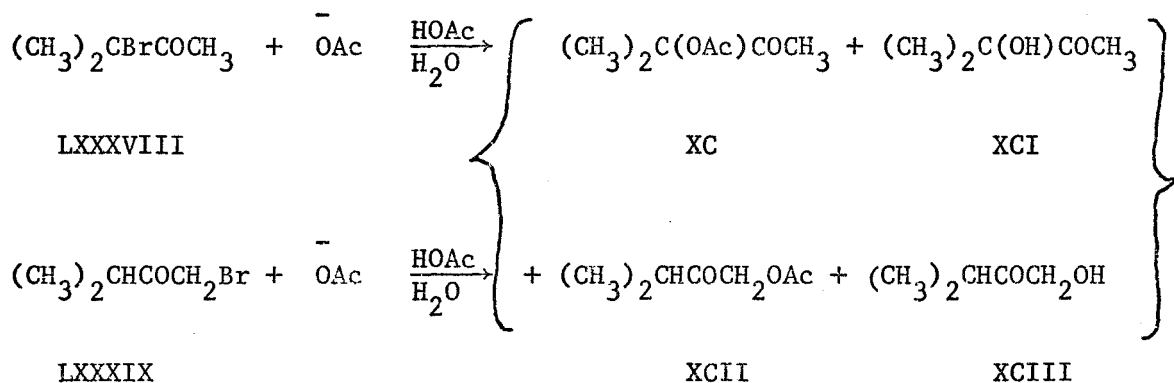
The conditions used were identical to those used for the other bromoketones — an acetic acid/acetate buffer, where $[HOAc] = [\overline{OAc}] = 1.00 \underline{M}$, and $[H_2O] \simeq 40 \underline{M}$. All four products (XC-XCIII) were obtained whether the starting material was LXXXVIII or LXXXIX, although the ratio of products was different. The product ratios were determined by glpc analysis, using FFAP as the stationary

phase. Compounds XC-XCIII were collected by preparative scale glpc

and identified by nmr. The average ratios of products obtained and

their per cent yield from each are given in Table XXI, p 138.

A possible route to these products is through solvolysis of

the enol allylic bromides, formed by enolization of the bromoketone,

as discussed in the Historical Introduction. This would account for

the formation of the α-hydroxyketones, while the α-acetoxyketones

could originate from direct substitution and/or from the enols. In

Chart 3, p 139, is outlined a possible mechanism to explain these

results. There is also the possibility that the enol allylic cation

cyclizes to a cyclopropanone intermediate, 2,2-dimethylcyclopropanone

(XCIV), which could open to products. To test this hypothesis, a pure

sample of XV was obtained. When the cyclopropanone was placed in the

buffer solution, the same products were obtained as with the bromoketones,

but the ratios and yields were much different (see Table XXI, p 138).

It appears that the cyclopropanone is not an important intermediate in

either of these reactions; first, because the product ratios are not

the same from the two bromoketones, and second, because neither bromoketone

gives product ratios close to those from the cyclopropanone. The fractions

XCIV

TABLE XXI

Formation of Anomalous Products from Displacement of Bromide by Acetate

in 24% Aqueous DME, 54.8°.
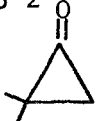
Starting Material	3-OAc/1-OAc	3-OH/1-OH	% Acetoxy Product	% Hydroxy Product
$(CH_3)_2CBrCOCH_3$	2.3	8.4	53	47
$(CH_3)_2CHCOCH_2Br$	0.075	0.28	78	22
	8.1	3.6	82	17

Chart 3

Anomalous Products from 3-Bromo-3-methyl-2-butanone and 1-Bromo-3-

methyl-2-butanone

$(CH_3)_2CBrCOCH_3$ $(CH_3)_2CHCOCH_2Br$

LXXXVIII   LXXXIX

HOAc / H_2O $-OAc$

$(CH_3)_2C-C=CH_2$ $\rightleftharpoons$ $(CH_3)_2C \cdots CH_2$ (OH) $\rightleftharpoons$ $(CH_3)_2C=C$ (OH) CH_2 Br

Br

Products   Intimate Ion Pair   Products

S_N2 or S_N2' S_N2 or S_N2'

$(CH_3)_2C \cdots CH_2$ (OH) $+$ Br^-

Solvent Separated (or Free) Ions

k_3^{OAc} $k_3^{H_2O}$ k_1^{OAc} $k_1^{H_2O}$

$(CH_3)_2C(OAc)COCH_3$ $(CH_3)_2C(OH)COCH_3$ $(CH_3)_2CHCOCH_2OAc$ $(CH_3)_2CHCOCH_2OH$

XC   XCI   XCII   XCIII
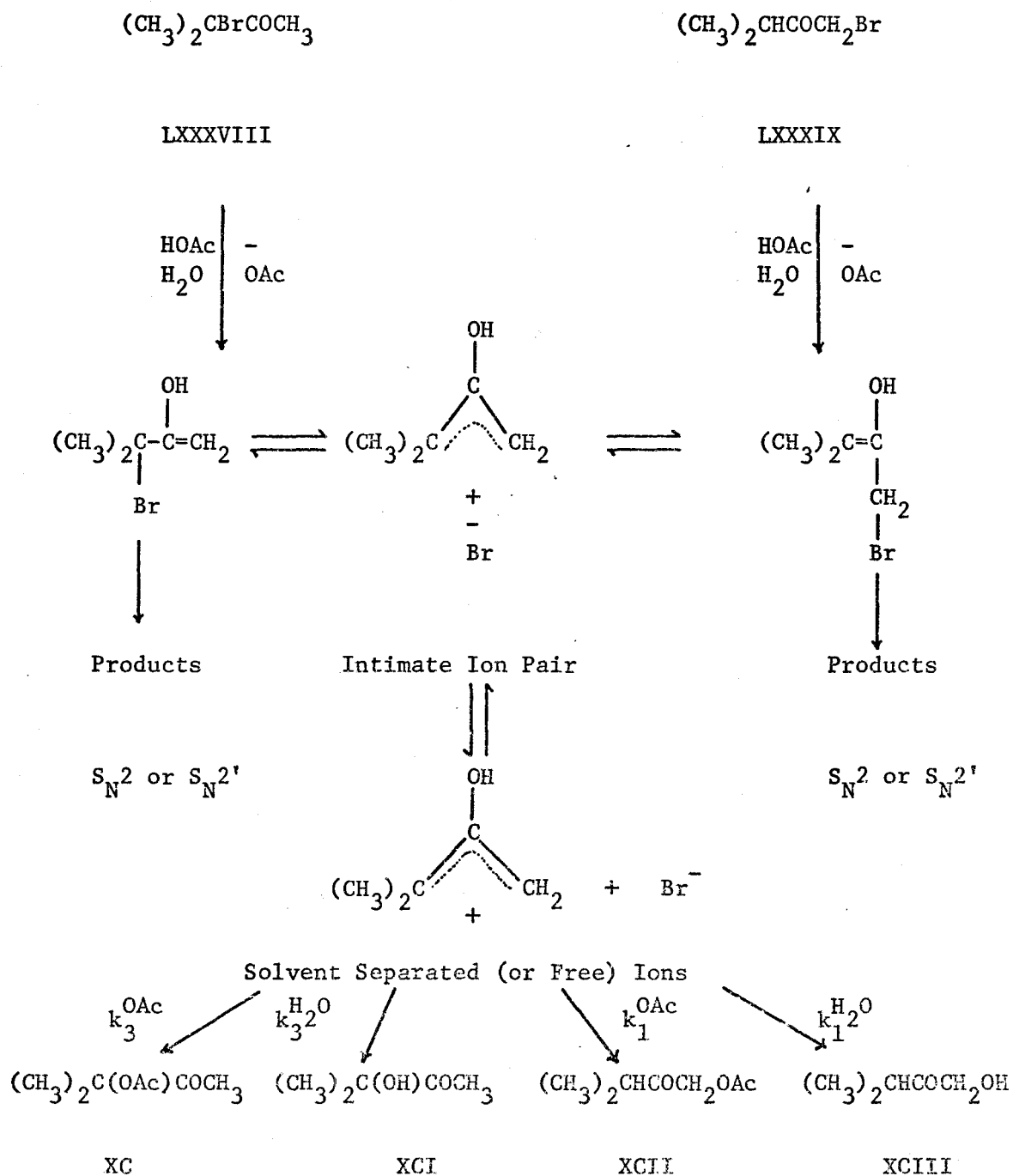
of reactions going via cyclopropanone, if any, can not be inferred from the data nor is it possible to calculate the contribution from S_N2 reactions on initial (or rearranged) bromoketone.

In conclusion, these results indicate that enolization, followed by solvolysis, of the α-haloketones is possible under these conditions, where the enol cation so formed is relatively stable. This reaction was found to occur with the only tertiary bromoketone used in this study, $(CH_3)_2CBrCOCH_3$, and its isomer, $(CH_3)_2CHCOCH_2Br$. These anomalous results were not obtained with the corresponding α-chloroketones; they gave only the α-acetoxyketone corresponding to direct substitution of chloride by acetate ion. Although it is possible that enolization of the chloroketones is slower than that of the bromoketones, it is much more likely that ionization of the enol allylic chlorides is slower.

General Conclusions

It has been shown that bimolecular nucleophilic displacement of bromide and chloride from α-bromo- and α-chloroketones, respectively, by acetate or azide ion, under the conditions described, yields only one product, that from α-substitution. There are two exceptions, described above.

Rate data from a series of α-bromo- and α-chloroketones with increasing methyl substitution at the reaction site and on the other

side of the carbonyl group are not consistent with a bridging mechanism, since the rate retardations observed are too small. The observed effects are more consistent with a conjugation mechanism, although the activation parameters for the bromo-compounds suggest that the rate enhancements observed with the bromoketones are due to a lower steric requirement of the carbonyl group rather than any special interaction with the nucleophile.

More definitive information was obtained from a study of a model system used to probe for the stereoelectronic requirements of these substitution reactions. The activation parameters for *cis*-2-chloro-4-*t*-butylcyclohexanone do not support either a bridging or conjugation mechanism for the observed rate enhancement, but are consistent with a smaller steric requirement of the carbonyl group. Only in one case, the *trans*-2-chloro-4-*t*-butylcyclohexanone, where the compound is conformationally held in such a manner that bridging is possible, does this interaction between the carbonyl group and the nucleophile occur at the transition state.

In conclusion, these results suggest that a bridging or conjugation mechanism for the bimolecular nucleophilic substitution reactions of α-haloketones is not a general one.

SUMMARY

In the first part of this section, it was shown that the regioselectivities of bromination and deuterium exchange of 2-butanone are the same, under identical conditions. This criterion must, of course, be met if the rate-determining step for these processes is enolization. By means of two methods, one approximate and one rigorous, it was shown that $k^H_{CH_2}/k^H_{CH_3}$ for the acetate-catalyzed bromination of 2-butanone is between 1.7 and 1.9 at 54.8°; the ratio for deuterium exchange is 1.7. This work firmly establishes that enolization is the rate-determining step for the former reaction, contrary to evidence presented by Rappe[30-33]. It is recommended that in general the enolization mechanism should be retained, even though reaction of bromine with unenolized ketone may occur under other conditions.

