SECONDARY β AND γ DEUTERIUM ISOTOPE EFFECTS IN THE SOLVOLYSES OF ISOBUTYRYL AND PIVALOYL CHLORIDES

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
ADAN A. EFFIO LEON
1971

LIBRARY
Michigan State
University

This is to certify that the

thesis entitled

Secondary β and γ Deuterium Isotope Effects
in the Solvolyses of
Isobutyryl and Pivaloyl Chlorides

presented by

Adan A. Effio

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

G. J. Karabatsos
Major professor

Date August 24, 1971

O-7639

ABSTRACT

SECONDARY β AND γ DEUTERIUM ISOTOPE EFFECTS IN THE SOLVOLYSES OF ISOBUTYRYL AND PIVALOYL CHLORIDES.

By

Adan A. Effio Leon

In order to assess the usefulness of secondary deuterium isotope effects as mechanistic criteria and to understand better the mechanism of solvolysis of aliphatic acid chlorides, we studied the solvolysis of isobutyryl chloride and pivaloyl chloride. The rates of solvolysis of isobutyryl chloride were determined over a temperature range from -29.120° to -4.987° and acetone-water concentrations of 75% to 95%. Those of pivaloyl chloride were studied at temperatures from -14.132° to +4.001° and acetone-water concentrations of 75% to 90%.

The β isotope effects in the solvolysis of isobutyryl chloride decreased as the water concentration and temperature decreased, <u>e.g.</u>, k_H/k_D (-24.985°) = 0.986 ± 0.003 (75), 0.956 ± 0.006 (90%); k_H/k_D (90%) = 0.955 ± 0.007 (-29.120°), 0.987 ± 0.008 (-4.987°). The γ isotope effect was nearly temperature independent, <u>e.g</u>., k_H/k_D (85%) = 0.964 ± 0.006 (-29.120°), 0.971 ± 0.0120 (-10.109°). k_H/k_D (95%) = 0.999 ± 0.022 (-19.793°), 0.994 ± 0.004 (-4.987°). It increased with decreasing polarity of the solvent, <u>e.g</u>., k_H/k_D (-15.616°) = 0.942 ± 0.008 (80%), 0.999 ± 0.003 (95%).

The γ isotope effect in the solvolysis of pivaloyl chloride followed the same trend; it was temperature independent and increased as the polarity of the solvent decreased, e.g., k_H/k_D (-9.344°) = 0.909 ± 0.004 (75%), 0.962 ± 0.006 (90%); k_H/k_D (85%) = 0.943 ± 0.004 (-14.312°), 0.938 ± 0.004 (+4.001°).

The above inverse isotope effects indicate that isobutyryl chloride and pivaloyl chloride solvolyze primarily by a nucleophilic mechanism. This conclusion is further supported by examination of the rates of solvolysis (80% acetone-water, -15.10°) and the activation parameters for acetyl, propionyl, isobutyryl and pivaloyl chlorides which are reported in Table 1.

TABLE 1. Rates of Solvolysis and Activation Parameters for a Series of Aliphatic Acid Chlorides.

RCOCl	CH_3COCl	CH_3CH_2COCl	$(CH_3)_2CHCOCl$	$(CH_3)_3CCOCl$
$k_{rel.}$	1	0.401	0.223	0.0395
$\Delta H^{\ddagger}$ (cal/m)	14,240 ± 50	13,822 ± 80	12,755 ± 123	13,326 ± 99
$\Delta S^{\ddagger}$ (e.u.)	-12.2 ± 0.2	-15.7 ± 0.3	-21.1 ± 0.5	-22.2 ± 0.4

Evans[1] and Kang[2] suggested that acetyl and propionyl chlorides solvolyze by a dual mechanism (S_N1-S_N2). The relative rates indicate that as R becomes more branched the reaction becomes more nucleophilic. This is also supported by the observation that the enthalpy of activation becomes less positive and the entropy of activation more negative. We conclude that isobutyryl chloride and pivaloyl chloride solvolyze predominantly by a nucleophilic mechanism.

---

1. T. A. Evans, Ph.D. Thesis, Michigan State University, 1968.
2. U. G. Kang, M.S. Thesis, Michigan State University, 1970.

SECONDARY β AND γ DEUTERIUM ISOTOPE EFFECTS IN THE SOLVOLYSES OF ISOBUTYRYL AND PIVALOYL CHLORIDES.

By

Adan A. Effio Leon

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1971

67[illegible]

In the Memory of My Parents

Adan and Esther

To Elva and Nena

ACKNOWLEDGEMENTS

I wish to thank Professor G. J. Karabatsos not only for the time and effort he has devoted contributing to my education, but also for suggesting this area of study and for his guidance and help during the course of this investigation.

The financial assistance provided by the National Science Foundation and Michigan State University is gratefully acknowledged.

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

LIST OF TABLES

LIST OF TABLES (Continued)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (Continued)

FIGURE Page

INTRODUCTION

Isotope effects are discussed within the framework of the Born - Oppenheimer approximation. Thus, the energy of motion of the electrons depends on the atomic number of the nuclei and the number of electrons, not on the nuclear masses. The electronic energy of the molecules can be calculated as a function of the relative position of the nuclei which will represent the potential energy surface for nuclear motion. Therefore potential energy surfaces for isotopic molecules are identical. Isotope effects are then nuclear mass effects resulting from the different energy of nuclear motion on the same isotope independent potential energy surface.[1,2] Exact equations (neglecting tunneling and transmission coefficient isotope effects) for the statistical mechanical formulation of kinetic isotope effects within the framework of transition state theory, in the harmonic approximation, have been derived by Bigeleisen[3] and Melander.[4]

Two equivalent forms for the isotopic rate ratio are, briefly:

$$k_H/k_D = \mathrm{MMI} \times \mathrm{EXC} \times \mathrm{ZPE}$$

$$k_H/k_D = \nu^{\ddagger}_{H}L/\nu^{\ddagger}_{D}L \times \mathrm{VP} \times \mathrm{EXC} \times \mathrm{ZPE}$$

Here k_H/k_D is the ratio of the isotope rate constants, MMI is the mass-moment of inertia term, EXC is the vibrational excitation term, ZPE is the zero point energy term, VP is the vibrational product term and $\nu^{\ddagger}_{H}L/\nu^{\ddagger}_{D}L$ is the isotopic ratio of the imaginary frequencies representing the motion along the reaction coordinate. Wolfsberg and Stern have performed detailed calculations for S_N1 and S_N2 type reactions.[5,6] Their results are shown in Tables I and II.

TABLE I. Secondary Isotope Effects in the Absence of Force Constant Changes at the Isotopic Position.

$$CD_3CH_2X \ + \ X \longrightarrow [CD_3CH_2X_2]^{\ddagger} \quad \nu^{\ddagger}_{H}L/\nu^{\ddagger}_{D}L \ = \ 1.039$$

T°K	MMI	EXC	ZPE	$k_H/k_D/\nu^{\ddagger}_{H}L/\nu^{\ddagger}_{D}L$
100	1.131	0.957	0.957	0.997
300	1.131	0.932	0.985	1.000
2000	1.131	0.920	0.998	1.000

TABLE II. Secondary Isotope Effects Produced by Different Force Constant Changes at the Isotopic Position.

$$CH_3CD_2CH_2X \longrightarrow [CH_3CD_2CH_2.....X]^{\ddagger} \quad \nu^{\ddagger}_{H}L/\nu^{\ddagger}_{D}L \ = \ 1.016$$

Force Constant Change	k_H/k_D 200°	300°	400°	500°
f_{CH} 4.5 to 4.2 md/A	1.229	1.152	1.105	1.044
f_{HCH} 0.53 to 0.35 md/A	1.238	1.153	1.109	1.083
f_{CCH} 0.68 to 0.60 md/A	1.241	1.150	1.079	0.980

It can be concluded that in the absence of force constant changes the isotope effect comes entirely from the ratio of the imaginary frequencies; that if the force constant decreases in going from the ground state to the transition state, the isotope effect will be normal; if the force constant increases, the isotope effect will be inverse.

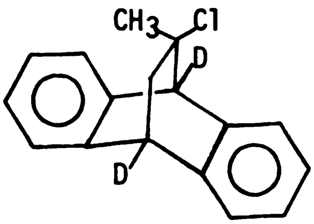
Isotope effects are generally recognized as evidence of force constant changes at the isotopic position between reactant and transition state. Most of the work in isotope effects is devoted to understanding the origin of force constant changes and elucidating the reaction mechanisms. At the present time secondary isotope effects are analyzed and discussed in term of hyperconjugation,[7] inductive effects[8] and non-bonded interactions.[9] The extent to which hyperconjugation may be important in determining β deuterium isotope effects has been a matter of considerable controversy.[10] However evidence favoring this postulate has been accumulated since then. Shiner and co-workers[11] have studied the solvolysis of t-butyl chloride and t-butyl $-d_1, -d_2, -d_3, -d_6, -d_9$ chlorides in 60% aqueous ethanol at 25°. Their results are reported in Table III.

TABLE III. Isotope Effects in the Solvolysis of t-Butyl Chlorides in 60% Ethanol at 25°.

Compound	k_H/k_D	k_H/k_D per D
$-d_1$	1.0922	1.0922
$-d_2$	1.2016	1.096
$-d_3$	1.3304	1.100
$-d_6$	1.7095	1.102
$-d_9$	2.3275	1.103

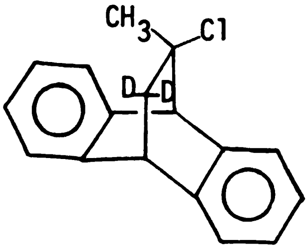
They interpreted their results in terms of hyperconjugation, whereby the force constants associated with the β C-H bond are weakened in going from ground state to transition state. The isotope effect is nearly cumulative, increasing slightly with the number of deuterium atoms.

The conformational dependence of the isotope effect was elegantly demonstrated by Shiner and Humphrey.[12] They observed a very small inverse isotope effect in the solvolysis of the bridge deuterated bicyclooctane derivative I, where the C-D bond is in the nodal plane of the developing "p" orbital at the reaction center.



I

$k_H/k_D = 0.986 \pm 0.01$

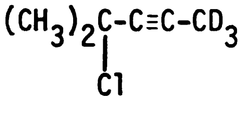


II

$k_H/k_D = 1.14$

With deuteration at the β position as in II, where hyperconjugation is possible, the isotope effect k_H/k_D was 1.14.

Transmission through a π bond was also demonstrated by Shiner and Kirz[13] in the solvolysis of the chloropentyne derivative, III.

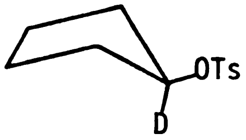


$$(CH_3)_2\underset{\displaystyle Cl}{\underset{|}{C}}\text{-}C\equiv C\text{-}CD_3$$

III

The isotope effect, $k_H/k_D = 1.092$, was explained again in terms of hyperconjugation through the unsaturated linkage.

Halevi proposed[8] the "inductive effect" in order to explain secondary deuterium isotope effects. Due to the small anharmonicity of the Morse Potential and the shorter length of the C-D bond over the C-H bond, the electron density of carbon should be greater in the C-D than in the C-H bond. Thus, placement of a positive charge near the carbon should be stabilized more by the C-D than the C-H. This argument predicts an inverse secondary isotope effect. This prediction, however, is the opposite of what is observed in both α and β secondary isotope effects. Streitwieser and co-workers[14] have observed an isotope effect, $k_H/k_D = 1.15$, in the solvolysis of cyclopentyl-1d-tosylate, IV.



IV

They ascribed this effect as arising predominantly from the change of a tetrahedral C-H bending vibration to an out-of-plane deformation in the transition state. Although the inductive effect explanation fails to explain the above isotope effects, it has been invoked to explain an impressive amount of experimental data. The dipole moments[15] of ND_3, CD_3ND_2, $(CH_3)_3CD$ are 0.01 to 0.04 Debye larger than those of the corresponding protium compounds. In the N.M.R. the proton signals in $-CH_2D$ are shielded by 0.015 ppm relative to those of the methyl[16] and the ^{19}F in $-CF_2D$ by 0.06 ± 0.05 ppm relative to those of $-CF_2H$.[17]

Streitwieser and Klein[18] have measured the isotope effects in the dissociation of a series of acids: They are reported in Table IV.

TABLE IV. Isotope Effects in the Acidity of Carboxylic Acids.

Acid	K_H/K_D
CD_3COOH	1.03
$(CD_3)_3CCOOH$	1.04
C_6D_5COOH	1.02

They also invoked the inductive effect to explain these isotope effects. It was previously stated that isotope effects may be used as a probe of force constant changes.[6] What is not known is the nature of the force constant that is changed by the inductive effect. Bell and Crooks[19] have performed a detailed calculation of the relative dissociation constants of HCOOH and DCOOH. Using fundamental frequencies for HCOOH, DCOOH, $HCOO^-$, $DCOO^-$, they calculated an isotope effect of 1.09. This value is in excellent agreement with the experimental one of 1.084 determined by Bell and Miller.[20] The authors concluded that the isotope effect was due not only to the C-H and C-D stretching vibrations, but also to the two bending vibrations as well as to those arising from coupling of these vibrations.

Kresge and Preto[21] have interpreted the isotope effect on the equilibrium constant for the ionization of triphenylcarbinol to triphenyl cation, V, as inductive in nature.

$$\phi_3COH + H_2SO_4/CH_3COOH \rightleftharpoons \phi_3C^+ + H_2O$$

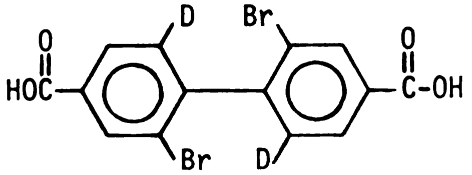
V

They found K_D/K_H = 1.013 for the _ortho_ and _meta_ deuterated analogs and K_D/K_H = 1.008 for the _para_ analog. Streitwieser and Humphrey[22] also invoked the inductive effect to rationalize the isotope effects in the protodedeuteration of α-_d_ toluene which was ring deuterated. Their findings of k_H/k_D at 50° per ring deuteration were:

1.024 (_ortho_), 1.004 (_meta_), and 1.018 (_para_).

Bartell suggested that secondary deuterium isotope effects are primarily due to non-bonded interactions. Because of the greater amplitude of the zero point vibrational motion of the C-H bond relative to the C-D bond, the effective size of deuterium is less than that of the hydrogen; therefore, in reactions in which non-bonded repulsions increase in going from reactant to transition state deuterium substitution will lead to faster rates.

The isotope effect found by Melander and Carter[23] in the racemization of the biphenyl derivative VI, k_D/k_H = 1.19, in ethanol at -19.8° can be safely attributed to non-bonded interactions.

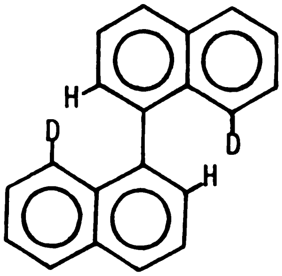


VI

Carter and Dahlgreen[24] studied the racemization of 1,1'-binaphtyl-2,2'-$\underline{d}_2$, VII, the results of which study are shown in Table V.

TABLE V. Isotope Effects in the Racemization of 1,1'-Binaphtyl and its 2,2'-Dideutero Derivative in N,N'-Dimethylformamide Solution.

T°K	k_D/k_H	$\Delta\Delta G^{\ddagger}$ cal/mole
337.20	1.14 ± 0.03	87.8 ± 17.8
330.77	1.14 ± 0.02	89.0 ± 11.7
323.85	1.14 ± 0.01	84.3 ± 7.3
316.33	1.15 ± 0.01	91.1 ± 7.1
309.18	1.18 ± 0.02	104.8 ± 11.0
302.43	1.17 ± 0.02	98.4 ± 10.3



VII

By use of suitable non-bonded potential functions and reasonable assumptions the authors showed that this inverse isotope effect arises from an increase of the force constant of the in-plane bending C-H frequency in going from ground state to transition state.

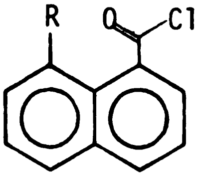
Brown and co-workers[25] have studied the reaction of methylpyridines with methyl iodide. Their results are reported in Table VI.

TABLE VI. Isotope Effects in the Reaction of Me-Pyridines and MeI.

Pyridine	k_D/k_H
4-Methyl-$\underline{d}_3$	1.001 ± .003
3-Methyl-$\underline{d}_3$	1.009 ± .002
2-Methyl-$\underline{d}_3$	1.030 ± .003
2,6-dimethyl-$\underline{d}_6$	1.095 ± .003

They explained the enhanced reactivity of the deuterated analog where methyl is at the "$\underline{2}$" position as steric in origin. They also observed[26] an inverse isotope effect, $k_H/k_D = 0.92$, in the reaction of 2,6-dimethylpyridine and BF_3, but a negligible one in the reaction with BH_3. Brown has taken the extreme position that secondary isotope effects arise predominantly from non-bonded interactions.

Karabatsos and co-workers[27] have examined the relative contributions of hyperconjugation and non-bonded interactions to secondary isotope effects. They observed a small isotope effect ($k_H/k_D = 1.029$) in the solvolysis of 8-substituted naphthalenes, VIII.



R = CH_3, CD_3

VIII

They rationalized their results as steric in origin. Extensive calculations within the framework of Bartell's theory gave values of 1.07 and 1.18 when the dihedral angle, ϕ, between the ring and the COCl planes was assumed to be 60° and 45°, respectively. In systems where hyperconjugation was possible, e.g. CD_3COCl, the calculated isotope effect, $k_H/k_D = 0.98$ at -22°, was lower than the experimental one, $k_H/k_D = 1.62$; in systems like $(CD_3)_3CCl$ the calculated isotope effect was 1.10 and the experimental one 2.39. This led the authors to conclude that, in systems where hyperconjugation was possible, less than 10% of the observed isotope effect is due to non-bonded interactions.

Jewett and Dunlop[28] studied δ deuterium isotope effects to assess the relative contributions of non-bonded interactions to secondary isotope effects. Their results are reported in Table VII.

TABLE VII. Secondary δ Isotope Effects in 95% Ethanol.

System	k_H/k_D	Ref.
$(CD_3)_3CCH_2C(CH_3)_2Cl$	0.983	28
$CD_3CH=CHCHClCH_3$	1.132	28
$CD_3C\equiv CC(CH_3)_2Cl$	1.095	13

The saturated system is known to react 20 times faster than t-butyl chloride and the inverse isotope effect can be rationalized as steric in origin; however, in the allylic and acetylenic systems, the normal isotope effect is better interpreted as due to hyperconjugation through the unsaturated linkage. These results support Karabatsos' conclusion that, in systems where hyperconjugation is possible, non-bonded interactions are of secondary importance.

Isotope effects have been used to help elucidate the mechanisms of solvolytic reactions. It has been suggested that α and β effects should be a useful criterion of the degree of nucleophilic participation by the solvent in the rate determining step, since S_N2 reactions showed effects near unity and S_N1 reactions showed effects around 1.14 per deuterium. Shiner and co-workers[29] have recently reported the α and β deuterium isotope effects for a series of substituted 1-phenylethyl halides. Their results are shown in Table VIII.

TABLE VIII. Isotope Effects of Substituted 1-Phenylethyl Chlorides in 50% Ethanol.

Substituent	$(k_H/k_D)_\alpha$	$(k_H/k_D)_\beta$
p-Methoxy	1.157	1.113
p-Phenoxy	1.157	1.164
p-Methyl	1.157	1.200
p-Fluor	1.152	1.211
m-Methyl	1.151	1.222
None	1.153	1.224
p-Bromo	1.133	1.221
p-Nitro	1.098	1.151

The observation that the α effect is nearly constant for the different substituents was taken as evidence that the reaction proceeds by a limiting mechanism. The smaller isotope effects for the p-bromo and p-nitro compounds were interpreted in terms of some nucleophilic character of the solvolytic mechanism. These conclusions were corroborated by the β isotope effects.

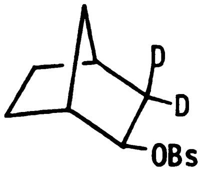
Streitwieser and Dufforn studied the solvolysis of isopropyl tosylate[30] in trifluoroacetic acid, a solvent of low nucleophilicity and high ionizing power[31]. Their results are shown in Table IX.

TABLE IX. Isotope Effects in the Trifluoroacetolysis of Isopropyl Tosylate.

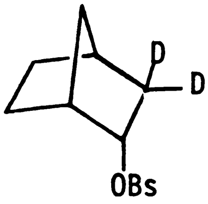
Compound	$(k_H/k_D)_\alpha$	$(k_H/k_D)_\beta$
$(CH_3)_2CDOTs$	1.22 ± 0.02	
$(CD_3)_2CHOTs$		2.12 ± 0.10

The α isotope effect is larger than the one reported by Mislow[32] in the acetolysis of isopropyl brosylate at 70°, $k_H/k_D = 1.12$. From the results the authors concluded that the acetolysis reaction is characterized by a higher degree of nucleophilic solvent participation than the trifluoroacetolysis one.

Secondary isotope effects have been use as a criterion in elucidating the nature of the norbornyl cation. Schaeffer and co-workers[33] have reported the β deuterium isotope effects for 2-norbornyl brosylate. They observed an isotope effect, $k_H/k_D = 1.04$, for the <u>exo</u> (IX) and 1.28 for the <u>endo</u> (X) compounds.



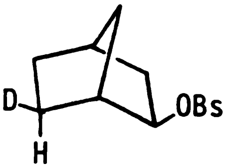
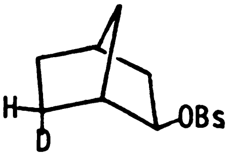
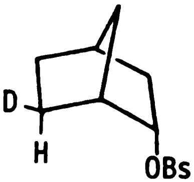
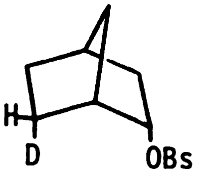
IX



X

They interpreted the data in terms of the rate determining formation of the non-classical norbornyl ion for the exo and of the classical ion for the endo. The γ isotope effects, studied by a number of workers,[34,35] are shown in Table X.

TABLE X. Secondary γ Isotope Effects in the Solvolysis of Norbornyl Brosylates.

				
KOAc-HOAc[a]	1.09 ± 0.03	1.11 ± 0.01	0.98 ± 0.01	0.99 ± 0.02
80% EtOH[a]	1.09 ± 0.01	1.11 ± 0.01	1.00 ± 0.02	0.97 ± 0.01
HOAc[b]	1.097 ± 0.011	1.082 ± 0.09	1.021 ± 0.012	0.998 ± 0.009

[a] Reference 34. [b] Reference 35.

These results were also interpreted as evidence for a non-classical ion for the exo compound and a classical one for the endo. That the isotope effects for the exo series varies with the degree of substitution have been confirmed by a number of workers.[36,37]

Hakka and co-workers[38] have studied the temperature dependence of the isotope effect in the solvolysis of t-butyl chloride and t-butyl-d_9 chloride in 50% ethanol 50% water mixture. They found that the isotope effect decreased from 2.542 at 5.686° to 2.086 at 55.686°. This decrease conformed closely to the expected approximation $\Delta\Delta G^{\ddagger} = \Delta\Delta H^{\ddagger}$. Leffek and co-workers[39] on the other hand found an unusual temperature independence of the secondary isotope effects in the solvolysis of isopropyl methanesulfonate ($k_H/k_D = 1.54$ from 5° to 30°), isopropyl tosylate ($k_H/k_D = 1.54$ from 6° to 30°) and isopropyl bromide ($k_H/k_D = 1.31$ from 40° to 70°). This temperature independence was shown to be due entirely to $\Delta\Delta S^{\ddagger}$. A reasonable explanation may be given either in terms of probable solvation differences, or in terms of the recent theoretical analysis of the temperature independence of some isotope effects carried out by Wolfsberg and Stern[5]. They showed that k_H/k_D could be virtually temperature independent for two compensating effects in the force constant changes. Their results are summarized in Table XI.

TABLE XI. Temperature Independent Secondary Hydrogen Isotope Effects.

$(CD_3)_2CHX$	$(CD_3)_2CH.......X^a$
T°K	k_H/k_D
250	1.4080
280	1.4110
300	1.4130
320	1.4151
340	1.4170
360	1.4188

[a] Assumed force constants changes f_{CH} in CH_3 4.8 to 3.5 md/A. $f_{torsion}$ 0.15 to 1.0 md/A. f_{HCC} in CH_3 0.68 to 1.0 md/A. One HCCC torsion coordinate was employed per methyl group.

The work described in this thesis deals with the temperature and solvent dependence of the isotope effects in the solvolysis of isobutyryl and pivaloyl chlorides and their deuterated analogs. It was undertaken in order to probe further into the usefulness of secondary isotope effects as mechanistic criteria especially after the findings by Evans[40] that the isotope effects in the solvolysis of acetyl chloride increase with increasing temperature and that of Kang[41] that some isotope effects in the solvolysis of propionyl chloride invert (inverse to normal) with increasing temperature.

EXPERIMENTAL

I. KINETICS

A. Preparation of Solvents.

Conductivity Water: Conductivity water was prepared, as described by Evans[40] by passing distilled water through a column containing a layer of Dowex 1-X8 (anion exchange resin) and a layer of Dowex 50W-X8 (cation exchange resin). Water treated in this manner had a specific conductance of 1×10^{-6} mho/cm.

Conductivity Acetone: Acetone (Fisher Certificate A-18) was treated with 50 g of potassium permanganate and 0.5 g of sodium hydroxide, refluxed overnight and distilled. Acetone obtained in this manner had a specific conductance of 1×19^{-8} mho/cm.

Mixed Solvents: Mixtures of acetone and water were prepared as described by Evans.[40]

B. Conductance Apparatus.

A Wayne Kerr conductance bridge (Model B221) equipped with an autobalance Adapter (Model AA 221) and a PS 109 power supply unit was used for all conductance measurements.

C. Conductance Cell.

The conductance cell used is described by Papaioannou.[42]

D. Measurement of Time.

A precision scientific electronic digital timer accurate to 1/100th of a minute was used.