In the second part of this section, the mechanism for the bimolecular nucleophilic substitution reactions of α-bromo- and α-chloroketones in an acetic acid/acetate medium was discussed. It was shown that both the steric factors and the activation parameters for the α-haloketones and alkyl halides are inconsistent with either a bridging or a conjugation mechanism for the observed rate enhancements of haloketone over alkyl halide.

From an examination of the stereoelectronic requirements of this mechanism, it was shown that substitution reactions of α-haloketones do not differ in mechanism from nucleophilic substitution at ordinary saturated carbon unless the α-haloketone is conformationally held so as to allow bridging without imposing additional constraints.

EXPERIMENTAL

Outline

The experimental section consists of five parts. In the first, the synthesis and purification of the bromo-compounds derived from 2-butanone is described. All of these bromoketones, as well as the two acetoxyketones, have been previously described in the literature. They were purified by distillation or by preparative gas-liquid partition chromatography (glpc). A nuclear magnetic resonance (nmr) spectrum and a mass spectrum consistent with the proposed structure were obtained in each case.

The second part describes the base-catalyzed bromination experiments performed to determine the relative rates of bromination in 2-butanone. In the third part, the method for determining the relative rates of acetate-catalyzed deuterium exchange in 2-butanone is described. Typical plots for the determination of the relative rates of deuterium exchange are presented.

The fourth part consists of a description of the preparation and purification of the bromo- and chloroketones used in the nucleophilic substitution studies. The identification of the products is also described. All of these compounds have been described in the literature with the exception of six acetoxyketones. Their ir and nmr spectral data and refractive indices are given.

144

In the last part, the methods used to obtain the kinetic data on the substitution reactions of the α-haloketones are given.

Instrumental Analysis

Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer or on a Varian T-60 spectrometer. Gas-liquid chromatographic analyses were performed on a Varian Aerograph Model 90-P3 instrument equipped with a thermal conductivity detector or on a Varian Aerograph Model 204-B instrument equipped with a flame ionization detector. Helium was used as the carrier gas in all cases. The following stationary phases were used, all on 60-80 mesh Chromosorb-W: 10% Silicone QF-1 (10' x 3/8"), 12% QF-1 (10' x 1/8"), 15% FFAP (5' x 1/4"), 10% FFAP (5' x 1/8"), 20% SE-30 (10' x 3/8"), 20% SE-30 (10' x 1/8"), 15% Carbowax 20 M (10' x 3/8"), and 15% Carbowax 20 M (10' x 1/8"). A Varian Aerograph Model 476 electronic digital integrator with a Victor printer was used to obtain quantitative peak ratios from glpc analyses.

Infrared spectra were recorded on a Beckman Model IR 10 or on a Perkin Elmer Model 337 spectrometer. Mass spectra were recorded on a Hitachi-Perkin Elmer Model RMU-6A mass spectrometer. Indices of refraction were obtained with a Bausch and Lomb refractometer equipped with a Haake circulating constant temperature bath. Spinning band distillations were performed on a Nester-Faust Auto Annular Spinning

Band distillation column. The nucleophilic substitution kinetic
results were obtained using Orion solid-state membrane, ion-selective,
electrodes with either an Orion double-junction electrode or a
Fisher Calomel electrode as reference.

They were connected to a Fisher Accumet Expanded Scale pH
Meter, Model 310, used in the expanded millivolt mode.

Bromo- and Acetoxyketones from 2-Butanone

2-Butanone

2-Butanone (Baker Analytical Grade) was distilled through
a 20 cm glass column, packed with glass helices, collecting the
fraction boiling from 79-80° [lit.[134] bp 79.6°]. The purified
ketone was stored over anhydrous sodium sulfate.

2-Buten-2-ol Acetate and 1-Buten-2-ol Acetate

A mixture of 2-butanone (28.8 g, 0.400 mole), isopropenyl
acetate (80.0 g, 0.800 mole, Aldrich Chemical Co.), and p-toluene-
sulfonic acid (0.500 g, 2.91×10^{-3} mole, Eastern Chemical Corp.,
reagent grade) was heated to distill a mixture of acetone and
isopropenyl acetate (~50°). The temperature gradually rose to 56°,
and acetone was slowly distilled for 5 hours. Next, 28 g of isopro-
penyl acetate was added, and heating was continued for 12 hours

longer. The temperature was raised, to distill off any remaining acetone, and then lowered prior to addition of ether.

The ether solution was washed with sodium bicarbonate and dried over sodium sulfate before the ether was removed at reduced pressure to yield a pale yellow liquid. This mixture of enol acetates was distilled through a spinning band column, and two fractions were collected: I, 115-120°, 7.1 g; and II, 120-122°, 9.2 g. Analysis of these fractions by nmr and glpc showed them to be a mixture of the three enol acetates[135] (two isomers of 2-buten-2-ol acetate not separated by glpc, and 1-buten-2-ol acetate). The overall yield of this mixture was 16.3 g (36.0%), after fractionation.

Enol Acetate Bromination

The procedure of Bedoukian[136] was used in the bromination of the enol acetates. The mixture of enol acetates (16.3 g, 0.143 mole) was added to 50 ml of dry carbon tetrachloride, and the solution was cooled in an ice-bath. Bromine (22.8 g, 0.143 mole) was dissolved in 10 ml of carbon tetrachloride, and this solution was added slowly to the enol acetates. The temperature was kept below 10° during the addition. Next the brominated mixture was added to an equal volume of 99.5-100% methanol, with cooling. After standing for 2 days, the solution was diluted with 175 ml of water, and the carbon tetrachloride layer was washed with 100 ml of a 5%

sodium carbonate solution. The carbon tetrachloride was then dried over anhydrous sodium sulfate, and most of the solvent was removed at reduced pressure. The residue was distilled *in vacuo* on a spinning band column, collecting the fraction from 40-85° (150 mm). At this point the pot residue was very dark, and nothing further was collected.

An nmr spectrum of this fraction showed it to be approximately 85% 3-bromo-2-butanone[18], contaminated with unreacted enol acetates. The residue in the pot consisted of 1-bromo-2-butanone (20%) and polybrominated ketones.

Acid-Catalyzed Bromination of 2-Butanone

The method of Catch and coworkers[137] was used to prepare the monobromoketones. Bromine (160 g, 10.0 moles) was added dropwise to a mechanically-stirred mixture of 2-butanone (124 g, 17.2 moles), potassium chlorate (30.0 g, 0.245 mole), and water (250 ml). The temperature was raised to 50° to initiate the reaction; it then proceeded at 35-45°. After the addition was complete, the mixture was allowed to stand for an hour. The bottom layer of crude bromoketone was separated, washed with water, shaken with magnesium oxide, washed with water again, and dried over anhydrous calcium chloride. The residue was distilled through a 20 cm glass column, packed with glass helices, and the following fractions were collected: I, bp 21-46° (23 mm);

II, bp 46-47° (23 mm); and III, bp 44-45° (10 mm). Fractions II and III were shown by nmr to be 3-bromo-2-butanone [lit.[137] bp 87° (150 mm)] and 1-bromo-2-butanone [lit.[137] bp 105° (150 mm)], respectively.

The refractive indices and nmr data are as follows. 3-Bromo-2-butanone had n^{22}D 1.4560 [lit.[137] n^{20}D 1.4571]; nmr (CCl$_4$) δ4.40 (q, 1, J = 7Hz, C$\underline{H}$Br), 2.32 (2, 3, C$\underline{H}_3$CO), 1.72 (d, 3, J = 7Hz, CHBrC$\underline{H}_3$), while 1-bromo-2-butanone had n^{22}D 1.4658 [lit.[137] n^{20}D 1.4670] and nmr (CCl$_4$) δ3.85 (s, 2, BrC$\underline{H}_2$CO), 2.68 (q, 2, J = 7Hz, COC$\underline{H}_2$), 1.08 (t, 3, J = 7Hz, CH$_2$C$\underline{H}_3$). Both compounds were better than 90% pure by nmr and glpc (SE-30 column).

1-Bromo-2-butanone (Diazomethane)

The method of Catch and coworkers[138] was used to prepare 1-bromo-2-butanone from propionyl chloride and diazomethane. To prepare the diazomethane, 25 ml of a 50% potassium hydroxide solution was mixed with 80 ml of 95% ethanol and heated to 60° on a water bath. Then a solution of N-nitroso-N-methyl-p-toluenesulfonamide, "Diazald", (54.0 g, 0.252 mole, Aldrich Chemical Co.) in 300 ml of ether was added dropwise to the alcoholic hydroxide solution over 2 hours.

The ethanol solution of diazomethane was collected by distillation in an ice-cooled flask. After drying over potassium hydroxide, the solution was reacted with propionyl chloride as described in the literature[138].

The ethereal solution of 1-bromo-2-butanone was washed with water,
shaken with magnesium oxide, and washed with water again. After
removal of the ether, the residue was distilled through a glass
helices-packed column, collecting the fraction boiling at 50° (12
mm) [lit.[137] bp 105° (150 mm)].

Acetoxyketones

The following were added to a 100 ml flask: acetic acid
(0.276 g, 4.60 x 10^{-3} mole), sodium acetate (3.75 g, 4.60 x 10^{-2}
mole), 2-butanone (7.20 g, 0.100 mole), bromine (4.00 g, 2.50 x
10^{-2} mole), and 90 ml of water. After 45 hours at 35°, the solution
was extracted with carbon tetrachloride and dried over sodium sulfate.
Most of the solvent was removed at reduced pressure, and the residue
was subjected to preparative glpc on a Carbowax 20 M column (10' x
3/8"). The retention times of two major components did not correspond
to either monobromoketone; therefore, enough of each was collected for
identification. The nmr spectra of the two showed the following
absorptions: compound A (CCl_4), δ4.95 (q, 1, J = 7Hz, $C\underline{H}(OAc)CH_3$),
2.04 (s, 6, $C\underline{H}_3COCH(OCOC\underline{H}_3)$), 1.30 (d, 3, J = 7Hz, $CH(OAc)C\underline{H}_3$);
Compound B (CCl_4), δ4.52 (s, 2, $C\underline{H}_2OAc$), 2.40 (q, 2, J = 7Hz, $COC\underline{H}_2$),
2.10 (s, 3, $OCOC\underline{H}_3$), and 1.07 (t, 3, J = 7Hz, $CH_2C\underline{H}_3$). The mass spectra
were very similar, with the molecular ion at *m/e* = 130. These data are

consistent with A being 3-acetoxy-2-butanone), n^{22} D 1.4118 [lit.[139]

n^{20} D 1.4129], and B being 1-acetoxy-2-butanone, n^{22} D 1.4177

[lit.[140] n^{19} D 1.4190].