E. Constant Temperature Bath.

The bath used is described by Papaioannou. It was equipped with a stirring motor, a submersible magnetic stirrer, a relay, a thermal control, a heater and a Beckmann Differential Thermometer. Temperatures constnat to ± 0.005° were obtained over a temperature range from -30° to +4°.

F. Measurement of Temperature.

The temperature was determined by means of a quartz thermometer (2801A Hewlett-Packard) accurate to ± 0.010°. One hundred readings were taken from the Quartz Thermometer and the average temperature was corrected for linearity and for the deviation of the ice point.

G. Rate Determinations.

The conductance cell containing a teflon stirring bar was filled with 250 ml of solvent, immersed in the bath, and allowed to attain the desired temperature by stirring for about 40 minutes. A drop of the acid chloride was then added and stirred for at least a minute to assure homogeneity. Conductance readings were taken over the first three half-lives and the infinity was obtained after 20 half-lives. The deuterated analogs were treated in the same manner.

H. Treatment of Data.

First order rate constants were obtained by a least squares solution of the integrated first order rate expression using PROGRAM RATE.

$$\ln (C_\infty - C_t) = -kt + \ln C_\infty$$

C_∞ = Conductance at infinite time

C_t = Conductance at time t.

The uncertainty in the rate constant is the standard error σ.

$$\sigma = \Sigma \, [(X_i - \overline{X}_i)^2/n-1]^{1/2}$$

X_i = observed rate

$\overline{X}_i$ = mean

n = number of observations

The uncertainty in the isotope effect, k_H/k_D, is the standard error σ, obtained from the expression

$$\sigma(k_H/k_d) = k_H/k_d[\sigma_H^2/k_H^2 + \sigma_d^2/k_d^2]^{1/2}$$

Three computer programs were used to determined the activation parameters. *Acteng* calculates both Arrhenius parameters (lnk/T *vs*. 1/T) and transition state theory parameters (lnk/T *vs*. 1/T) by an iterative least squares method. *AKTIV* calculates activation parameters by a single least squares solution of lnk/T *vs*. 1/T and *HANDS* calculates $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{+}$ by a single least squares solution of ln k_H/k_d *vs*. 1/T.

II. SYNTHESIS.

A. *Isobutyric Acid*.

1. *2-Propanol-2d*: Acetone, 50 g (0.86 mole), was added dropwise to a slurry of 10 g of lithium aluminum deuteride in 205 ml of dry ether. After the reaction mixture was kept overnight, it was treated with 10% solution of sodium hydroxide, as described by Fisher.[43] The yield of the alcohol distilled from the reaction mixture was 90%.

2. 2-Bromopropane 2-d: The above alcohol was cooled at -30° and 35 ml of phosphorous tribromide was added dropwise. After the reaction mixture was completed, the bromide was distilled, washed with dilute sulfuric acid, dried over sodium sulfate and redistilled. The bromide was obtained in 70% yield.[44]

3. Isobutyric 2-d Acid: The above bromide was added dropwise to 12 g of magnesium in 50 ml of ether. After refluxing for 6 hrs it was cooled to -50° and 20 g of dry ice was poured into the flask. When this attained room temperature, 20 ml of D_2O was added, the mixture was acidified and immediately extracted with ether. The acid was obtained in 30% yield. The same sequences were used for the preparation of isobutyric-d_6 acid by starting with acetone-d_6. The isotopic purity of the acids was checked by n.m.r.

B. Pivalic Acid.

1. Pinacol-d_{12}: Acetone-d_6, 66 g (1 mole), and 13 g of mercuric chloride were added to 12 g of magnesium in 120 ml of dry benzene. After the reaction was completed, 40 ml of water was added, the solution concentrated to 1/3rd of its volume and cooled in an ice bath. The yield of pinacol hexahydrate was 60 g.[45]

2. Pinacolone-d_{12}: The above pinacol was added to 250 ml of 6N sulfuric acid and distilled immediately. After being dried and distilled, 20 ml of pinacolone was obtained.

3. Pivalic-d_9 Acid: To 750 ml of H_2O and 85 g of sodium hydroxide was added 38 ml of bromine at such a rate as to keep the temperature below 5°. The solution was then cooled at 0° and the pinacolone was added dropwise.

After refluxing for three hours the solution was then concentrated, acidified with sulfuric acid and extracted with ether. The yield of the acid was 7 g. The n.m.r. showed an isotopic purity of 97%.

III. PREPARATION OF ACID CHLORIDES.

The acids were prepared by the method described by Brown.[46] The method is described below.

To a round-bottomed flask equipped with a vigraux fractionating column and standard distillation head was added 0.1 mole of the acid and 0.2 mole of benzoyl chloride. The acid chloride was distilled in an ice-cooled receiver as quickly as possible. The distillate was refluxed for 30 minutes to purge the hydrochloric acid. The distillation was repeated a second time, The yield was 70%. The isotopic purity of the deuterated acids was determined by n.m.r.

IV. KINETIC RESULTS.

The rates of solvolysis of isobutyryl chloride and isobutyryl-$\underline{d}_1$, -$\underline{d}_6$ chlorides are reported in Tables XII to XVII. The rates of solvolysis of pivaloyl chloride and pivaloyl-$\underline{d}_9$ chloride are reported in Tables XVIII to XXII. The average rate constants were used to determine the isotope effects in the solvolysis of isotutyryl chloride and pivaloyl chloride systems.

TABLE XII. Rates of Solvolysis of Isobutyryl-d_0, -d_1, -d_6 Chlorides in Aqueous Acetone.

T = -29.120 ± .015

75% acetone

$k \times 10^4$

d_0	d_1	d_6
8.5745	8.7467	9.1765
8.5591	8.8079	9.1856
8.5712	8.7604	9.2185
8.5683 ± .0082	8.7717 ± .0300	9.1935 ± .0220

80% acetone

$k \times 10^4$

d_0	d_1	d_6
4.7480	4.9025	4.9972
4.7420	4.9026	4.9520
4.7417	4.8868	5.0240
4.7439 ± .0035	4.8986 ± .0079	4.9911 ± .0360

85% acetone

$k \times 10^4$

d_0	d_1	d_6
2.8891	3.0401	3.0111
2.8830	3.0423	3.0086
2.9046	3.0342	2.9918
2.9082		
2.8962 ± .0148	3.0388 ± .0043	3.0035 ± .0106

90% acetone

$k \times 10^4$

d_0	d_1	d_6
1.6291	1.7161	1.6575
1.6289	1.7161	1.6567
1.6487	1.7061	1.6591
		1.6646
1.6356 ± .0114	1.7128 ± .0058	1.6594 ± .0042

TABLE XIII. Rates of Solvolysis of Isobutyryl -d_0, -d_1, -d_6 Chlorides in Aqueous Acetone.

T = -24.985 ± .015

75% acetone

$k \times 10^3$

d_0	d_1	d_6
1.3962	1.4176	1.5196
1.3959	1.4163	1.5215
1.3991	1.4168	1.5271
1.4040	1.4206	1.5194
1.3988 ± .0038	1.4178 ± .0023	1.5219 ± .0044

80% acetone

$k \times 10^4$

d_0	d_1	d_6
7.6814	7.9690	8.1829
7.7022	7.9651	8.1813
7.6882	7.9591	8.1505
7.7208	7.9090	
7.6982 ± .0170	7.9505 ± .0280	8.1716 ± .0180

85% acetone

$k \times 10^4$

d_0	d_1	d_6
4.6444	4.8573	4.8376
4.6410	4.8619	4.8211
4.6394	4.8363	4.8001
4.6416 ± .0025	4.8518 ± .0136	4.8196 ± .0188

90% acetone

$k \times 10^4$

d_0	d_1	d_6
2.5393	2.6774	2.5427
2.5486	2.6559	2.5697
2.5401	2.6499	2.5454
2.5426 ± .0052	2.6611 ± .0144	2.5536 ± .0149

TABLE XIV. Rates of Solvolysis of Isobutyryl -$\underline{d}_0$, -$\underline{d}_1$, -$\underline{d}_6$ Chlorides in Aqueous Acetone.

T = -20.004 ± .005

75% acetone

$k \times 10^3$

$\underline{d}_0$	$\underline{d}_1$	$\underline{d}_6$
2.4218	2.4844	2.6664
2.4319	2.4639	2.6399
2.4476	2.4622	2.6276
2.4482	2.4705	2.6306
2.4498		
2.4398 ± .0120	2.4703 ± .0101	2.6412 ± .0150

T = -19.793 ± .005

80% acetone

$k \times 10^3$

$\underline{d}_0$	$\underline{d}_1$	$\underline{d}_6$
1.2954	1.3249	1.3771
1.3010	1.3275	1.3876
1.2932	1.3369	1.4110
1.2965 ± .0041	1.3298 ± .0063	1.3919 ± .0170

T = -20.004 ± .005

85% acetone

$k \times 10^4$

$\underline{d}_0$	$\underline{d}_1$	$\underline{d}_6$
7.7299	7.9917	8.1457
7.7054	7.9566	8.1465
7.7364	7.9399	8.1621
	7.9417	
7.7243 ± .0162	7.9575 ± .0240	8.1516 ± .0095

TABLE XIV. (Continued)

T = -20.004 ± .005

90% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_1$	$\underline{d}_6$
4.0232	4.1697	4.1397
4.0111	4.1794	4.1372
4.0083	4.1545	4.1357
4.0142 ± .0079	4.1679 ± .0125	4.1375 ± .0020

T = -19.793 ± .005

95% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_1$	$\underline{d}_6$
1.5493	1.6958	1.5868
1.5789	1.6792	1.5841
1.6191	1.6629	1.5835
1.5824 ± .0350	1.6793 ± .0160	1.5835 ± .0036

TABLE XV. Rates of Solvolysis of Isobutyryl -d_0, -d_1, -d_6 Chlorides in Aqueous Acetone.

T = -15.616 ± .005

80% acetone

$k \times 10^3$

d_0	d_1	d_6
1.9803	2.0597	2.1126
1.9789	2.0647	2.1295
1.9983	2.0607	2.0968
2.0047	2.0592	2.1149
2.0075	2.0543	2.1253
	2.0454	
	2.0376	
1.9939 ± .0135	2.0545 ± .0096	2.1158 ± .0127

85% acetone

$k \times 10^3$

d_0	d_1	d_6
1.1510	1.1974	1.2024
1.1474	1.1961	1.2002
1.1563	1.1953	1.2151
1.1474	1.1959	1.2159
	1.1857	1.1835
	1.1852	1.1835
1.1505 ± .0045	1.1926 ± .0072	1.2034 ± .0132

90% acetone

$k \times 10^4$

d_0	d_1	d_6
5.8224	6.0884	5.9884
5.8241	6.0833	5.9915
5.8605	6.0832	6.0083
5.8277	6.0819	5.9656
	6.0888	6.0005
5.8336 ± .0230	6.0768 ± .0192	5.9908 ± .0164

95% acetone

$k \times 10^4$

d_0	d_1	d_6
2.2049	2.2965	2.2028
2.2105	2.3096	2.2122
2.2104	2.2855	2.2111
2.2051	2.2811	2.2087
2.2077 ± .0032	2.2932 ± .0127	2.2089 ± .0044

TABLE XVI. Rates of Solvolysis of Isobutyryl -d_0, -d_1, -d_6 Chlorides in Aqueous Acetone.

T = -10.109 ± .005

85% acetone

k x 10^3

d_0	d_1	d_6
1.9496	2.0131	1.9939
1.9785	2.0076	2.0279
1.9769	2.0217	2.0575
1.9797	2.0214	2.0412
1.9712 ± .0140	2.0159 ± .0069	2.0301 ± .0120

90% acetone

k x 10^4

d_0	d_1	d_6
9.7869	10.0761	10.0252
9.8373	9.9674	9.9364
9.7941	10.0860	10.0340
9.8106	10.0940	9.9990
9.8073 ± .0194	10.0412 ± .0610	9.9986 ± .0440

95% acetone

k x 10^4

d_0	d_1	d_6
3.5008	3.6114	3.5257
3.4615	3.5937	3.4898
3.4648	3.5828	3.4812
3.4669	3.5842	3.4735
3.4735 ± .0183	3.5930 ± .0137	3.4926 ± .0230

TABLE XVII. Rates of Solvolysis of Isobutyryl -d_0, -d_1, -d_6 Chlorides in Aqueous Acetone.

T = -4.978 ± .010

90% acetone
$k \times 10^3$

d_0	d_1	d_6
1.5333	1.5501	1.5823
1.5509	1.5599	1.5814
1.5391	1.5687	1.5838
1.5267		1.5795
1.5410		
1.5382 ± .0091	1.5596 ± .0093	1.5818 ± .0018

95% acetone
$k \times 10^4$

d_0	d_1	d_6
5.4199	5.4910	5.4336
5.3649	5.5252	5.4357
5.4053	5.5438	5.4336
5.4081		5.4353
5.3996 ± .0239	5.5200 ± .0218	5.4351 ± .0009

TABLE XVIII. Rates of Solvolysis of Pivaloyl -$\underline{d}_0$, -$\underline{d}_9$ Chlorides in Aqueous Acetone.

$T = -14.312 \pm .008$

75% acetone

$k \times 10^4$

$\underline{d}_0$	$\underline{d}_9$
7.9523	8.7668
7.9516	8.7923
7.9409	8.7456
7.9192	8.7408
7.9408 ± .0150	8.7614 ± .0230

80% acetone

$k \times 10^4$

$\underline{d}_0$	$\underline{d}_9$
4.2564	4.5827
4.2532	4.5896
4.2427	4.5702
4.2393	4.5853
4.2479 ± .0082	4.5819 ± .0084

85% acetone

$k \times 10^4$

$\underline{d}_0$	$\underline{d}_9$
2.5017	2.6646
2.5159	2.6644
2.5026	2.6558
2.5060	2.6520
2.5066 ± .0065	2.6592 ± .0068

TABLE XIX. Rates of Solvolysis of Pivaloyl -$\underline{d}_0$, -$\underline{d}_9$ Chlorides in Aqueous Acetone.

T = -9.344 ± .008

75% acetone

k x 10^3

$\underline{d}_0$	$\underline{d}_1$	$\underline{d}_9$
1.3396		1.4734
1.3414		1.4827
1.3483		1.4783
1.3452		1.4793
1.3436 ± .0039		1.4784 ± .0039

80% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_9$
7.1353	7.6886
7.1232	7.6981
7.1308	7.6762
7.1309	7.6918
7.1301 ± .0050	7.6887 ± .0092

85% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_9$
4.1154	4.3726
4.1187	4.3829
4.1329	4.3864
4.1264	4.3948
4.1234 ± .0078	4.3841 ± .0092

90% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_9$
2.1014	2.1925
2.1106	2.1915
2.1219	2.2076
2.1244	2.2042
2.1146 ± .0106	2.1989 ± .0082

TABLE XX. Rates of Solvolysis of Pivaloyl -$\underline{d}_0$, -$\underline{d}_9$ Chlorides in Aqueous Acetone.

T = -4.978 ± .010

75% acetone

k x 10^3

$\underline{d}_0$	$\underline{d}_9$
2.0543	2.2359
2.0696	2.2346
2.0024	2.2533
1.9895	2.2646
2.0289 ± .0380	2.2731
	2.2523 ± .0156

80% acetone

k x 10^3

$\underline{d}_0$	$\underline{d}_9$
1.0689	1.1549
1.0842	1.1676
1.0708	1.1681
1.0704	1.1641
1.0736 ± .0071	1.1637 ± .0061

85% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_9$
6.2387	6.6446
6.2558	6.6475
6.2468	6.6369
6.2735	6.6206
6.2537 ± .0149	6.6373 ± .0122

90% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_9$
3.1422	3.2622
3.1565	3.2649
3.1381	3.2581
3.1573	3.2744
3.1485 ± .0098	3.2649 ± .0069

TABLE XXI. Rates of Solvolysis of Pivaloyl -$\underline{d}_0$, -$\underline{d}_9$ Chlorides in Aqueous Acetone.

T = -0.255 ± .005

80% acetone

$k \times 10^3$

$\underline{d}_0$	$\underline{d}_9$
1.7069	1.8459
1.6982	1.8432
1.7043	1.8469
1.7118	1.8539
1.7199	1.8478
1.7082 ± .0082	1.8475 ± .0039

85% acetone

$k \times 10^4$

$\underline{d}_0$	$\underline{d}_9$
9.7293	10.269
9.7136	10.244
9.6874	10.311
9.7207	10.322
9.7128 ± .0179	10.2865 ± .0037

90% acetone

$k \times 10^4$

$\underline{d}_0$	$\underline{d}_9$
4.7432	4.9411
4.7529	4.9429
4.7537	4.9536
4.7448	4.9747
4.7487 ± .0054	4.9531 ± .0150

TABLE XXII. Rates of Solvolysis of Pivaloyl -$\underline{d}_0$, -$\underline{d}_9$ Chlorides in Aqueous Acetone.

T = +4.001 ± .005

80% acetone

k x 10^3

$\underline{d}_0$	$\underline{d}_9$
2.5329	2.7497
2.5038	2.7417
2.5460	2.7265
2.5168	2.7584
2.5302	2.7424
2.5259 ± .0160	2.7580
	2.7460 ± .0120

85% acetone

k x 10^3

$\underline{d}_0$	$\underline{d}_9$
1.4145	1.5040
1.4090	1.5054
1.4044	1.5041
1.4143	1.5020
1.4106 ± .0048	1.5039 ± .0014

90% acetone

k x 10^4

$\underline{d}_0$	$\underline{d}_9$
6.8778	7.1708
6.8969	7.1475
6.8631	7.1698
6.8623	7.1526
6.8407	
6.8682 ± .0200	7.1602 ± .0119

RESULTS AND DISCUSSION

I. MECHANISM OF ACID CHLORIDE SOLVOLYSIS.

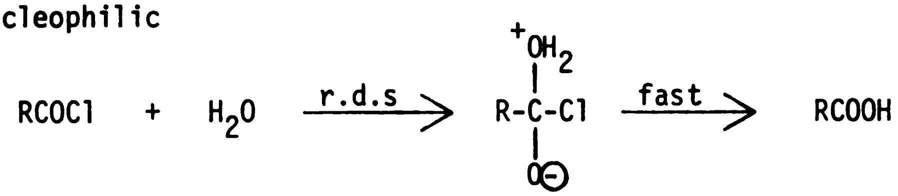
The nucleophilic substitution reactions of various derivatives of carboxylic acids, especially the hydrolysis of esters, have been studied thoroughly and their mechanisms are well understood.[47] However, the mechanism of hydrolysis and alcoholysis of acid chlorides is still mechanistically ambiguous.

Gold and co-workers[48] have suggested that aromatic acid chlorides hydrolyze by either S_N1 or S_N2 mechanisms. The two paths they proposed are as follows:

1. Limiting

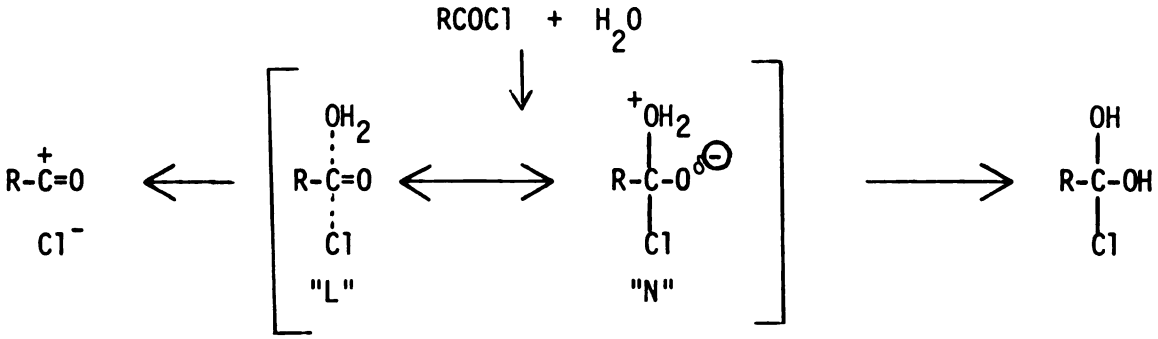
$$\mathrm{RCOCl} \xrightarrow{\text{r.d.s}} \mathrm{R\text{-}\overset{+}{C}{=}O} \;+\; \mathrm{Cl}^{\ominus} \;+\; \xrightarrow[\text{fast}]{H_2O} \mathrm{RCOOH}$$

2. Nucleophilic



$$\mathrm{RCOCl} + H_2O \xrightarrow{\text{r.d.s}} \mathrm{R\text{-}\underset{O^{\ominus}}{\underset{|}{\overset{\overset{+}{O}H_2}{\overset{|}{C}}}}\text{-}Cl} \xrightarrow{\text{fast}} \mathrm{RCOOH}$$

Johnston,[49] in reviewing the solvolysis of aromatic acid chlorides, also supports the idea of two mechanisms operating simultaneously. A unified mechanism has been proposed by Evans.[40] The activation process is depicted as:



The transition state is shifted from "L" to "N" with decreasing solvent polarity. Evidence favoring this idea has been presented.

In the solvolysis of substituted benzoyl chlorides, the Hammett reaction constant, ρ, varies with the solvent polarity. Solvolysis in 40% ethanol - 60% ether gives a straight line Hammett plot with positive ρ.[50] In 1% water-99% formic acid the substituent effect is completely reversed, and a negative ρ is obtained.[51] The plots are represented in Figures <u>1</u> and <u>2</u>. From the values of ρ it was concluded that in the former reaction the solvolysis of benzoyl chloride goes predominantly by a nucleophilic path and in the latter by a limiting path.

II. SOLVENT AND TEMPERATURE DEPENDENCE OF SECONDARY DEUTERIUM ISOTOPE EFFECTS.

It is recognized that reactions that proceed by a limiting mechanism show 10% - 12% rate retardation upon isotopic substitution at the <u>beta</u> carbon. In bimolecular displacement reactions the effect is near unity. Calculations carried out by Miller[52] predict an inverse isotope effect ($k_H/k_D < 1$) for reactions whose mechanism is nucleophilic with k_H/k_D increasing with temperature; and a normal effect ($k_H/k_D > 1$) for reactions

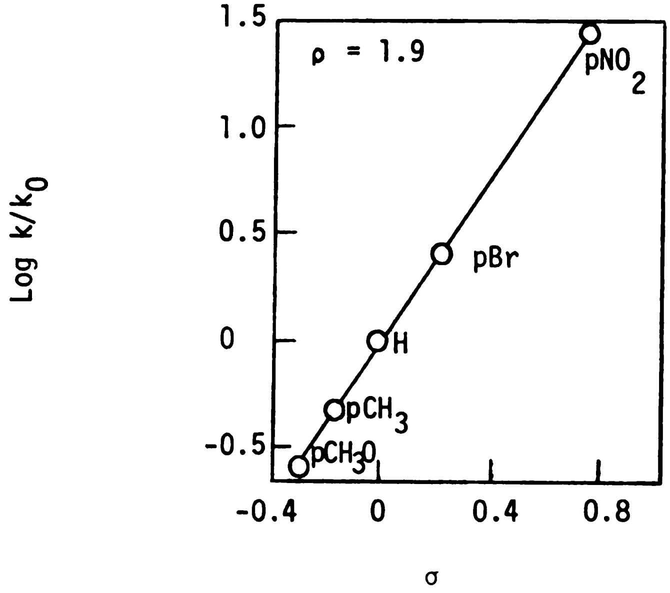


FIGURE 1. Hammett relations for p-substituted benzoyl chlorides in 40% ethanol and 60% ether.

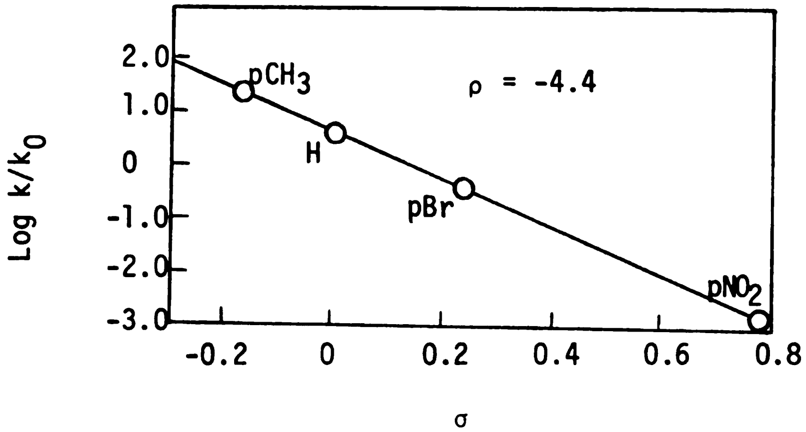


FIGURE 2. Hammett relations for p-substituted benzoyl chlorides in 1% water and 99% formic acid.

whose mechanism is limiting, with k_H/k_D decreasing with temperature. However, there are certain reactions in the borderline region whose mechanisms cannot be unambiguously classified as either limiting or nucleophilic.

Saunders and co-workers[53] studied the formolysis and acetolysis of 2-phenylethyl p-toluenesulfonate, XII. In the formolysis the β deuterium

$$\phi CH_2CH_2OTs$$

XII

isotope effect was 1.17 and in the acetolysis 1.02. They interpreted the results in terms of a predominantly S_N1 mechanism in the former solvent and in terms of a borderline S_N1-S_N2 mechanism in the latter solvent. However, the small isotope effect is not conclusive evidence that the mechanism of the acetolysis is borderline in nature; it may well be that, in view of the low ionizing power of the solvent, the substrate is reacting exclusively by a nucleophilic path.

Evans[40] studied the β isotope effect in the solvolysis of acetyl chloride. His results are summarized in Table XXIII. The decrease of the β isotope effect with decreasing solvent polarity was attributed to a duality in mechanism, changing from limiting in highly polar solvents to nucleophilic in less polar solvents. In terms of a unified mechanism the transition state shifts from "L" to "N" with decreasing solvent polarity.

The β and γ isotope effects in the solvolysis of propionyl chloride were studied by Kang.[41] The results are summarized in Table XXIV. The β effect was found to be near unity or inverse, depending on the solvent.

He suggested that the compound solvolyzed predominantly by a nucleophilic mechanism. He also supported the idea of a dual mechanism.