Products from Acetate-Catalyzed Bromination of 2-Butanone

To isolate the products formed in the acetate-catalyzed

bromination of 2-butanone, the procedure of Rappe[18] was used

(experiments 4, 24, and 28). The following were placed in a 100 ml

flask: 2-butanone (3.60 g, 0.050 mole), acetic acid (50.0 g, 0.834

mole), sodium acetate (10.0 g, 0.122 mole), and bromine (8.00 g, 0.050

mole). The reaction was allowed to proceed at room temperature, with

stirring, until decolorization of the bromine occurred. After extracting

the solution with six 5-ml portions of carbon tetrachloride, the extracts

were combined and dried over sodium sulfate. Most of the solvent was

removed at reduced pressure, and the residue was chromatographed by

preparative glpc on a 20% SE-30 column.

The following compounds were collected and identified by nmr

and mass spectra: 3-bromo-2-butanone (3-BrK), 1-bromo-2-butanone (1-BrK),

3-acetoxy-2-butanone (3-OAc), 1-acetoxy-2-butanone (1-OAc), 1,1,1-tribromo-

2-butanone (1,1,1-BrK), n^{21} D 1.5647 [lit.[141] n^{25} D 1.5626]; nmr (CCl_4)

δ3.51 (q, 2, J = 8Hz, $COCH_2$), 1.64 (t, 3, J = 8Hz, CH_2CH_3); mass

spectrum, M^+ at m/e = 309 (quartet); 1,1,1,3-tetrabromo-2-butanone

(1,1,1,3-BrK), n^{22} D 1.6341 [lit. not reported]; nmr (CCl_4) δ5.42

(q, 1, J = 7Hz, COC$\underline{H}$Br), 2.18 (d, 3, J = 7Hz, CHBrC$\underline{H}_3$); mass spectrum, M$^+$ at m/e = 388 (quintet); and bromoform, n^{22} D 1.5965 [lit.[142] n^{20} D 1.5976]; nmr (CCl$_4$) δ7.24 (s, 1, - C$\underline{H}$); mass spectrum, M$^+$ at m/e = 253 (quartet).

In order to prepare 3,3-dibromo-2-butanone (3,3-BrK), the following were placed in a 100 ml flask: 3-bromo-2-butanone (3.00 g, 0.020 mole), acetic acid (30.0 g, 0.500 mole) and sodium acetate (5.00 g, 0.061 mole). Bromine (3.20 g, 0.020 mole) was added to the above solution which was stirred at room temperature. After work-up as before, the residue was subjected to preparative glpc on a 10% QF-1 column to yield 3,3-dibromo-2-butanone (3,3-BrK), n^{21} D 1.5072 [lit.[143] n^{25} D 1.5050]; nmr (CCl$_4$) δ2.62 (2, 3, CBr$_2$C$\underline{H}_3$), 2.47 (s, 3, COC$\underline{H}_3$); mass spectrum, M$^+$ at m/e = 230 (triplet). An analogous experiment, using 1-bromo-2-butanone in place of 3-bromo-2-butanone and preparative glpc on a 20% SE-30 column, yielded 1,1-dibromo-2-butanone (1,1-BrK), n^{22} D 1.5126 [lit.[144] n^{25} D 1.5112]; nmr (CCl$_4$) δ6.15 (s, 1, C$\underline{H}$Br$_2$), 3.15 (q, 2, J = 8Hz, COC$\underline{H}_2$), 1.42 (t, 3, J = 8Hz, CH$_2$C$\underline{H}_3$); mass spectrum, M$^+$ at m/e = 230 (triplet).

The order of elution of these compounds on a 12% QF-1 column (10' x 1/8") was: CHBr$_3$, 3-BrK, 3,3-BrK, 1-BrK, 1,1-BrK, 3-OAc, 1-OAc, 1,1,1-BrK, and 1,1,1,3-BrK. On a 20% SE-30 column (10' x 1/8"), the order was: 3-BrK, 1-BrK, 3-OAc, CHBr$_3$, 3,3-BrK, 1-OAc, 1,1-BrK, 1,1,1-BrK, and 1,1,1,3-BrK.

Base-Catalyzed Bromination of 2-Butanone, 3-Bromo-2-butanone, and

1-Bromo-2-butanone

Hydroxide-Catalyzed Bromination of 2-Butanone

To a 100 ml flask was added 2-butanone (10.0 g, 0.139 mole),

1.10 ml of a 1.00×10^{-2} $\underline{M}$ sodium hydroxide solution, and water to

make 100 ml. Bromine (0.5 µl, 1.00×10^{-5} mole) was added to this

stirred solution at 35°. The reaction was quenched after 5 minutes

with a phosphate buffer solution (pH = 7.00). Analysis by glpc on a

20% SE-30 column showed several components in addition to a small

amount of 3-bromo- and 1-bromo-2-butanone. This experiment was repeated

under the same conditions, with the exclusion of bromine. The results

were identical with those of the first experiment, except for the

absence of the two bromoketones. The other products, which were not

identified, probably resulted from reactions of enolates with ketone

(condensation).

Calibration of Glpc Columns

A mixture of 3-bromo-2-butanone (0.5025 g, 3.330×10^{-3} mole)

and 1-bromo-2-butanone (0.5025 g, 3.330×10^{-3} mole) was added to 20.0 ml

of carbon tetrachloride (Fisher Scientific, Certified ACS Spectroanalyzed).

This solution was chromatographed on a 12% QF-1 Column (10' x 1/8"), using

sample volumes from 0.60 to 1.30 µl. The number of moles of bromoketone in

each sample injected was calculated, and this was divided by the integral area determined by the digital integrator. From 7 different sample sizes (3 injections each), the average ratio was calculated to be 1.1127×10^{-12} for the bromoketones. This same number was found for bromoform, while for the acetoxyketones 9.8576×10^{-13} was calculated. The relationship between integral area and amount of material injected was used to check material balances in the bromination of 2-butanone and for kinetic determinations. The above procedure was repeated using a 20% SE-30 (10' x 1/8") column; the observed constants were 5.8752×10^{-13} for the bromocompounds, and 5.1265×10^{-13} for the acetoxyketones.

Acetate-Catalyzed Bromination of 2-Butanone

To a 100 ml volumetric flask, the following were added: acetic acid (6.00 g, 0.100 mole), sodium acetate (8.20 g, 0.100 mole), 2-butanone (14.4 g, 0.200 mole), bromine (0.800 g, 5.00×10^{-3} mole), and water to 100 ml. After the flask was shaken vigorously, it was placed in a water bath at $54.8 \pm 0.04°$. The solution was stirred, using a submersible magnetic stirrer, until decolorization occurred. At this point the solution was added quickly to 50 ml of ice water in a separatory funnel, and the cold aqueous mixture was extracted six times with 5-ml portions of carbon tetrachloride. After the combined extracts were dried over sodium sulfate, most of the carbon tetrachloride was removed at reduced pressure. The

residue was analyzed by glpc using a 12% QF-1 column (10' x 1/8")

and a 20% SE-30 column (10' x 1/8"). The relative yields (mole

percent), were determined by an electronic digital integrator. At

least 5 injections were made for each run, and the results were

averaged. Both columns had been previously calibrated (p153),

and the retention times of each component were compared with those

of authentic samples. The relative yields for one run were: 1-BrK,

10.7; 1-OAc, 12.9; 3-BrK, 15.8; 3-OAc, 14.2; 1,1-BrK, 5.7; 1,1,1-BrK,

17.1; 3,3-BrK, 1.4; 1,1,1,3-BrK, 5.9 and $CHBr_3$, 16.1.

Another experiment was performed under the same conditions,

except that the amount of bromine used was doubled to decrease the

yield of monobromoketones. Work-up and analysis were as described

above, except that only the QF-1 column was used to determine the

relative yields. These yields were: 1-BrK, 1.23; 1-OAc, 19.1; 3-BrK,

1.05; 3-OAc, 13.6; 1,1-BrK, 7.43; 1,1,1-BrK, 17.2; 3,3-BrK, 8.12;

1,1,1,3-BrK, 9.07; and $CHBr_3$, 23.2.

Cleavage of 1,1,1-Tribromo-2-butanone by Acetate Ion

A sample of 1,1,1-tribromo-2-butanone was analyzed by glpc on

a 20% SE-30 column (10' x 1/8") and was found to contain approximately

1.4% 1,1-dibromo-2-butanone and 0.3% of an unknown. To a 50 ml volumetric

flask was added 2-butanone (7.20 g, 0.100 mole), acetic acid (3.00 g,

0.050 mole), sodium acetate (4.10 g, 0.050 mole), 1,1,1-tribromo-2-

butanone (9.20 x 10^{-2} g, 2.98 x 10^{-4} mole, impurities described above),

and water to 50 ml. After vigorous shaking, the flask was placed in a

water bath at 54.8 ± 0.04°. The solution was worked-up, as described

previously (p 154), after 24 hours and analyzed by glpc on a 20%

SE-30 column (10' x 1/8"). From the integrated peak areas, the amount

of bromoform produced was calculated to be 17.0% of the total, with

the remainder being 1,1,1-tribromo-2-butanone (75.0%) and unidentified

material (8.0%).

Cleavage of 1,1,1,3-Tetrabromo-2-butanone by Acetate Ion

The above procedure was repeated using 1,1,1,3-tetrabromo-2-

butanone in place of 1,1,1-tribromo-2-butanone. Analysis of the starting

material by glpc showed it to be 95% pure; the major contaminant (2.50%)

was 1,1,1-tribromo-2-butanone. After 24 hours at 54.8 ± 0.04°, the

solution was worked-up as usual and analyzed by glpc. The analysis

showed the presence of bromoform (21.0%), starting material (72.0%)

and unidentified product (7.0%).

Acetate-Catalyzed Bromination of 3-Bromo-2-butanone

The following were placed in a 50 ml volumetric flask: acetic

acid (3.00 g, 0.050 mole), sodium acetate (4.10 g, 0.050 mole), 1,2-

dimethoxyethane (9 ml), bromine (0.294 g, 1.84 x 10^{-3} mole), 3-bromo-

2-butanone (0.152 g, 1.01 x 10^{-3} mole), and water to make 50 ml. The

flask was shaken vigorously and then placed in a water bath at 54.8 ±

0.04°. After 39 minutes, the bromine colour had disappeared, and the

solution was worked-up as described for 2-butanone above. Analysis by

glpc on a 12% QF-1 column (10' x 1/8") showed the following relative

yields (mole percent): 3-BrK, 19.6; 3-OAc, 57.3; 3,3-BrK, 4.8; and

$CHBr_3$, 18.3.

Acetate-Catalyzed Bromination of 1-Bromo-2-butanone

An experiment analogous to the one above was performed, but with 1-bromo-2-butanone (0.150 g, 9.94×10^{-4} mole) in place of 3-bromo-2-butanone. Using the buffer solution and bromine (0.288 g, 1.80×10^{-3} mole), the colour was discharged in 8 minutes. Relative yields were: 1-BrK, 13.0; 1-OAc, 19.2; 1,1-BrK, 12.2; 1,1,1-BrK, 33.6; 1,1,1,3-BrK, 5.2; and $CHBr_3$, 16.8.

Bromination of 3-Bromo- and 1-Bromo-2-butanone Together

The procedure was that described above for the bromination of 3-bromo-2-butanone. Bromine (0.571 g, 3.57×10^{-3} mole), 3-bromo-2-butanone (0.2136 g, 1.41×10^{-3} mole), and 1-bromo-2-butanone (0.2141 g, 1.42×10^{-3} mole) were allowed to react in the buffer solution until the bromine colour disappeared. Work-up and analysis as usual gave the following relative yields: 1-BrK, 10.7; 1-OAc, 11.3; 3-BrK, 42.4; 3-OAc, 11.2; 1,1-BrK, 1.4; 1,1,1-BrK, 1.9; 3,3-BrK, 1.2; and $CHBr_3$, 19.8.

Acetate-Catalyzed Deuterium Exchange of 2-Butanone

Experimental Method

An acetic acid/acetate buffer was prepared by adding acetic acid (0.609 g, 0.010 mole) and sodium acetate (0.832 g, 0.0101 mole) to 8.20 ml of deuterium oxide (99.5% D, Columbia Organic Chemicals Co.). To 0.82 ml of this buffer solution, 0.18 ml of 2-butanone was added by calibrated

pipette for each sample in an nmr tube. After mixing, the tubes were

sealed and then placed in a water bath at 54.8 ± 0.04°. The acetic

acid and acetate concentration in each sample was 0.832 $\underline{M}$, and the

concentration of 2-butanone was 2.00 $\underline{M}$. The samples were integrated at

appropriate intervals on a Varian A-60 nmr spectrometer, after quenching

exchange by chilling the tube with ice. Reaction outside the bath was

negligible, and time outside the bath was not counted.

The above procedure was repeated using a buffer concentration

of 0.610 $\underline{M}$ (1:1 HOAc/OAc). Integrations were performed on a Varian

T-60 nmr spectrometer.

Relative Rates of Deuterium Exchange

Exchange was followed to at least one half-life by integrating

the signals from the 1- and 3- positions, using the non-exchanging

β-methyl group as an internal standard. The methyl group signal from

the buffer components present did not interfere, being well separated

from the α-methyl group of 2-butanone. Each sample was integrated six

times, and an average was taken.

The integral from the β-methyl group was taken as representing

3 protons, and the areas for the 1- and 3- positions were converted

into the average number of protons per molecule remaining at these

positions. On plotting the logarithms of these numbers (I_t) against time,

good straight lines were obtained, even for exchange followed to more

than two half-lives. An example of the rate data is given in

Table XXII, p 160. Each graph contained at least 15 points. Pseudo

first-order rate constants and their standard derivations obtained

were: $k_{CH_3}^{obsd} = 6.85 \pm 0.16 \times 10^{-7}$ sec^{-1}, $k_{CH_2}^{obsd} = 11.64 \pm 0.44 \times 10^{-7}$

sec^{-1} for a buffer concentration of 0.832 $\underline{M}$; $k_{CH_3}^{obsd} = 4.10 \pm 0.13 \times$

10^{-7} sec^{-1}, $k_{CH_2}^{obsd} = 6.89 \pm 0.28 \times 10^{-7}$ sec^{-1} for a buffer concentration

of 0.610 $\underline{M}$. These rate constants give $k_{CH_2}^{obsd}/k_{CH_3}^{obsd} = 1.70 \pm 0.10$ and

1.68 ± 0.12, respectively.

Preparation of the α-Haloketones and Identification of the Substitution Products

Preparation and Purification of the α-Bromoketones

As a typical example, the preparation of 3-bromo-4,4-dimethyl-2-pentanone and 1-bromo-4,4-dimethyl-2-pentanone is described. The method of Catch and coworkers[137] was used to prepare a mixture of bromoketones at 50-60°. The compounds used were: 4,4-dimethyl-2-pentanone (2.40 g, 0.0211 mole), bromine (1.87 g, 0.0117 mole), potassium chlorate 0.350 g, 2.87 $\times 10^{-3}$ mole), and water (100 ml). After work-up, as described for 2-butanone (p 148), the crude mixture was separated by preparative glpc on a 10% QF-1 column (10' x 3/8") at 145° and 60 ml./min of helium. Four compounds were collected and identified by nmr and ir to be 3-bromo-4,4-dimethyl-2-pentanone, 1-bromo-4,4-dimethyl-2-pentanone,

Table XXII

Rate Data for Deuterium Exchange of 2-Butanone, Buffer Concentration 0.610 $\underline{M}$

$\dfrac{I}{t}$		$\text{Log } \dfrac{I}{t}$		
CH_3	CH_2	CH_3	CH_2	Time, sec x 10^{-5}
2.96	2.00	0.471	0.301	0.00
2.91	1.94	0.464	0.288	0.864
2.78	1.80	0.444	0.246	1.76
2.55	1.57	0.407	0.197	3.34
2.47	1.47	0.393	0.168	4.94
2.32	1.35	0.365	0.130	5.74
2.30	1.29	0.362	0.110	6.56
2.23	1.24	0.348	0.0934	7.34
2.18	1.21	0.340	0.0827	8.13
2.02	1.04	0.304	0.0176	9.85
1.89	0.965	0.276	-0.0150	10.7
1.81	0.904	0.260	-0.0437	11.5
1.80	0.866	0.255	-0.0623	12.3
1.72	0.826	0.236	-0.0831	13.3
1.60	0.710	0.204	-0.149	14.8
1.49	0.653	0.173	-0.185	16.6
1.41	0.586	0.149	-0.232	18.2
1.32	0.518	0.120	-0.285	19.9
1.22	0.474	0.0964	-0.324	21.6

$$k_{CH_2}^{obsd} = 6.89 \pm 0.28 \times 10^{-7} \text{ sec}^{-1}$$

$$k_{CH_3}^{obsd} = 4.10 \pm 0.13 \times 10^{-7} \text{ sec}^{-1}$$

1,1-dibromo-4,4-dimethyl-2-pentanone, and 1,3-dibromo-4,4-dimethyl-2-

pentanone, in order of elution. The refractive indices found for the

monobromoketones were: 3-BrK, n^{22} D 1.4620 [lit.[145] n^{20} D 1.4629];

1-BrK, n^{22} D 1.4617 [lit.[145] n^{20} D 1.4627].

$$6(CH_3)_3CCH_2COCH_3 + 3Br_2 + KClO_3 \longrightarrow 6\begin{cases} (CH_3)_3CCHBrCOCH_3 \\ (CH_3)_3CCH_2COCH_2Br \end{cases} + KCl + 3H_2O$$
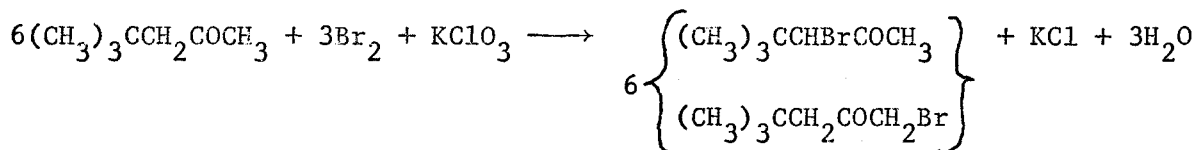
All of the bromoketones used in the kinetic studies were prepared

by this method, with two exceptions. The first, 3-bromo-3-methyl-2-butanone,

was distilled through a glass helices-packed column, bp 70-74° (100 mm),

n^{22} D 1.4532 [lit.[146] bp 83-84° (150 mm), n^{16} D 1.4590]. The second, 1-bromo-

3-methyl-2-butanone, was prepared by the method of Catch and coworkers[138]

from the diazoketone (cf. p 149), and also from bromination of the enol

acetate (cf. p 147).

1-Bromo-3-methyl-2-butanone (Diazomethane)

Isobutyryl chloride was prepared from isobutyric acid (44.0 g,

0.500 mole) and thionyl chloride (70.0 g, 0.588 mole) at room temperature.

After standing overnight, the crude acid chloride was distilled through a

glass helices-packed column. A clear fraction bp 40° (150 mm) was shown by

nmr to be pure isobutyryl chloride. The acid chloride (24.5g, 0.230 mole)

was reacted with diazomethane (19.3 g, 0.460 mole), as described earlier

for 1-bromo-2-butanone (p 149). The resulting diazoketone was

reacted with hydrogen bromide as described by Catch and coworkers[138].

After work-up, the mixture was chromatographed in a 10% QF-1 column

(10' x 3/8") at 150° and 24 ml/min flow rate. The major component

was collected and shown by nmr, ir, and refractive index to be

1-bromo-3-methyl-2-butanone, n^{20} D 1.4412 [lit.[138] $n^{14.5}$ D 1.4467].

1-Bromo-3-methyl-2-butanone (Enol Acetate)

A mixture of enol acetates was prepared as described previously

for 2-butanone (p 146), using 3-methyl-2-butanone (17.2 g, 0.200 mole),

isopropenyl acetate (40.0 g, 0.400 mole), and p-toluenesulfonic acid

(0.250 g, 1.46 x 10^{-3} mole). The resulting enol acetate mixture was

chromatographed on a 10% QF-1 column (10' x 3/8") at 110° and 60 ml/min

flow rate, collecting the two enol acetates, 3-methyl-2-buten-2-ol

acetate and 3-methyl-1-buten-2-ol acetate, which were identified by nmr.

The latter compound (2.00 g, 1.72 x 10^{-2} mole), was reacted with bromine

(2.75 g, 1.72 x 10^{-2} mole) as described on p 147. After work-up, the

crude mixture was chromatographed on a 10% QF-1 column (10' x 3/8") at

130° and 50 ml/min flow rate. The major component was collected and

identified by nmr and refractive index as 1-bromo-3-methyl-2-butanone,

n^{21} D 1.4414 [lit. [138] $n^{14.5}$ D 1.4467].

Products from Displacement of Halide by Acetate Ion

A total of twelve bromoketones were prepared, by the methods described in the previous three sections, and identified by nmr, ir, and mass spectral analysis. These compounds are listed in Table XXIII, p 164, along with the refractive indices found and those reported in the literature. In cases where there is poor agreement with the literature values, the values reported here are probably the better ones, because they are from glpc-pure samples.

Each bromoketone was reacted with acetate ion in a 1.00 $\underline{M}$ acetic acid/acetate buffer at 54.8 ± 0.04°, to displace bromide. After the kinetic studies were completed on each compound, the reaction was allowed to proceed for several half-lives longer before work-up. The aqueous solution was extracted at least six times with 5-ml portions of carbon tetrachloride (Fisher Spectroanalyzed Grade) and/or purified ether. After concentration of the solvent, the residue was analyzed by glpc. Each component was collected by preparative glpc, usually on a QF-1 column, and identified by nmr. All but six of the products were known compounds. They are listed in Table XXIV, p 165, with their refractive indices.