The β and γ isotope effects in the solvolysis of isobutyryl chloride and pivaloyl chloride are summarized in Tables XXV and XXVI, respectively. The β effect in isobutyryl chloride indicates that it solvolyzes predominantly by a nucleophilic mechanism. The decrease of this isotope effect with decreasing solvent polarity may be attributed either to an increase of the contribution of the nucleophilic path, or, in terms of a single unified mechanism, to a shift toward "N". In contrast to the β isotope effect, the γ isotope effect in propionyl, isobutyryl and pivaloyl chloride increased with decreasing solvent polarity. The temperature dependence of the normal β isotope effect of acetyl chloride was found by Evans to be unusual, i.e., it increased with increasing temperature. Such behavior was not observed with the β effect in propionyl and isobutyryl chlorides; they behaved normally. The γ effect in propionyl, isobutyryl and pivaloyl chlorides were found to be temperature independent. A plot of log k_H/k_D vs. 1/T in 75%, 80%, 85%, 90%, 95% acetone-water are reported in Figures 3-7.

III. CORRELATION OF ACTIVATION PARAMETERS AND ISOTOPE EFFECTS.

A serious problem concerning the interpretation and mechanistic application of secondary deuterium isotope effects is our lack of understanding of the dependence of the isotope effects on the enthalpies and entropies of activation. As pointed out previously, Evans[40] and Kang[41] found isotope effects that either increased or crossed over (inverse to normal) with increasing temperature. It is obvious, therefore, that in such cases

TABLE XXIII. Temperature Dependence of the β Secondary Deuterium Isotope Effects in the Solvolysis of Acetyl Chloride and Acetyl-d_3 Chloride.

Solvent (Acetone-Water)	T°C	k_H/k_D
80%	- 21.18	1.119 ± 0.017
	- 22.01[a]	1.106 ± 0.006
	- 26.37[a]	1.114 ± 0.006
	- 28.88[a]	1.105 ± 0.043
	- 31.32[a]	1.130 ± 0.021
	- 34.92	1.108 ± 0.008
85%	- 21.18	1.101 ± 0.004
	- 25.47	1.109 ± 0.010
	- 31.00	1.112 ± 0.013
90%	- 9.54	1.070 ± 0.010
	- 15.72[a]	1.072 ± 0.015
	- 22.01[a]	1.059 ± 0.002
	- 28.88[a]	1.044 ± 0.009
	- 33.68[a]	1.026 ± 0.010
95%	- 0.20	1.030 ± 0.007
	- 9.55	1.018 ± 0.004
	- 15.51	1.018 ± 0.004
	- 22.62	1.008 ± 0.001
	- 25.47	1.004 ± 0.004

[a] Values determined by C. G. Papaionnou.

TABLE XXIV. Temperature Dependence of the β and γ Secondary Deuterium Isotope Effects in the Solvolysis of Propionyl $-\underline{d}_0$, 2, 2-$\underline{d}_2$ and -3, 3, 3-$\underline{d}_3$ Chlorides.

Solvent (Acetone-Water)	T°C	$(k_H/k_D)_\beta$	$(k_H/k_D)_\gamma$
90%	- 15.14	0.948 ± 0.003	0.973 ± 0.005
	- 10.56	0.965 ± 0.007	0.988 ± 0.005
	- 5.53	0.967 ± 0.005	0.990 ± 0.005
	- 0.54	0.965 ± 0.005	0.978 ± 0.004
85%	- 26.17	0.961 ± 0.004	0.976 ± 0.039
	- 20.47	0.995 ± 0.018	0.973 ± 0.005
	- 15.54	0.978 ± 0.005	0.976 ± 0.005
	- 10.57	0.985 ± 0.004	0.977 ± 0.007
80%	- 30.58	0.989 ± 0.007	0.976 ± 0.010
	- 25.41	0.998 ± 0.010	0.976 ± 0.005
	- 20.47	1.001 ± 0.007	0.967 ± 0.021
	- 15.54	1.001 ± 0.007	0.982 ± 0.006
	- 10.56	1.008 ± 0.005	
75%	- 30.58	0.988 ± 0.004	0.939 ± 0.004
	- 25.55	1.008 ± 0.007	0.960 ± 0.005
	- 20.55	1.011 ± 0.005	0.957 ± 0.005

TABLE XXV. Temperature Dependence of the β and γ Secondary Deuterium Isotope Effects in the Solvolysis of Isobutyry-$\underline{d}_0$,-$\underline{d}_1$,-$\underline{d}_6$ Chlorides.

Solvent (Acetone-water)	T°C	$(k_H/k_D)_\beta$	$(k_H/k_D)_\gamma$
75%	- 29.120	0.977 ± 0.004	0.932 ± 0.002
	- 24.985	0.986 ± 0.003	0.919 ± 0.003
	- 20.004	0.988 ± 0.009	0.924 ± 0.008
80%	- 29.120	0.968 ± 0.002	0.951 ± 0.007
	- 24.985	0.968 ± 0.009	0.942 ± 0.003
	- 19.793	0.975 ± 0.007	0.932 ± 0.012
	- 15.616	0.971 ± 0.009	0.942 ± 0.008
85%	- 29.120	0.953 ± 0.003	0.964 ± 0.006
	- 24.985	0.957 ± 0.003	0.963 ± 0.004
	- 20.004	0.970 ± 0.004	0.948 ± 0.003
	- 15.616	0.965 ± 0.007	0.956 ± 0.012
	- 10.109	0.978 ± 0.008	0.971 ± 0.012
90%	- 29.120	0.955 ± 0.007	0.986 ± 0.007
	- 24.985	0.956 ± 0.006	0.996 ± 0.006
	- 20.004	0.963 ± 0.004	0.970 ± 0.002
	- 15.616	0.959 ± 0.005	0.974 ± 0.005
	- 10.109	0.977 ± 0.006	0.981 ± 0.005
	- 4.987	0.987 ± 0.008	0.972 ± 0.008
95%	- 19.793	0.942 ± 0.022	0.999 ± 0.022
	- 15.616	0.963 ± 0.006	0.999 ± 0.003
	- 10.109	0.967 ± 0.016	0.995 ± 0.017
	- 4.987	0.978 ± 0.006	0.994 ± 0.004

TABLE XXVI. Temperature Independence of the γ Secondary Deuterium Isotope Effects in the Solvolysis of Pivaloyl-$\underline{d}_0$, $\underline{d}_9$ Chlorides.

T°C	Solvent	75%	80%	85%	90%
- 14.312		0.906 ± 0.003	0.927 ± 0.002	0.943 ± 0.004	
- 9.344		0.909 ± 0.004	0.927 ± 0.002	0.941 ± 0.003	0.962 ± 0.006
- 4.978		0.901 ± 0.018	0.923 ± 0.008	0.942 ± 0.003	0.964 ± 0.004
- 0.255			0.925 ± 0.005	0.944 ± 0.006	0.959 ± 0.003
+ 4.001			0.919 ± 0.007	0.938 ± 0.004	0.959 ± 0.003

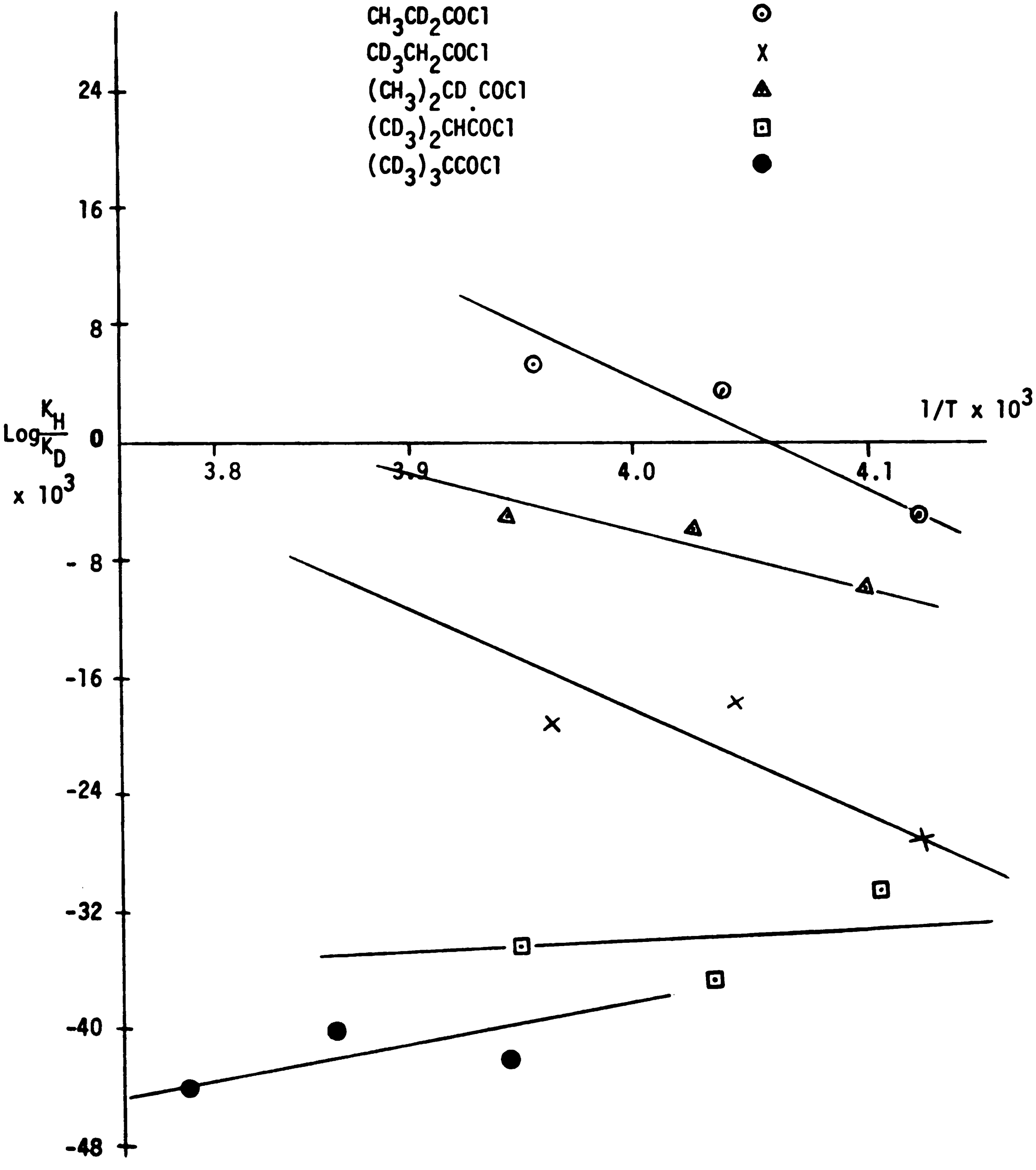


FIGURE 3. Temperature dependence on the secondary β and γ deuterium isotope effects in the solvolysis of propionyl, isobutyryl and pivaloyl chlorides in 75% acetone-water.

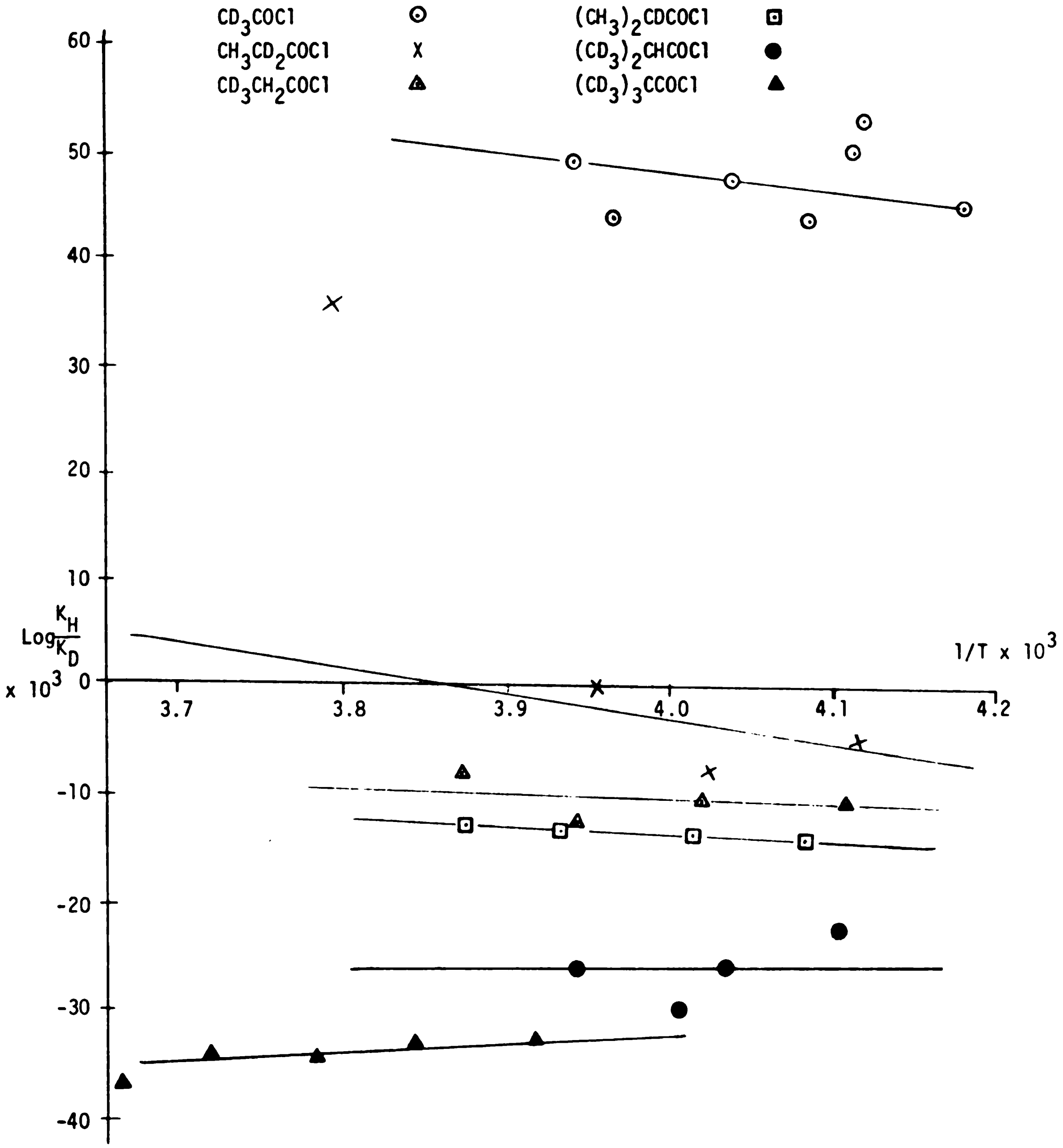


FIGURE 4. Temperature dependence on the secondary β and γ deuterium isotope effects in the solvolysis of acetyl, propionyl, isobutyryl and pivaloyl chloride in 80% acetone-water.

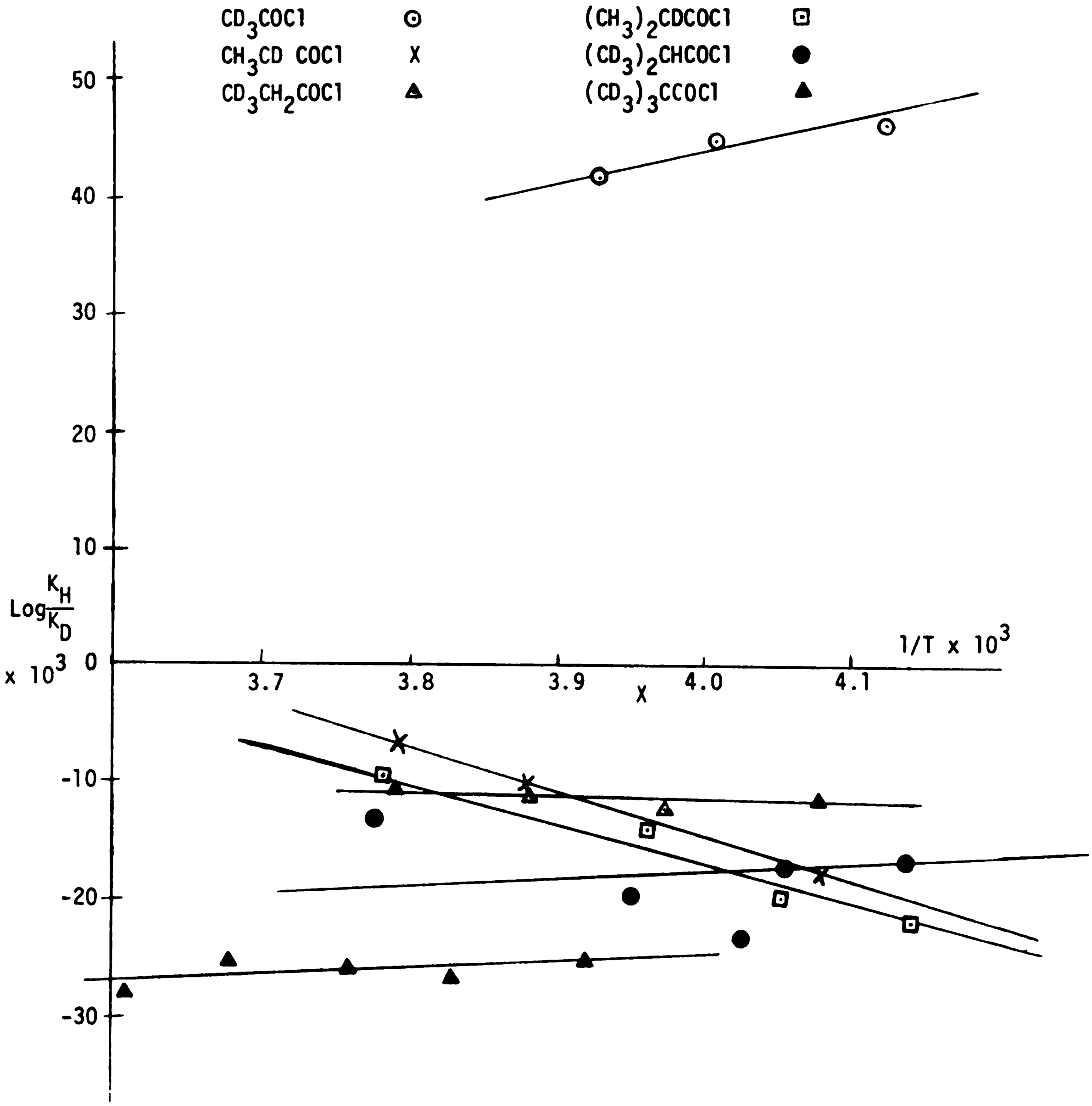


FIGURE 5. Temperature dependence on the secondary β and γ deuterium isotope effects in the solvolysis of acetyl propionyl, isobutyryl and pivaloyl chloride in 85% acetone-water.

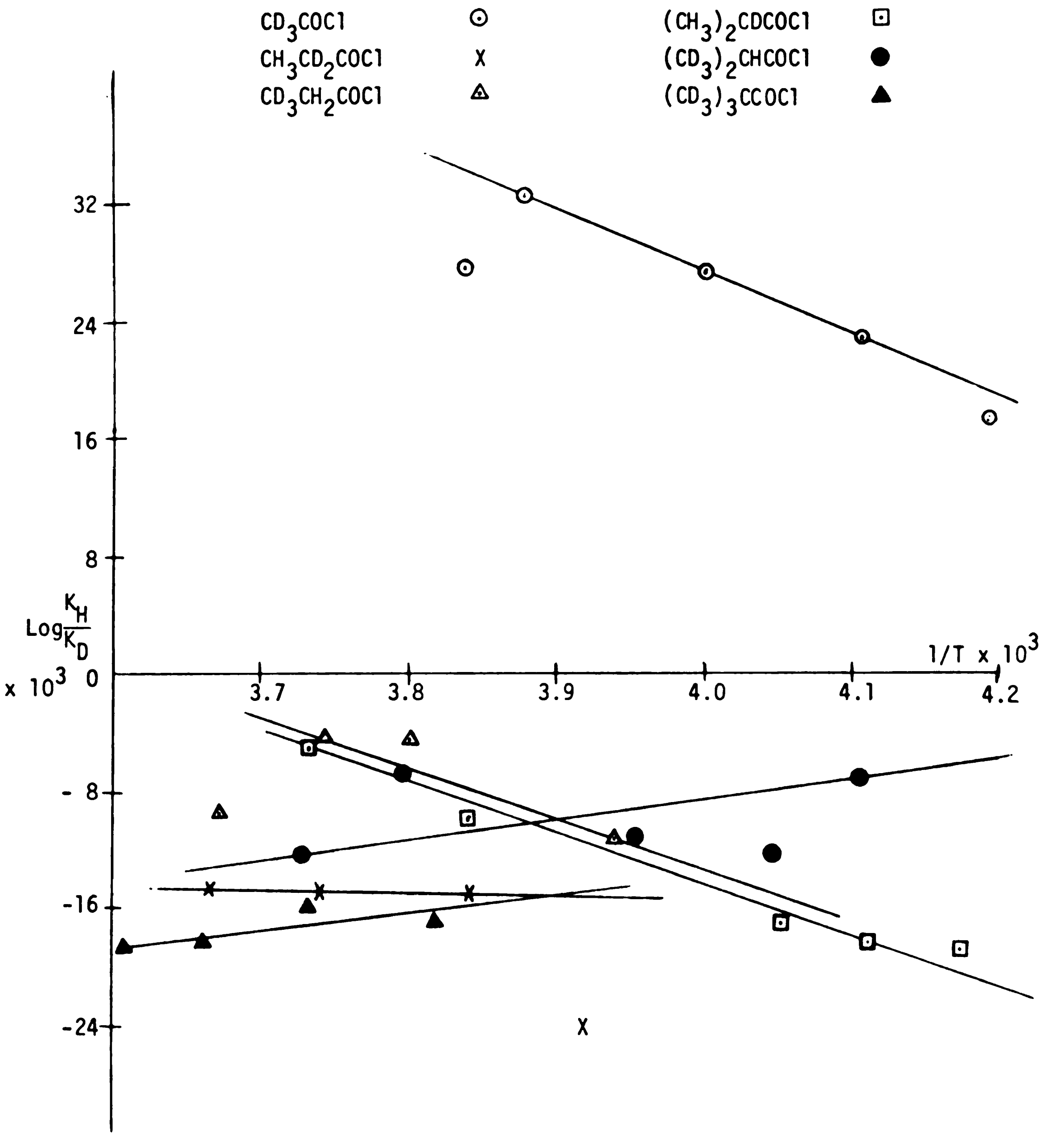


FIGURE 6. Temperature dependence on the secondary β and γ deuterium isotope effects in the solvolysis of acetyl, propionyl, isobutyryl and pivaloyl chloride in 90% acetone-water.

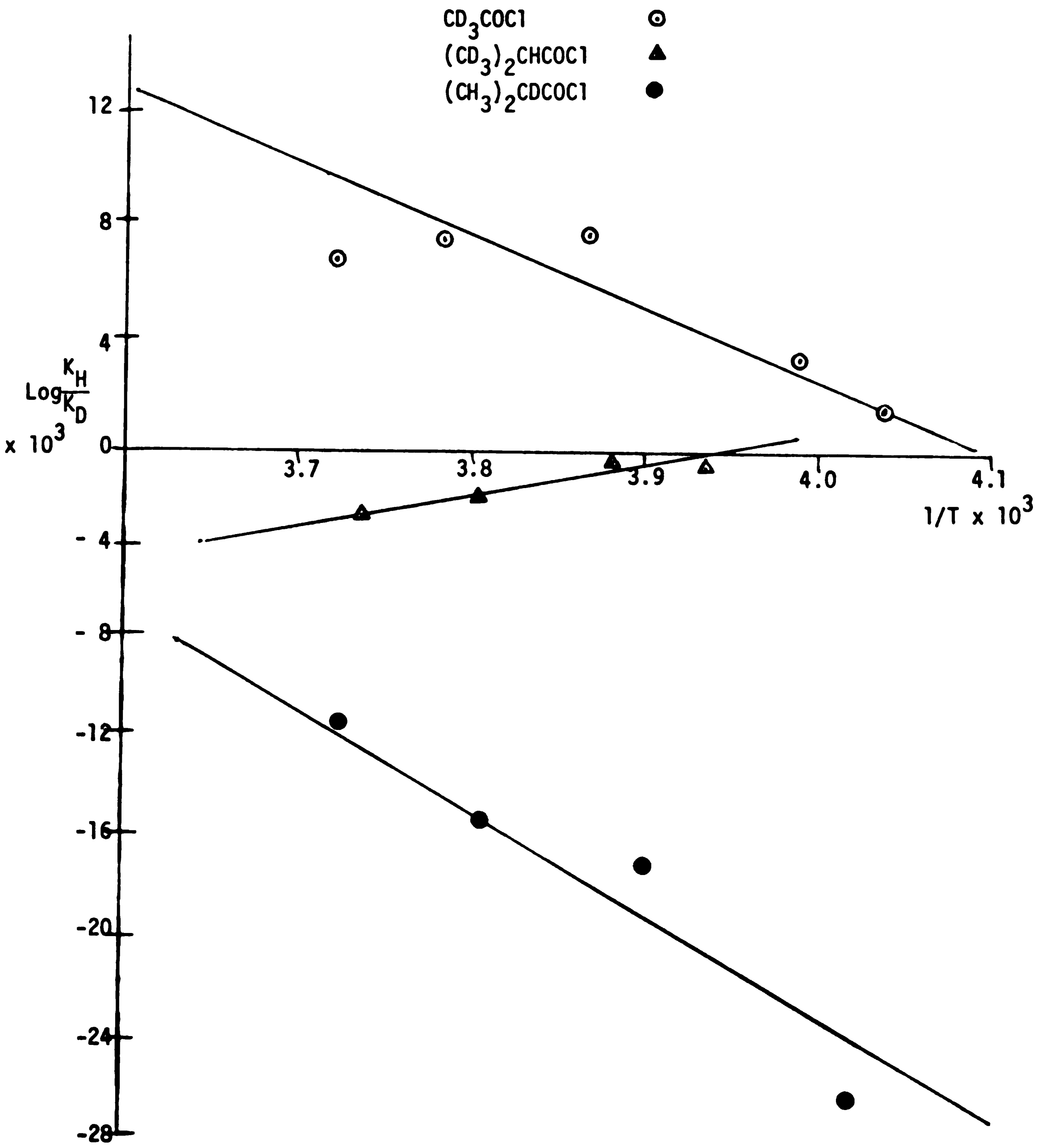


FIGURE 7. Temperature dependence on the secondary β and γ deuterium isotope effects in the solvolysis of acetyl and isobutyryl chloride in 95% acetone-water.