The previously unreported compounds are listed with their nmr and ir spectra data and refractive indices. Because the structure of these compounds is simple and there is no doubt as to their identity, elemental analyses were not performed.

Table XXIII

Refractive Indices of the α-Bromoketones

COMPOUND	REFRACTIVE	INDICES
	Found	Literature
CH_3COCH_2Br	$n^{25}_D = 1.4680$	$n^{15}_D = 1.4697$ (137)
$CH_3CH_2COCH_2Br$	$n^{22}_D = 1.4658$	$n^{20}_D = 1.4670$ (137)
$(CH_3)_2CHCOCH_2Br$	$n^{20}_D = 1.4412$	$n^{14.5}_D = 1.4467$ (138)
$(CH_3)_3CCOCH_2Br$	$n^{25}_D = 1.4630$	$n^{20}_D = 1.4640$ (147)
$CH_3CH_2CH_2COCH_2Br$	$n^{22}_D = 1.4623$	$n^{23}_D = 1.4620$ (146)
$(CH_3)_2CHCH_2COCH_2Br$	$n^{22}_D = 1.4581$	$n^{17}_D = 1.4595$ (138)
$(CH_3)_3CCH_2COCH_2Br$	$n^{22}_D = 1.4617$	$n^{20}_D = 1.4627$ (145)
$CH_3CHBrCOCH_3$	$n^{22}_D = 1.4560$	$n^{20}_D = 1.4571$ (137)
$(CH_3)_2CBrCOCH_3$	$n^{22}_D = 1.4532$	$n^{16}_D = 1.4590$ (146)
$CH_3CH_2CHBrCOCH_3$	$n^{25}_D = 1.4555$	$n^{22}_D = 1.4563$ (146)
$(CH_3)_2CHCHBrCOCH_3$	$n^{25}_D = 1.4605$	$n^{20}_D = 1.4622$ (148)
$(CH_3)_3CCHBrCOCH_3$	$n^{22}_D = 1.4620$	$n^{20}_D = 1.4629$ (145)

Table XXIV

Refractive Indices of the α-Acetoxy- and α-Hydroxyketones

REFRACTIVE INDICES

Compound	Found	Literature
$CH_3COCH_2OCOCH_3$	$n^{25}_D = 1.4153$	$n^{21}_D = 1.4165$ (140)
$CH_3CH(OCOCH_3)COCH_3$	$n^{22}_D = 1.4118$	$n^{20}_D = 1.4129$ (139)
$CH_3CH_2COCH_2OCOCH_3$	$n^{22}_D = 1.4177$	$n^{19}_D = 1.4190$ (140)
$(CH_3)_2C(OCOCH_3)COCH_3$	$n^{25}_D = 1.4146$	$n^{20}_D = 1.4155$ (149)
$(CH_3)_2C(OH)COCH_3$	$n^{25}_D = 1.4103$	$n^{20}_D = 1.4115$ (150)
$(CH_3)_2CHCOCH_2OH$	$n^{25}_D = 1.4249$	$n^{20}_D = 1.4267$ (151)
$CH_3CH_2CH(OCOCH_3)COCH_3$	$n^{25}_D = 1.4158$	$n^{18}_D = 1.4180$ (152)
$CH_3CH_2CH_2COCH_2OCOCH_3$	$n^{25}_D = 1.4196$	$n^{20}_D = 1.4210$ (153)

These six acetoxyketones are: <u>1-acetoxy-3-methyl-2-butanone</u>, n^{25} D 1.4191; nmr (CCl$_4$) δ 4.54 (s, 2, C$\underline{H}_2$OCOCH$_3$), 2.52 (m, 1, J = 7Hz, COC$\underline{H}$(CH$_3$)$_2$), 2.08 (s, 3, COC$\underline{H}_3$), 1.11 (d, 6, J = 7Hz, CH(C$\underline{H}_3$)$_2$); ir (CCl$_4$) cm^{-1}: 2980 (m), 2940 (m), 2880 (w), 1755 (s), 1740 (s), 1410 (w) 1370 (m), 1265 (w), 1225 (s), 1020 (m), and 825 (w); <u>3-acetoxy-4-methyl-2-pentanone</u>, n^{25} D 1.4152; nmr (CCl$_4$) δ 4.74 (d, 1, J = 4Hz, C$\underline{H}$(OCOCH$_3$)), 2.24 (m, 1, J = 4Hz, C$\underline{H}$(CH$_3$)$_2$), 2.07 (s, 3, OCOC$\underline{H}_3$), 2.04 (s, 3, COC$\underline{H}_3$),

1.00 (d, 3, J = 4Hz, $\underset{\underset{\text{H}}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}}}$ - CH$_3$), 0.88 (d, 3, J = 4Hz, $\underset{\underset{\text{H}}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}}}$ - C$\underline{H}_3$); ir (CCl$_4$)

cm^{-1} : 2980 (m). 2945 (w), 2880 (w), 1745 (s), 1735 (s), 1465 (w), 1420 (w), 1370 (m), 1350 (w), 1265 (m), 1230 (s), and 1030 (m) [It should be noted that the methyl groups of the isopropyl group in this compound are not equivalent; this is because C-3 is asymmetric]; <u>1-acetoxy-4-methyl-2-pentanone</u>, n^{25} D 1.4195 nmr (CCl$_4$) δ 4.42 (s, 2, COC$\underline{H}_2$OCOCH$_3$), 2.17 (m, 3, C$\underline{H}$C$\underline{H}_2$CO), 2.08 (s, 3, OCOC$\underline{H}_3$), 0.93 (d, 6, J = 6Hz, CH(C$\underline{H}_3$)$_2$); ir (CCl$_4$) cm^{-1} : 2970 (m), 2940 (w), 2875 (w), 1755 (s), 1740 (s), 1415 (w), 1370 (m), 1270 (w), 1225 (s), 1165 (w), 1140 (w), and 1030 (m); <u>3-acetoxy-4,4-dimethyl-2-pentanone</u>, n^{25} D 1.4153; nmr (CCl$_4$) δ 4.00 (s, 1, C$\underline{H}$OCOCH$_3$), 2.23 (s, 3, COC$\underline{H}_3$), 2.07 (s, 3, OCOC$\underline{H}_3$), 1.06 (s, 9, C(C$\underline{H}_3$)$_3$); ir (CCl$_4$) cm^{-1} : 2975 (m), 2945 (w), 2880 (w), 1748 (s), 1730 (s), 1460 (w), 1415 (w), 1370 (m), 1345 (w), 1265 (m), 1230 (s), 1025 (m), and 830 (w); <u>1-acetoxy-4,4-dimethyl-2-pentanone</u>, n^{25} D 1.4187; nmr (CCl$_4$) δ 4.44 (s, 2, C$\underline{H}_2$OCOCH$_3$), 2.18 (s, 2,

$\underline{CH}_2C(CH_3)_3$), 2.05 (s, 3, OCOC$\underline{H}_3$), 1.02 (s, 9, C(C$\underline{H}_3$)$_3$); ir (CCl$_4$) cm^{-1} :

2960 (m), 2880 (w), 1758 (s), 1740 (s), 1465 (w), 1410 (w), 1368 (m),

1265 (w), 1225 (s), 1055 (m), and 1020 (w); and 1-acetoxy-3,3-dimethyl-

2-butanone, n^{25} D 1.4182; nmr (CCl$_4$) δ 4.72 (s, 2, COC$\underline{H}_2$), 2.10 (s, 3,

OCOC$\underline{H}_3$), 1.17 (s, 9, C(C$\underline{H}_3$)$_3$); ir (CCl$_4$) cm^{-1} : 2975 (m). 2950 (m),

2910 (w), 2880 (w), 1755 (s), 1730 (s), 1475 (w), 1415 (w), 1368 (m),

1270 (w), 1222 (s), 1042 (m), 1000(w), 980 (w), and 830 (w).

Preparation and Purification of the α-Chloroketones

A method analogous to that of Catch and coworkers[137] was used

to prepare a series of α-chloroketones corresponding to the bromoketones

in Table XXIII, p 164. The following procedure for the preparation and

purification of 3-chloro-4,4-dimethyl-2-pentanone and 1-chloro-4,4-

dimethyl-2-pentanone is a typical example.

The following were placed in a 500 ml 3-necked flask containing

a magnetic stirrer : water (150 ml), 4,4-dimethyl-2-pentanone (11.4 g,

0.100 mole), and potassium chlorate (1.67 g, 1.36 x 10^{-2} mole). Chlorine

gas was passed into the solution until an excess was present. After

work-up, as described for 2-butanone (p 148), the crude mixture was

chromatographed on a 10% QF-1 column (10' x 3/8") at 135° and 50 ml/min

flow rate. Six components were collected, the first was unreacted ketone,

the second was 3-chloro-4,4-dimethyl-2-pentanone, and the third was

1-chloro-4,4-dimethyl-2-pentanone. The remaining components were not identified. The nmr spectrum of the 1-chloroketone indicated the presence of an impurity; it was purified by chromatography of the sample again, at 110° and 40 ml/min flow rate. The impurities were separated under these conditions to yield a pure sample of 1-chloro-4,4-dimethyl-2-pentanone.

Ten other chloroketones were prepared in an analogous manner, with the exception of chloroacetone, which was commercially available (Eastman Chemical Co.). It was purified by preparative glpc. All of these chloroketones are reported in the literature. When reacted with acetate in the acetic acid/acetate buffer, the same products were obtained as with the corresponding bromoketones. These chloroketones are listed in Table XXV, p 169, along with their refractive indices. No refractive indices could be found in the literature for 1-chloro-2-butanone, 1-chloro-2-pentanone, and 1-chloro-4-methyl-2-pentanone.

Trans-3-*t*-Butylcychlohexyl Chloride

The method of Eliel and Martin[162] was used to prepare *trans*-3-*t*-butylcyclohexyl chloride from *cis*-3-*t*-butylcyclohexanol [donated by Professor Eliel] (4.53 g, 2.90 x 10^{-2} mole) and phosgene (3.72 g, 3.71 x 10^{-2} mole). The chloroformate ester was converted to the *trans*-chloride by the addition of 10 ml of dry pyridine. After concentration

Table XXV

Refractive Indices of α-Chloroketones

Refractive Indices

Compound	Found	Literature
CH_3COCH_2Cl	$n^{25}D = 1.4431$	$n^{20}D = 1.4457$ (154)
$CH_3CH_2COCH_2Cl$	$n^{25}D = 1.4422$	Not reported
$(CH_3)_2CHCOCH_2Cl$	$n^{25}D = 1.4241$	$n^{28}D = 1.4252$ (155)
$(CH_3)_3CCOCH_2Cl$	$n^{25}D = 1.4337$	$n^{30}D = 1.4393$ (156)
$CH_3CH_2CH_2COCH_2Cl$	$n^{25}D = 1.4326$	Not reported
$(CH_3)_2CHCH_2COCH_2Cl$	$n^{25}D = 1.4277$	Not reported
$(CH_3)_3CCH_2COCH_2Cl$	$n^{25}D = 1.4371$	$n^{20}D = 1.4412$ (145)
$CH_3CHClCOCH_3$	$n^{25}D = 1.4205$	$n^{20}D = 1.4220$ (157)
$(CH_3)_2CClCOCH_3$	$n^{25}D = 1.4366$	$n^{25}D = 1.4378$ (158)
$CH_3CH_2CHClCOCH_3$	$n^{25}D = 1.4280$	$n^{20}D = 1.4297$ (159)
$(CH_3)_2CHCHClCOCH_3$	$n^{25}D = 1.4313$	$n^{20}D = 1.4330$ (160)
$(CH_3)_3CCHClCOCH_3$	$n^{25}D = 1.4341$	$n^{20}D = 1.4365$ (161)

on the rotary evaporator, the residue was distilled on a spinning

band column. However, the distillation was slow, and after 12 hours

the solution had turned a dark colour. Distillation was abandoned

in favour of purification by glpc. The residue was chromatographed

on a 10% QF-1 column (10' x 3/8") at 135° and 50 ml/min flow rate.