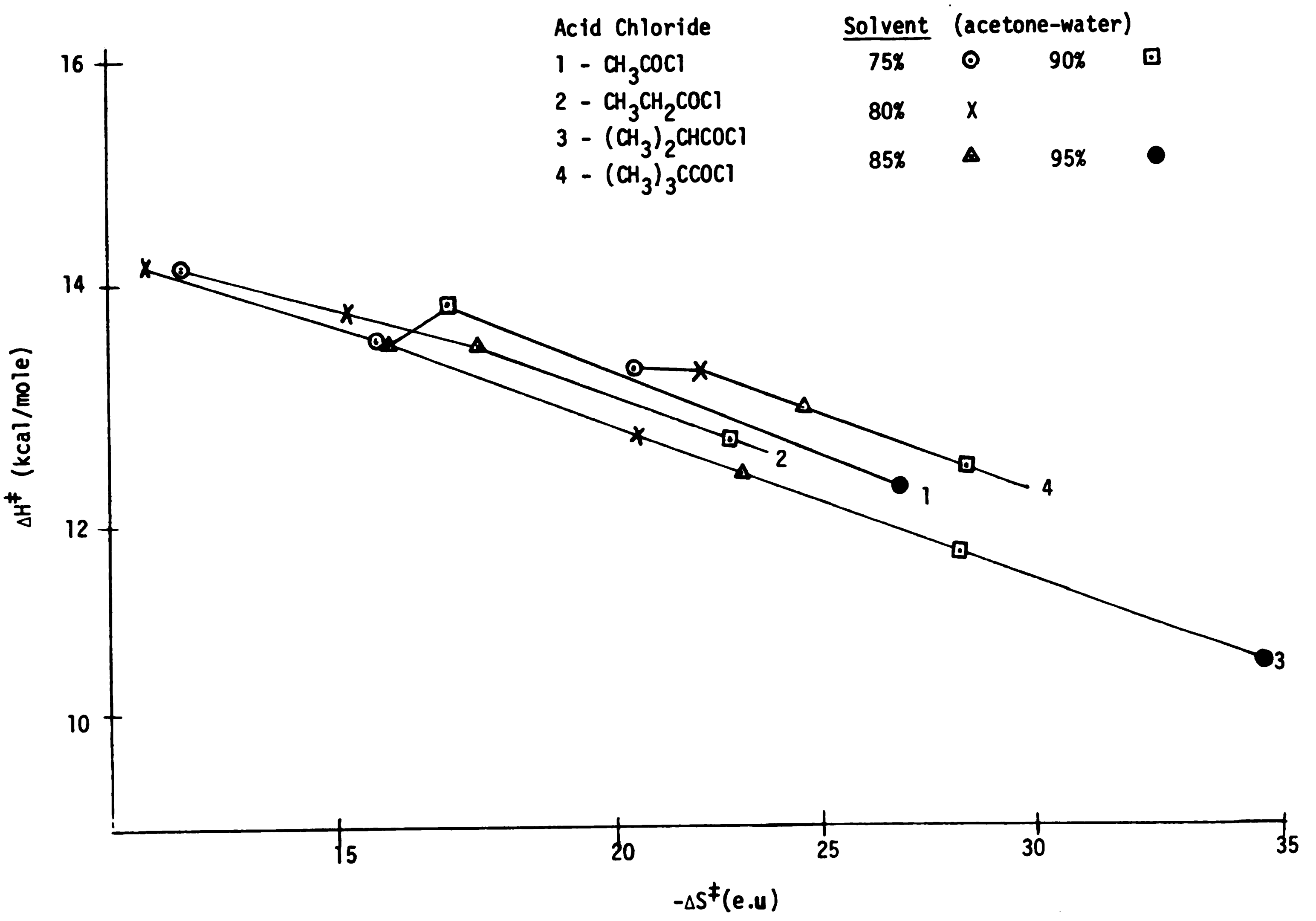


FIGURE 8. Isokinetic relationship for acetyl, propionyl, isobutyryl and pivaloyl chloride in acetone-water concentrations of 75% to 95%.

mechanistic interpretations based on isotope effects measured at a single temperature are meaningless. The possibility that an isokinetic relationship for some secondary isotope effects may exist requires careful scrutiny.

Leffler,[54] in studying the relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, stated that in related reactions involving moderate changes in structure or solvent the enthalpies and entropies vary, but not independently, This effect has been called the isokinetic relationship:

$$\Delta H^{\ddagger} = \beta \Delta S^{\ddagger}$$

Here, β is the isokinetic temperature where all rates or equilibrium constants are the same within the precision of the relationship. Several workers[55,56-58] have pointed out that large errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ may lead to linear relationships. Thus, an apparent straight line plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ does not necessarily prove the existence of an isokinetic relationship.

The activation parameters, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta\Delta H^{\ddagger}$, for isobutyryl chloride are reported in Tables XXVII, XXVIII and XXIX, respectively. Those for pivaloyl chloride are summarized in Table XXX, XXXI and XXXII.

A plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ for a series of aliphatic acid chlorides is shown in Figure 8. A fairly linear correlation is obtained, although complex behavior of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ plots with solvent variation has not been uncommon. Winstein and Feinberg[59] showed that in the solvolysis of *t*-butyl chloride in various binary solvent mixtures, a plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ gives rather complex curves. Tomila[60] and Hine[61] have also reported a complex pattern of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ with solvent composition.

TABLE XXVII. Arrehenius and Transition State Theory Parameters for Isobutyryl-d_0, -d_1, -d_6 Chlorides.

Solvent	Parameter	$\underline{d}_0$	$\underline{d}_1$	$\underline{d}_6$
75%	$A \times 10^{-9}$	3.53 ± 1.36	2.68 ± 1.03	4.81 ± 1.85
	E_a	14089 ± 190	13945 ± 190	14203 ± 190
	$\Delta H^{\ddagger}$	13594 ± 190	13450 ± 190	13709 ± 190
	$\Delta S^{\ddagger}$	-16.48 ± 0.76	-17.03 ± 0.76	-15.87 ± 0.76
80%	$A \times 10^{-8}$	3.53 ± 0.86	3.35 ± 0.83	4.81 ± 1.85
	E_a	13253 ± 123	13212 ± 123	13356 ± 123
	$\Delta H^{\ddagger}$	12755 ± 123	12714 ± 123	12858 ± 123
	$\Delta S^{\ddagger}$	-21.08 ± 0.49	-21.18 ± 0.49	-20.55 ± 0.49
85%	$A \times 10^{-7}$	7.84 ± 1.33	5.89 ± 0.99	7.83 ± 1.32
	E_a	12761 ± 85	12599 ± 85	12740 ± 85
	$\Delta H^{\ddagger}$	12258 ± 85	12096 ± 85	12237 ± 85
	$\Delta S^{\ddagger}$	-24.09 ± 0.34	-24.65 ± 0.34	-24.09 ± 0.34
90%	$A \times 10^{-6}$	8.59 ± 1.08	6.32 ± 0.79	1.04 ± 0.13
	E_a	11970 ± 64	11797 ± 64	12058 ± 64
	$\Delta H^{\ddagger}$	11460 ± 64	11288 ± 64	11549 ± 64
	$\Delta S^{\ddagger}$	-28.50 ± 0.25	-29.11 ± 0.25	-28.12 ± 0.25
95%	$A \times 10^{-5}$	5.36 ± 1.23	3.09 ± 0.72	6.02 ± 1.38
	E_a	11054 ± 119	10747 ± 119	11111 ± 119
	$\Delta H^{\ddagger}$	10536 ± 119	10229 ± 119	10593 ± 119
	$\Delta S^{\ddagger}$	-34.05 ± 0.46	-35.15 ± 0.46	-33.82 ± 0.45

TABLE XXVIII. Transition State Theory Parameters for Isobutyryl-$\underline{d}_0$,-$\underline{d}_1$,-$\underline{d}_6$ Chlorides.

Solvent	Parameter [a]	d_0	d_1	d_6
75%	$\Delta H^{\ddagger}$	13584 ± 54	13439 ± 10	13698 ± 139
	$\Delta S^{\ddagger}$	- 16.59 ± 0.21	- 17.05 ± 0.04	- 15.88 ± 0.56
80%	$\Delta H^{\ddagger}$	12744 ± 144	12712 ± 143	12849 ± 202
	$\Delta S^{\ddagger}$	- 21.09 ± 0.58	- 21.16 ± 0.57	- 20.55 ± 0.81
85%	$\Delta H^{\ddagger}$	12254 ± 127	12092 ± 112	12233 ± 163
	$\Delta S^{\ddagger}$	- 24.07 ± 0.50	- 24.64 ± 0.44	- 24.07 ± 0.64
90%	$\Delta H^{\ddagger}$	11459 ± 104	11286 ± 89	11546 ± 87
	$\Delta S^{\ddagger}$	- 28.48 ± 0.41	- 29.09 ± 0.35	- 28.10 ± 0.34
95%	$\Delta H^{\ddagger}$	10536 ± 224	10229 ± 261	10594 ± 230
	$\Delta S^{\ddagger}$	- 34.01 ± 0.86	- 35.12 ± 1.00	- 33.79 ± 0.88

[a] Values determined from AKTIV program.

TABLE XXIX. Activation Parameters Determined from the β and γ Isotope Effects in Isobutyryl-$\underline{d}_0$, -$\underline{d}_1$, -$\underline{d}_6$ Chlorides.

Solvent	75%	80%	85%	90%	95%
$\underline{d}_0 - \underline{d}_1$[a]					
$\Delta\Delta H^{\ddagger}$	148 ± 36	47 ± 27	163 ± 29	184 ± 32	308 ± 52
$\Delta\Delta S^{\ddagger}$	0.56 ± 0.14	-0.13 ± 0.11	0.57 ± 0.12	0.61 ± 0.12	1.10 ± 0.19
$\underline{d}_0 - \underline{d}_6$[a]					
$\Delta\Delta H^{\ddagger}$	-109 ± 90	-109 ± 68	20.1 ± 68	-87 ± 47	-52 ± 9
$\Delta\Delta S^{\ddagger}$	-0.59 ± 0.36	-0.55 ± 0.27	0.0 ± 0.2	-0.38 ± 0.18	-0.2 ± 0.03

[a] Values determined by HANDS program.

TABLE XXX. Transition State Theory Parameters for Pivaloyl-$\underline{d}_0$, -$\underline{d}_9$ Chlorides.

Solvent	Parameter[a]	$\underline{d}_0$	$\underline{d}_9$
75%	$\Delta H^{\ddagger}$	13359 ± 180	13443 ± 117
	$\Delta S^{\ddagger}$	-21.81 ± 0.67	-20.29 ± 0.44
80%	$\Delta H^{\ddagger}$	13325 ± 65	13383 ± 54
	$\Delta S^{\ddagger}$	-22.19 ± 0.24	-21.82 ± 0.20
85%	$\Delta H^{\ddagger}$	12931 ± 31	12950 ± 23
	$\Delta S^{\ddagger}$	-24.76 ± 0.12	-24.57 ± 0.09
90%	$\Delta H^{\ddagger}$	12271 ± 31	12316 ± 26
	$\Delta S^{\ddagger}$	-28.59 ± 0.12	-28.34 ± 0.10

[a] Values determined by AKTIV program.

TABLE XXXI. Arrhenius and Transition State Theory Parameters for Pivaloyl-$\underline{d}_0$, -$\underline{d}_9$ Chlorides.

Solvent	Parameter[a]	$\underline{d}_0$	$\underline{d}_9$
75%	$A \times 10^{-8}$	4.17 ± 1.66	5.40 ± 2.15
	E_a	13882 ± 209	13966 ± 209
	$\Delta H^{\ddagger}$	13359 ± 209	13442 ± 209
	$\Delta S^{\ddagger}$	-20.84 ± 0.8	-20.33 ± 0.8
80%	$A \times 10^{-8}$	2.12 ± 0.39	2.56 ± 0.48
	E_a	13858 ± 99	13917 ± 99
	$\Delta H^{\ddagger}$	13326 ± 99	13384 ± 99
	$\Delta S^{\ddagger}$	-22.22 ± 0.37	-21.85 ± 0.37
85%	$A \times 10^{-7}$	5.82 ± 1.08	6.40 ± 1.07
	E_a	13464 ± 99	13483 ± 99
	$\Delta H^{\ddagger}$	12932 ± 99	12951 ± 99
	$\Delta S^{\ddagger}$	-24.79 ± 0.37	-24.60 ± 0.37
90%	$A \times 10^{-6}$	8.56 ± 2.31	9.69 ± 2.61
	E_a	12808 ± 145	12853 ± 145
	$\Delta H^{\ddagger}$	12270 ± 145	12316 ± 145
	$\Delta S^{\ddagger}$	-28.79 ± 0.37	-28.37 ± 0.54

[a] Values determined by ACTENG program.