Two components were collected; the first was the olefin formed by

elimination of hydrogen chloride, and the second was the desired

trans-3-*t*-butylcyclohexyl chloride. The chemical shift of the

equatorial proton of this compound in carbon tetrachloride relative

to TMS according to Eliel and Martin[162] is 269.8 Hz; the compound

isolated by preparative glpc had a chemical shift of 270 Hz. A trace

of *cis*-chloride was present in this sample of *trans*-chloride.

Cis-and *Trans* -2-Chloro-4-*t*-butylcyclohexanone[163]

A 500 ml 3-necked flask containing 340 ml of formic acid was

equipped with a magnetic stirrer and inlet and outlet tubes, and placed

in the hood. Dry chlorine gas was added until the chlorine/formic acid

solution was 0.21 $\underline{M}$ in chlorine. The strength of this solution was

determined by adding 10 ml of a 20% potassium iodide solution to 1 ml

of the chlorine/formic acid solution, and titrating the liberated

iodine against standard thiosulfate to the starch end point. This

chlorine/formic acid solution (7.14 x 10^{-2} mole, 10% excess), was added

to 4-*t*-butylcyclohexanone (Koch-Light Laboratories, 10.0 g, 6.50 x 10^{-2}

mole) in 10 ml of formic acid. The solution was allowed to react, with

stirring, from 0-10° for 1 hour. After dilution with water, the crude product was extracted with methylene chloride, washed with saturated sodium bicarbonate, water, brine, and then dried over anhydrous magnesium sulfate. The solvent was removed at 40° under vacuum to yield 11.0 g (90%) of a light yellow oil.

The *cis-* and *trans*-2-chloro-4-*t*-butylcyclohexanone were separated by column chromatography on silica gel (BDH, 80-100 mesh). The column (i.d. 5 cm) was filled with 250 g of adsorbent and charged with petroleum ether (60-80°). The mixture of isomers (11.0 g, 5.85 x 10^{-2} mole) in a minimum amount of petroleum ether was placed on the column. The following mixed solvent fractions were eluted : (1) 100% petroleum ether (250 ml); (2) 99% petroleum ether - 1% benzene (250 ml); (3) 98% petroleum ether - 2% benzene (250 ml); (4) 95% petroleum ether - 5% benzene (250 ml); (5) 90% petroleum ether - 10% benzene (1000 ml); (6) 85% petroleum ether - 15% benzene (500 ml); (7) 80% petroleum ether - 20% benzene (4000 ml); (8) 70% petroleum ether - 30% benzene (750 ml); (9) 50% petroleum ether - 50% benzene (2000 ml); (10) 100% benzene (1750 ml); (11) 50% benzene - 50% ethyl ether (500 ml); and (12) 100% ethyl ether (500 ml). Fraction (7) contained nearly pure *trans*-2-chloro-4-*t*-butylcyclohexanone (2.68 g) as determined by nmr; fraction (8) contained a mixture of *trans*-isomer and 2,6-dichloroketone; fraction (9) contained the dichloroketone (essentially pure); fraction (10) was *cis*-2-chloro-4-*t*-butylcyclohexanone (4.30 g), identified by nmr; fraction

(11) contained a mixture of the *cis*-chloroketone and unreacted ketone; and fraction (12) was unreacted ketone.

The *trans*-compound was purified by a simple bulb-to-bulb distillation at the lowest possible pressure. The *cis*-isomer was recrystallized from pentane, mp 58-59° (uncorrected).

Products from Displacement of Chloride from the Cyclohexyl Compounds

The *cis*- and *trans*-3-*t*-butylcyclohexyl chlorides were placed in the buffer solution separately and allowed to react at reflux temperature for several days. After work-up of each solution in the usual manner, the products were chromatographed on a 12% QF-1 column (10' x 1/8"). In each case only one component in addition to starting material was observed. An nmr spectrum of each solution showed no absorptions in the vinyl hydrogen region; thus products of elimination were absent. The two solutions were then chromatographed on a 10% QF-1 column (10' x 3/8"), and the products were collected.

An nmr spectrum of the product was recorded in each case, and an equatorial methine proton was observed in the product from the *cis*-chloro-compound, while an axial methine proton was observed from the *trans*-chloro-compound. There was an absorption at 2.10 δ in each spectrum (COCO$\underline{CH}_3$). The reaction of the α-chlorocyclohexanones with acetate ion also went very cleanly and gave rise to only one product – displacement of chloride by acetate ion. The product from the reaction of the *cis*-chloroketone had

OAc
|
an nmr absorption at 250 Hz (C - H$_{equatorial}$), which is similar to

that observed in the *trans*-chloroketone (255 Hz)[162]. Similarly, the

product from the *trans*-chloroketone had an nmr absorption at 274 Hz

OAc
|
(C - H$_{axial}$), which is similar to an absorption in the spectrum of the

cis-chloroketone (270 Hz)[162]. The above results are consistent with

inversion of configuration at the reaction site in the displacement

of chloride by acetate ion.

Displacement Reactions of the α-Haloketones

Measurement of Halide Ion Concentration

The first method chosen to follow the displacement of halide by

acetate ion from the α-haloketones was glpc analysis. However, there

were losses experienced on extraction with carbon tetrachloride and ether;

a better method was then sought. A relatively new method (since 1967) of

ion detection is the specific ion, solid-state membrane electrode[164-174].

In the displacement reactions on the α-haloketones, a bromide

ion electrode and a chloride ion electrode were used to follow the increase

in halide ion concentration with time. The former was an Orion Bromide Ion

Activity Electrode, Model 94-35, and the latter was an Orion Chloride Ion

Activity Electrode, Model 94-17. These electrodes are solid-state membrane

electrodes, which makes possible the direct and rapid measurement of bromide

or chloride ion in both aqueous and non-aqueous solutions. The bromide

electrode can be used from 1 $\underline{M}$ in Br^- down to 5.0×10^{-6} $\underline{M}$ in Br^-, while the chloride electrode can be used from 1 $\underline{M}$ in Cl^- down to 5.0×10^{-5} $\underline{M}$ in Cl^-. The theory of operation of specific ion electrodes is given in Appendix II, p 189. The bromide ion electrode was used in conjunction with a saturated calomel electrode (Fisher Model 13-639-52), while the chloride ion electrode was used with an Orion Double Junction Reference Electrode, Model 90-02. The latter was used because the filling solution of the saturated calomel electrode (KCl) contains the chloride ion, which is being measured. Possible contamination is avoided by the use of a double junction electrode, where there is no direct contact between the solution being studied and chloride ion from the reference electrode. The electrodes were connected to an expanded-scale pH meter. (Fisher Accumet, Model 310), used in the expanded millivolt mode. The change in halide ion concentration was monitored during a kinetic run.

Calibration of the Specific Ion Electrodes

The specific ion electrodes develop potentials which are proportional to the logarithm of the activity of the halide ion (see p 191); thus the millivolt potentials may be correlated with the halide ion concentration by means of a calibration curve for each electrode. The following procedure was used to calibrate the bromide ion electrode, and a similar procedure was used for the chloride ion

electrode. The buffer solution (100 ml) was placed in a 125 ml 3-necked

flask, in which the central neck was a B 24/40 ẞ joint and the outside

necks were both B 19/40 ẞ joints. Tapered Teflon rings were used to

fit the bromide ion electrode and the saturated calomel electrode

securely to the flask. The flask was placed in a water bath at 54.8 ±

0.04°, and the solution was stirred.

When equilibration had occurred, the solution was made approxi-

mately 6.0×10^{-5} $\underline{M}$ in Br^- by the addition of standard Br^- from a stock

solution. Stock solutions from 1.00×10^{-2} $\underline{M}$ to 1.00 $\underline{M}$ in Br^- were used.

A 100 µl syringe was used to add standard Br^- solution to the buffer,

the system was allowed to equilibrate for 10 minutes, and then the

potential of the solution was recorded. The concentration was varied

between 5.4×10^{-6} $\underline{M}$ and 3.3×10^{-3} $\underline{M}$ in bromide ion, and readings were

taken approximately every 10 millivolts. The raw data for calibration

of the bromide ion electrode are given in Table XXVI, p 176.

The same procedure was used to calibrate the chloride ion

electrode, except that a slightly different range of concentration was

used. The limiting potential of the chloride ion electrode occurs at

5.0×10^{-5} $\underline{M}$ in Cl^-, while for the bromide ion electrode the limiting

potential is 2.0×10^{-7} $\underline{M}$ in Br^-. The lower limit for the halide ion

electrodes is determined by the low but finite solubility of the silver

halide sensing element in the electrode. The raw data for calibration of

the chloride ion electrode are given in Table XXVII, p 177.

Table XXVI

Calibration of the Bromide Ion Electrode

Br$^-$ Added	Volume of Solution, ml	[Br$^-$], $\underline{M}$	$\underline{mV}$
55.0 µl of A	100.0	5.50×10^{-6}	148
90.0 µl of A	100.1	1.45×10^{-5}	134
15.0 µl of B	100.1	2.95×10^{-5}	121
25.0 µl of B	100.1	5.45×10^{-5}	107
40.0 µl of B	100.2	9.45×10^{-5}	92.0
75.0 µl of B	100.2	1.70×10^{-4}	76.0
100 µl of B	100.3	2.69×10^{-4}	64.0
20.0 µl of C	100.4	4.68×10^{-4}	49.5
35.0 µl of C	100.4	8.15×10^{-4}	34.5
60.0 µl of C	100.5	1.41×10^{-3}	20.0
80.0 µl of C	100.5	2.21×10^{-3}	8.00
100 µl of C	100.6	3.20×10^{-3}	-2.00

Solution A was 1.00×10^{-2} $\underline{M}$ in Br$^-$

Solution B was 1.00×10^{-1} $\underline{M}$ in Br$^-$

Solution C was 1.00 $\underline{M}$ in Br$^-$

Table XXVII

Calibration of the Chloride Ion Electrode

Cl⁻ Added	Volume	$[Cl^-]$, $\underline{M}$	mV
0.20 ml of A	100.0	1.01×10^{-4}	120
20 µl of B	100.02	3.01×10^{-4}	110.5
20 µl of B	100.04	5.01×10^{-4}	102.5
25 µl of B	100.06	7.50×10^{-4}	95.0
25 µl of B	100.09	9.99×10^{-4}	91.0
100 µl of B	100.19	2.00×10^{-3}	72.5
100 µl of B	100.29	2.99×10^{-3}	62.0
100 µl of B	100.39	3.98×10^{-3}	54.5
100 µl of B	100.49	4.97×10^{-3}	48.0
200 µl of B	100.69	6.95×10^{-3}	40.0
200 µl of B	100.89	8.92×10^{-3}	33.0
100 µl of B	100.99	9.90×10^{-3}	30.0

Solution A was 5.03×10^{-2} $\underline{M}$ in Cl⁻

Solution B was 1.00 $\underline{M}$ in Cl⁻

A 1-millivolt recorder (Leeds and Northrup Speedomax H) was connected to the expanded scale pH meter for use with the faster haloketones. Some of the displacement reactions were too fast to take accurate readings from the millivolt scale on the pH meter. A variable resistance box was used to adjust the recorder range so that 140 to 0 millivolts was included in the recorder scale. A calibration curve was used to convert the recorder chart divisions to bromide ion concentration. The recorder was useful because a permanent record was obtained of the kinetic run, and in theory an inifinite number of points could then be obtained from the recorder trace.

Derivation of Rate Plots

Because acetate ion was in large excess in the reactions ($\sim 10^{-3}$ $\underline{M}$ in haloketone versus 1.00 $\underline{M}$ in acetate), the system could be treated with pseudo first-order kinetics. Thus, for the appearance of bromide ion, we have:

$$\ln \frac{\left\{ [Br^-]_\infty - [Br^-]_i \right\}}{\left\{ [Br^-]_\infty - [Br^-]_t - [Br^-]_i \right\}} = kt$$

where

$[Br^-]_\infty$ = initial bromoketone concentration, or final bromide ion concentration; minus the initial bromide ion concentration

$[Br^-]_i$ = initial bromide ion concentration

$[Br^-]_t$ = bromide ion concentration at time t.

If the initial concentration of bromide ion, $[Br^-]_i$, is zero, the

equation can be rewritten as follows.

$$\log \left\{ [Br^-]_\infty - [Br^-]_t \right\} = -\frac{k}{2.303} t + \log [Br^-]_\infty$$

A plot of $\log \left\{ [Br^-]_\infty - [Br^-]_t \right\}$ against time in seconds will

therefore yield a straight line of slope $-\frac{k}{2.303}$ and intercept

$\log [Br^-]_\infty$.

Kinetic Procedure - Bromoketones

The following procedure was used for all the displacement

reactions by acetate on the α-bromoketones. Into a 100 ml volumetric

flask was placed acetic acid (6.00 g, 0.100 mole), sodium acetate

(8.20 g, 0.100 mole), 1,2-dimethoxyethane (24.0 ml), and water to

100 ml. After shaking the flask vigorously, the buffer solution was

added to the 125 ml 3-necked flask fitted for the bromide ion and

reference electrodes as described on p 175. This flask was placed

in a water bath at 54.8 ± 0.04°, as determined by N.R.C.-calibrated

thermometers. Stirring was accomplished by means of a 0.5" Teflon-

coated bar magnet, driven by a TRI-R submersible magnetic stirrer

(TRI-R Instruments).

When the solution had reached equilibrium with the bath, the

bromide ion and reference electrodes were placed in the flask. The

electrodes were connected to the expanded-scale pH meter, with the

latter in the expanded millivolt mode. After a period of equilibration (15-20 minutes), the bromoketone was added by means of a 100 μl syringe. The following procedure for 1-bromo-4-methyl-2-pentanone is a typical example.

The bromoketone (5.43×10^{-2} g, 3.05×10^{-4} mole) was weighed out in the syringe and injected into the buffer solution at $54.8 \pm 0.04°$. The reaction was followed for 37.5 minutes (3 half-lives) during which time the potential changed from an initial reading of 140 millivolts to 4 millivolts. After 24 hours an infinity reading was taken before the solution was extracted with carbon tetrachloride and ether for product analysis as described previously. The raw kinetic data for 1-bromo-4-methyl-2-pentanone are given in Table XXVIII, p 181. The pseudo first-order rate constant for this run was 9.31×10^{-4} sec^{-1}. This procedure was repeated with a four-fold lower bromoketone concentration to verify the order in bromoketone. In all cases at least two runs of different bromoketone concentration were made, and the results were averaged. In most cases it was possible to get a value of $[Br^-]_\infty$, which is critical to the slope of the pseudo first-order plot. This value was compared with the amount of bromoketone weighed into the buffer solution, and in all cases the agreement was within 2%.

Table XXVIII

Kinetics of Nucleophilic Substitution : 1-Bromo-4-methyl-2-pentanone

plus Acetate, 24% Aqueous DME, 54.8°, $[Br^-]_\infty = 3.05 \times 10^{-3}$ M

$[Br^-]_t$, M	$[Br^-]_\infty - [Br^-]_t$	Log $[Br^-]_\infty - [Br^-]_t$	Time, sec x 10^{-2}
1.28×10^{-4}	2.92×10^{-3}	-2.534	0.600
3.10×10^{-4}	2.74×10^{-3}	-2.562	1.20
4.04×10^{-4}	2.65×10^{-3}	-2.577	1.80
5.68×10^{-4}	2.48×10^{-3}	-2.605	2.40
7.88×10^{-4}	2.26×10^{-3}	-2.646	3.60
1.08×10^{-3}	1.96×10^{-3}	-2.706	4.80
1.24×10^{-3}	1.81×10^{-3}	-2.743	6.00
1.46×10^{-3}	1.59×10^{-3}	-2.799	7.20
1.67×10^{-3}	1.38×10^{-3}	-2.860	8.40
1.79×10^{-3}	1.26×10^{-3}	-2.900	9.60
1.92×10^{-3}	1.13×10^{-3}	-2.947	10.8
2.02×10^{-3}	1.03×10^{-3}	-2.989	12.0
2.16×10^{-3}	8.85×10^{-4}	-3.053	13.2
2.34×10^{-3}	7.13×10^{-4}	-3.147	15.6
2.47×10^{-3}	5.82×10^{-4}	-3.235	18.0
2.54×10^{-3}	5.06×10^{-4}	-3.296	19.2

$$k^{obsd} = 9.31 \times 10^{-4} \text{ M}^{-1} \text{ sec}^{-1}$$

Kinetic Procedure - Chloroketones

A procedure very similar to that for the bromoketones was used, except that due to the characteristics of the chloride ion electrode, the most suitable chloride ion concentration range was from 1.00×10^{-4} $\underline{M}$ to 1.00×10^{-2} $\underline{M}$. Therefore, potential measurements were taken only after the chloride ion concentration had risen to 1.00×10^{-4} $\underline{M}$ during each kinetic determination. As a typical example, the procedure used for chloroacetone is described. Chloroacetone (9.34×10^{-2} g, 1.01×10^{-3} mole) was weighed out in a 100 μl syringe and added to the buffer solution at $54.8 \pm 0.04°$. The reaction was followed for 30 minutes (3 half-lives) during which time the potential changed from an initial reading greater than 140 millivolts (off-scale) to 34 millivolts. After 24 hours an infinity reading was taken before the solution was extracted with carbon tetrachloride and ether for product analysis. The raw kinetic data for chloroacetone are given in Table XXIX, p 183.

The pseudo first-order rate constant for this experiment was 1.16 $\times 10^{-3}$ sec^{-1}. The procedure was duplicated using a two-fold lower chloro-acetone concentration to verify the order in chloroketone.

Displacement by Azide Ion

Bromide was displaced by azide in a series of nine bromoketones at $54.8°$. Sodium azide (3.25 g, 0.050 mole), acetic acid (3.00 g, 0.050 mole), and 1,2-dimethoxyethane (24 ml) were placed in a 100 ml volumetric

Table XXIX

Kinetics of Nucleophilic Substitution : Chloroacetone plus Acetate, 24%

Aqueous DME, 54.8°, $[Cl^-]_\infty = 1.01 \times 10^{-2}$ $\underline{M}$

$[Cl^-]_t$, $\underline{M}$	$[Cl^-]_\infty - [Cl^-]_t$	Log $[Cl^-]_\infty - [Cl^-]_t$	Time, sec x 10^{-2}
1.15×10^{-3}	8.95×10^{-3}	-2.0482	2.40
2.27×10^{-3}	7.83×10^{-3}	-2.1063	3.60
3.42×10^{-3}	6.68×10^{-3}	-2.1751	4.80
4.30×10^{-3}	5.80×10^{-3}	-2.2366	6.00
5.00×10^{-3}	5.10×10^{-3}	-2.2924	7.20
5.80×10^{-3}	4.30×10^{-3}	-2.3665	8.40
6.25×10^{-3}	3.85×10^{-3}	-2.4148	9.60
6.67×10^{-3}	3.43×10^{-3}	-2.4650	10.8
7.27×10^{-3}	2.83×10^{-3}	-2.5476	12.0
7.60×10^{-3}	2.50×10^{-3}	-2.6021	13.2
7.88×10^{-3}	2.22×10^{-3}	-2.6527	14.4
8.19×10^{-3}	1.91×10^{-3}	-2.7183	15.6
8.64×10^{-3}	1.46×10^{-3}	-2.8355	18.0
9.00×10^{-3}	1.10×10^{-3}	-2.9574	20.0

$$k^{obsd} = 1.16 \times 10^{-3} \ \underline{M}^{-1} \ sec^{-1}$$

flask, and water was added to 100 ml. The bromide ion electrode was

shown to be compatible with the azide solution in a preliminary

experiment. The procedure was analogous to that described above for

the displacement reactions by acetate, and the reaction was followed

to at least 3 half-lives. After extraction with carbon tetrachloride

and ether, the solution was analyzed for products by glpc. In every

case, only the product was found. Duplicate kinetic runs were performed

on each bromoketone, changing the bromoketone concentration to ensure

that the rate-determining step of bromide ion formation is displacement

by azide rather than dissolution of bromoketone in the medium.

In a typical experiment, 3-bromo-4-methyl-2-pentanone (5.38 x

10^{-2} g, 3.01 x 10^{-4} mole) was added to the equilibrated acetic acid/

azide solution at 54.8 ± 0.04° by means of a 100 μl syringe. The reaction

was followed for 19 minutes (3 half-lives) during which time the potential

changed from 140 millivolts to 4 millivolts. After 4 hours an infinity

reading was taken before the solution was extracted with carbon tetra-

chloride and ether for product analysis. Only one component in addition

to starting bromoketone was found by glpc; the product was found by nmr

spectroscopy to be the α-azidoketone[175]. The pseudo first-order rate

constant was determined in the usual manner. Dividing this constant by the

azide concentration (0.500 $\underline{M}$) gives the second-order rate constant.
These rate constants for 3-bromo-4-methyl-2-pentanone were 1.83 x
10^{-3} sec^{-1} and 3.66 x 10^{-3} $\underline{M}$ sec^{-1}, respectively.

Reaction of *Cis-* and *Trans*-3-*t*-Butylcyclohexyl Chlorides with Acetate

At least two kinetic experiments were performed on both the
cis- and *trans*-chlorides, to ensure that displacement of chloride by
acetate was being followed, rather than the rate of solution of the
cyclohexyl chloride. In a typical experiment, *cis*-3-*t*-butylcyclohexyl
chloride (8.85 x 10^{-2} g, 5.07 x 10^{-4} mole) was added to 100 ml of the
buffer solution at 54.8 ± 0.04° by means of a 100 μl syringe. Almost
a week was required to reach 1 half-life of the reaction. Due to the
length of time involved, the kinetic measurements were not continued
beyond 1 half-life. However, the solution was refluxed for several days
and then analyzed for products in the usual manner. There was only one
component other than starting cyclohexyl chloride present by glpc, and
the nmr spectrum showed the absence of any products arising from
elimination reactions which might have occurred. From a plot of log
$\left\{ [Br^-]_\infty - [Br^-]_t \right\}$ versus time, the pseudo first-order rate constant was
calculated to be 1.20 x 10^{-6} sec^{-1}. A similar set of experiments with
the *trans*-3-*t*-butylcyclohexyl chloride yielded observed rate constants
of 2.59 x 10^{-6} and 2.49 x 10^{-6} sec^{-1}.

Reaction of *Cis-* and *Trans*-2-Chloro-4-*t*-butylcyclohexanone
with Acetate

Experiments analogous to the above were performed on the *cis-*
and *trans*-chlorocyclohexanones. Two runs, differing in initial
concentration of chloroketone, were performed for each compound. In a
typical experiment, *trans*-2-chloro-4-*t*-butylcyclohexanone (8.70 x 10^{-2}
g, 4.61 x 10^{-4} mole) was added to the buffer at 54.8 ± 0.04° in the
usual manner. The reaction was followed for 70 minutes (3 half-lives)
during which time the potential had fallen to 54 millivolts. After 6
hours the solution was analyzed for the products in the usual manner.
The pseudo first-order rate constant for this experiment was 4.98 x
10^{-4} sec^{-1}.

This procedure was repeated for the *cis-* compound, except
for the following. The *cis*-chloroketone is a solid; thus a different
method for addition to the reaction medium was used. The solid was
weighed out in a 5 ml volumetric flask, filled to the mark with 1,2-
dimethoxyethane (DME) and shaken vigorously. This solution was then
added to a buffer solution which contained only 19 ml of 1,2-dimethoxy-
ethane. Mixing therefore brought the DME content of the medium to that
used in other runs.

Activation Parameters

Kinetic measurements were performed on *n*-butyl bromide and on
1-bromo-2-butanone at 3 different temperatures: 40.0 ± 0.025°, 54.8 ±

0.04°, and 70.0 ± 0.07° for n-butyl bromide, and 0.20 ± 0.01°, 30.0 ±

0.02°, and 54.8 ±0.04° for 1-bromo-2-butanone. The bath temperatures

were determined by N.R.C.-calibrated thermometers and the variations

with a Beckman thermometer. In each case approximately 3.50 x 10^{-4}

mole of the bromo-compound was used in experiments analogous to those

reported above at 54.8°.

With the cyclohexyl chlorides, kinetic measurements were

performed at 75.0 ± 0.08° in addition to those done at 54.8°. Duplicate

runs were made at each temperature. The chloroketones were studied at

35.0 ± 0.02°, 54.8 ± 0.04°, and 75.0 ± 0.08°.

The activation parameters were derived from the standard

expression[176]:

$$k = \frac{kKT}{h} \exp\left(-\frac{\Delta H^{\ddagger}}{RT}\right) \exp\left(\frac{\Delta S^{\ddagger}}{R}\right) \tag{9}$$

Dividing equation 9 by T and taking logarithms, we obtain equation

10:

$$\log\frac{k}{T} = \log\frac{kK}{h} - \frac{\Delta H^{\ddagger}}{2.303RT} + \frac{\Delta S^{\ddagger}}{2.303R} \tag{10}$$

Values of k (second-order rate constants) and T were used to obtain

$\log\frac{k}{T}$, which was plotted against 1/T for the bromo-compounds and for

the chloro-compounds. These graphs were treated using the linear

least-squares computer program (Appendix I, p 189) to obtain the best

values of slope and intercept. From these,

$$\Delta H^{\ddagger} = - (\text{slope}) \ (2.303R)$$

$$\Delta S^{\ddagger} = (\text{intercept} - \log \frac{\kappa K}{h}) \ (2.303R)$$

The constants used were[177]:

$$h = 6.626 \times 10^{-27} \text{erg-sec}$$

$$R = 1.987 \text{ cal mole}^{-1} \ ^{\circ}K^{-1}$$

$$\kappa = 1 \ (\text{assumed})$$

$$K = 1.380 \times 10^{-16} \text{erg} \ ^{\circ}K^{-1}$$

$$\log \frac{\kappa K}{h} = 10.32$$

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were obtained for both the bromo-compounds and chloro-compounds in this manner.

APPENDIX I

Linear Least-Squares Computer Program

This fits a series of data points (x and y) to the straight-line equation $y = mx + c$, using a standard method[1]. The input data is the number of points (N) and values of x and y. The program prints out the slope (m) and intercept (c), with their standard deviations. The program is on p 190.

APPENDIX II

The Theory of Operation of Specific Ion Electrodes

A relatively new method[164-174] of ion detection is the specific ion solid-state membrane electrode. To follow the displacement of halide from the α-haloketones, a bromide ion electrode and a chloride electrode were used. The former was an Orion Bromide Ion Activity Electrode, Model 94-35 (Orion Research Incorp.), and the latter was an Orion Chloride Ion Activity Electrode, Model 94-17 (Orion Research Incorp.). They are solid-state membrane electrodes, which makes possible the direct and rapid measurement of bromide or chloride ion in both aqueous and non-aqueous solutions.

EXECUTE PROGRAM LOADING

000MI 01SEC00900=

```
          $IBJOB          NODECK                                                    $$
          $IBFTC                                                                    $$
          C-----LEAST SQUARES PROGRAM.                                             $$
   1           DIMENSION X(40), Y(40)                                              $$
   2      100 READ 1, N                                                            $$
   3        1 FORMAT(I3)                                                           $$
   4           DO 2 J = 1,N                                                        $$
   5        2 READ 3, X(J), Y(J)                                                   $$
   6        3 FORMAT(2F10.0)                                                       $$
   7           A = N                                                               $$
  10           SIGX = 0.0                                                          $$
  11           SGDXY = 0.0                                                         $$
  12           SGDX2 = 0.0                                                         $$
  13           SIGY = 0.0                                                          $$
  14           SIGY2 = 0.0                                                         $$
  15           SIGXY = 0.0                                                         $$
  16           DO 4 I = 1,N                                                        $$
  17        4 SIGX = SIGX + X(I)                                                   $$
  20           XBAR = SIGX/A                                                       $$
  21           DO 5 L = 1,N                                                        $$
  22           DELX = X(L) - XBAR                                                  $$
  23           SGDXY = SGDXY + Y(L)*DELX                                           $$
  24           SGDX2 = SGDX2 + DELX**2                                             $$
  25           SIGY2 = SIGY2 + Y(L)**2                                             $$
  26           SIGY = SIGY + Y(L)                                                  $$
  27           SIGXY = SIGXY + X(L)*Y(L)                                           $$
  30        5 CONTINUE                                                             $$
  31           SLOPE = SGDXY/SGDX2                                                 $$
  32           SYDX2 = (SIGY2 - ((SIGY**2)/A) - SLOPE*SIGXY + (SLOPE*SIGX*SIGY/A)  $$
               1)/(A - 2.0)                                                        $$
  33           SB = SQRT(SYDX2/SGDX2)                                              $$
  34           YBAR = SIGY/A                                                       $$
  35           CEPT = YBAR - SLOPE*XBAR                                            $$
  36           SA = SQRT(SYDX2/A)                                                  $$
  37           PRINT 6, SLOPE, SB                                                  $$
  40        6 FORMAT(1H0,4X,8HSLOPE   =,E14.6,5X,20HSTANDARD DEVIATION =,E13.6)    $$
  41           PRINT 7, CEPT, SA                                                   $$
  42        7 FORMAT(1H0,12HINTERCEPT  =,E14.6,5X,20HSTANDARD DEVIATION =,E13.6)   $$
  43           PRINT 8                                                            $$
  44        8 FORMAT(1H0,15X,10H**********)                                        $$
  45           GO TO 100                                                          $$
  46           END                                                               $$
          $ENTRY
```

190

The electrode sensing element is a solid silver halide membrane which separates an internal filling solution from the sample solution. The membrane is an ionic conductor for silver, and the internal filling solution contains a fixed level of silver ion. The potential developed between the internal reference and the internal filling solution is fixed, as is the potential between the filling solution and the inside surface of the membrane. Thus the electrode develops potentials due (in addition to E_a) to changes in the sample silver ion activity:

$$E = E_a + 2.303 \frac{RT}{F} \log a_{Ag^+} \qquad \qquad 11)$$

where   E = the measured total potential of the system

E_a = the portion of the total potential due to the

choice of internal and external reference electrodes

and internal solutions.

$2.303 \frac{RT}{F}$ = the Nernst factor (59.16 mV at 25°C). R and F

are constants, and T is degrees Kelvin.

a_{Ag^+} = the silver ion activity in the sample solution

Even though the original sample may not contain silver ions, a very few are produced by the extremely small solubility of the silver halide membrane. The silver ion activity depends on the halide ion activity in the sample solution. Using the chloride ion electrode as an

example, the silver ion activity can be calculated from the solubility product (K_{sp}) of silver chloride.

$$a_{Ag^+} = \frac{K_{sp}}{a_{Cl^-}} \qquad \qquad 12)$$

When this value for a_{Ag^+} is substituted in equation 11, the relationship between total electrode potential and chloride ion activity in the sample solution is:

$$E = E_a + 2.303 \frac{RT}{F} \log K_{sp} - 2.303 \frac{RT}{F} \log a_{Cl^-} \qquad 13)$$

Since K_{sp} is constant at any given temperature, a new constant can be defined:

$$E_b = E_a + 2.303 \frac{RT}{F} \log K_{sp} \qquad \qquad 14)$$

$$\therefore E = E_b - 2.303 \frac{RT}{F} \log a_{Cl^-} \qquad \qquad 15)$$

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