TABLE XXXII. Activation Parameters Determined from the Isotope Effects of Pivaloyl-$\underline{d}_0$, -$\underline{d}_9$ Chlorides.

Solvent	75%	80%	85%	90%
$\Delta\Delta H^{\ddagger a}$	-77 ± 61	-60 ± 17	-23 ± 19	-48 ± 21
$\Delta\Delta S^{\ddagger}$	-0.48 ± 0.24	-0.38 ± 0.07	-0.20 ± 0.08	-0.25 ± 0.08

[a] Values determined by HANDS program.

Leffek and Matheson[62] used plots of $\Delta\Delta H^{\ddagger}$ vs $\Delta\Delta S^{\ddagger}$ per deuterium to distinguish between S_N1 and S_N2 reactions. The differences observed were ascribed to differences in the solvation of S_N1 and S_N2 transition states.

Thornton and Kaplan[63] found $k_H/k_D = 0.88$ at 51° in the reaction of dimethyl and dimethyl-$\underline{d}_6$ aniline with methyl p-toluenesulfonate in nitrobenzene. They rationalized this result in terms of frequency changes arising from steric interactions. Within the zero point energy approximation the isotope effect in reactions in which non-bonded repulsions increase in going from ground state to transition state should arise from differences in the enthalpies of activation, with $\Delta H_D^{\ddagger}-\Delta H_H^{\ddagger}$ being negative. Leffek and Matheson[62] studied the temperature dependence of this reaction, they found $\Delta H_D^{\ddagger}-\Delta H_H^{\ddagger} = -134 \pm 30$ cal/mole and $\Delta S_D^{\ddagger}-\Delta S_H^{\ddagger} = -0.15 \pm 0.09$ cal/mole-deg. For reactions where non-bonded repulsions decrease in going to transition state, $\Delta H_D^{\ddagger}-\Delta H_H^{\ddagger}$ ought to be positive.

In the solvolysis of isobutyryl chloride $\Delta\Delta H^{\ddagger}$ is positive, but the contribution of $\Delta\Delta S^{\ddagger}$ is not negligible. Except for 80% acetone-water, $\Delta\Delta S^{\ddagger}$ is also positive. Both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ increase as solvent polarity decreases. In contrast to this, both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ are negative, except for $\Delta\Delta H^{\ddagger}$ in 85% acetone-water, in the solvolysis of the γ deuterated isobutyryl and pivaloyl chloride. However, this behavior of the γ isotope effects was reversed in the solvolysis of propionyl chloride, where $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ were found to be positive.

In view of this complex behavior, it would be best to defer speculations on the solvent dependence of the γ isotope effect until more work is done on other mechanistically less ambiguous systems.

Activation parameters have been used to describe the mechanisms of various solvolytic reactions. Schlager and Long[64] have suggested that entropies and enthalpies of acitivation might serve as a convenient criterion of mechanism. Substrates that react by a nucleophilic path should show more negative entropies of activation and less positive enthalpies of activation than those substrates reacting by a limiting path. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for acetyl, propionyl, isobutyryl and pivaloyl chlorides are reported in Tables XXXIII and XXXIV respectively. Two trends are observed: The enthalpies and entropies of activation decrease with decreasing solvent polarity. They also decrease in going from the less branched acetyl chloride to the more branched pivaloyl chloride. Theye results suggest that propionyl, isobutyryl and pivaloyl chlorides solvolyze predominantly by a nucleophilic mechanism.

This conclusion is further confirmed by comparing the relative rates of solvolysis of these chlorides in 80% acetone-water at -15.10°. The results are as follows:

	CH_3COCl	CH_3CH_2COCl	$(CH_3)_2CHCOCl$	$(CH_3)_3CCOCl$
$k_{relt.}$	1	0.401	0.223	0.0395

TABLE XXXIII. Enthalpies of Activation for a Series of Aliphatic Acid Chlorides and Their Deuterated Analogs.

Acid		75%	80%	85%	90%	95%
CH_3COCl	$\underline{d}_0$		14240 ± 50	13544 ± 105	13832 ± 150	11927 ± 120
	$\underline{d}_3$		14298 ± 60	13664 ± 105	13610 ± 120	11819 ± 120
CH_3CH_2COCl	$\underline{d}_0$	14193 ± 171	13822 ± 80	13536 ± 111	12525 ± 121	
	$\underline{d}_2$	13904 ± 172	13693 ± 80	13380 ± 111	12359 ± 73	
	$\underline{d}_3$	13959 ± 172	13954 ± 111	13525 ± 111	12481 ± 43	
$(CH_3)_2CHCOCl$	$\underline{d}_0$	13594 ± 190	12755 ± 123	12258 ± 85	11460 ± 64	10536 ± 119
	$\underline{d}_1$	13450 ± 190	12714 ± 123	12096 ± 85	11288 ± 64	10229 ± 119
	$\underline{d}_6$	13709 ± 190	12858 ± 123	12237 ± 85	11549 ± 64	10593 ± 119
$(CH_3)_3CCOCl$	$\underline{d}_0$	13359 ± 209	13326 ± 99	12932 ± 99	12270 ± 145	
	$\underline{d}_9$	13442 ± 209	13384 ± 99	12951 ± 99	12316 ± 145	

TABLE XXXIV. Entropies of Activation for a Series of Aliphatic Acid Chlorides and Their Deuterated Analogs.

Acid		75%	80%	85%	90%	95%
CH_3COCl	d_0		-12.2 ± 0.2	-16.6 ± 0.4	-17.6 ± 0.4	-28.1 ± 0.5
	d_3		-12.2 ± 0.2	-16.3 ± 0.4	-18.6 ± 0.4	-28.5 ± 0.5
CH_3CH_2COCl	d_0	-12.7 ± 0.7	-15.7 ± 0.3	-18.2 ± 0.4	-23.8 ± 0.5	
	d_2	-13.9 ± 0.7	-16.2 ± 0.3	-18.7 ± 0.4	-24.3 ± 0.3	
	d_3	-13.5 ± 0.7	-15.0 ± 0.4	-18.2 ± 0.4	-23.9 ± 0.2	
$(CH_3)_2CHCOCl$	d_0	-16.5 ± 0.8	-21.1 ± 0.5	-24.1 ± 0.3	-28.5 ± 0.3	-34.1 ± 0.5
	d_1	-17.1 ± 0.8	-21.2 ± 0.5	-24.7 ± 0.3	-29.1 ± 0.3	-35.2 ± 0.5
	d_6	-15.9 ± 0.8	-20.6 ± 0.5	-24.1 ± 0.3	-28.1 ± 0.3	-33.8 ± 0.5
$(CH_3)_3CCOCl$	d_0	-20.8 ± 0.8	-22.2 ± 0.4	-24.8 ± 0.4	-28.6 ± 0.4	
	d_9	-20.3 ± 0.8	-21.9 ± 0.4	-24.6 ± 0.4	-28.4 ± 0.4	

IV. CONCLUSIONS.

From the experimental data it can be concluded that the solvolysis if isobutyryl chloride and pivaloyl chloride is best rationalized in terms of a nucleophilic mechanism. This conclusion is borne out from the observation that the isotope effects in these systems are inverse regardless of the polarity of the solvent. The activation parameters also support this conclusion. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are indicative of a bimolecular mechanism. The $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ are meaningless. A fairly good linear relationship has been obtained between $\Delta H^{\ddagger}$ *vs*. $\Delta S^{\ddagger}$. However, in view of the fact that complex patterns have been observed between these parameters and the polarity of the solvent, this linearity may be fortuitous. We can not offer a good explanation of the γ and β isotope effects behave differently with changes in solvent polarity. We only hope that this will encourage further investigation on the solvent and temperature dependence of the isotope effect, thus contribute more reliable data for a useful generalization regarding reaction mechanisms in organic chemistry.

BIBLIOGRAPHY

1. M. Wolfsberg, *Ann. Rev. Phys. Chem.*, **20**, 449 (1969).
2. E. R. Thornton, *ibid.*, **17**, 342 (1966).
3. J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).
4. L. Melander, *Isotope Effects on Reaction Rates*, Ronald Press Co., New York, 1960.
5. M. Wolfsberg and M. J. Stern, *Pure and Appl. Chem.*, **8**, 325 (1964).
6. M. Wolfsberg and M. J. Stern, *J. Pharm. Sc.*, **54**, 849 (1969).
7. a) E. S. Lewis, *Tetrahedron*, **5**, 143 (1959).
   b) V. J. Shiner, Jr., *ibid.*, **5**, 243 (1959).
8. E. A. Halevi, "Secondary Isotope Effects", *Progress in Physical Organic Chemistry*, **Vol. 1**, S. G. Cohen, A. Streitweiser, and R. W. Taft, ed., John Wiley and Sons, New York, 1963.
9. L. S. Bartell, *J. Amer. Chem. Soc.*, **83**, 3567 (1961).
10. M. J. Dewar, *Hyperconjugation*, Ronald Press Co., New York (1962).
11. V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, *J. Amer. Chem. Soc.*, **85**, 2413 (1963).
12. V. J. Shiner, Jr., and J. S. Humphrey, *ibid.*, **85**, 2416 (1963).
13. V. J. Shiner, Jr., and G. S. Kriz, *ibid.*, **86**, 2643 (1964).
14. A. Streitweiser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *ibid.*, **80**, 2326 (1958).
15. a) D. R. Lide, *J. Chem. Phys.*, **27**, 343 (1957).
    b) D. R. Lide, *ibid.*, **33**, 1519 (1960).

16. G. V. D. Tiers, *ibid*., **29**, 963 (1958).

17. G. V. D. Tiers, *J. Amer. Chem. Soc*., **79**, 5585 (1957).

18. A. Streitweiser, Jr., and H. S. Klein, *ibid*., **85**, 2759 (1963).

19. R. P. Bell and J. E. Crooks, *Trans. Faraday. Soc*., **58**, 1409 (1962).

20. R. P. Bell and W. B. T. Miller, *ibid*., **59**, 1147 (1963).

21. A. J. Kresgo and R. J. Preto, *J. Amer. Chem. Soc*., **89**, 5510 (1967).

22. A. Streitweiser, Jr., and J. S. Humphrey, *ibid*., **89**, 3767 (1967).

23. L. Melander and R. E. Carter, *ibid*., **86**, 295 (1964).

24. R. E. Carter and L. Dahlgreen, *Act. Chem. Scand*., **23**, 504 (1969).

25. H. C. Brown and G. J. McDonald, *J. Amer. Chem. Soc*,, **88**, 2514 (1966).

26. H. C. Brown, M. E. Azzaro, J. K. Koelling and G. J. McDonald, *ibid*., **88**, 2520 (1966).

27. G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaionou, S. E. Sheppele and R. L. Shone, *ibid*., **89**, 463 (1967).

28. J. G. Jewett and R. P. Dunlop, *ibid*., **90**, 809 (1968).

29. V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Burr and G. Lamaty, *ibid*., **90**, 418 (1968).

30. A. Streitweiser, Jr., and G. Alan Dufforn, *Tetrahedron Letters*, **16**, 1263 (1969).

31. J. E. Nordlander,and W. G. Deadman, *J. Amer. Chem. Soc*., **90**, 1590 (1968).

32. K. Mislow, S. Borcik and V. Prelog, *Helv. Chem. Act*., **40**, 2477 (1957).

33. J. Schaeffer, S. Weinberg, and M. Dagani, *J. Amer. Chem. Soc*., **89**, 6938 (1967).

34. B. L. Murr, A. Nicken, T. Swartz and N. H. Werstnink, *ibid*., **89**, 1730 (1966).

35. J. Jerkunica, S. Borcik, and D. E. Sunko, *ibid.*, **90**, 1734 (1967).

36. J. Jerkunica, S. Borcik and D. E. Sunko, *Chem. Comm.*, 1488 (1968).

37. J. Schaeffer, J. Foester, and M. Dagani, *J. Amer. Chem. Soc.*, **90**, 4497 (1968).

38. L. Hakka, A. Queen and R. E. Robertson, *ibid.*, **87**, 161 (1965).

39. K. T. Leffek, R. E. Robertson, and S. Sugamury, *Can. J. Chem.*, **39**, 1989 (1961).

40. T. A. Evans, Ph.D. Thesis, Michigan State University, 1968.

41. U. G. Kang, M. S. Thesis, Michigan State University, 1967.

42. C. G. Papaioannou, Ph.D. Thesis, Michigan State University, 1967.

43. L. Fieser and M. Fieser, *Reagents for Organic Chemistry*, John Wiley and Sons, Inc., New York, 1968, p. 583.

44. A. Murray, III, and D. Lloyd Williams, *Organic Synthesis with Isotopes*, Interscience, New York, 1958, Vol. 2, p. 1482.

45. H. Gilann and H. Blatt, *Organic Synthesis*, John Wiley and Sons, Inc., New York, Eleventh printing 1967, Vol. 1, pp 459, 462, 526.

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

47. M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

48. V. Gold, J. Hilton and G. E. Jefferson, *J. Chem. Soc.*, 2756 (1956).

49. S. C. Johnston, "General Base and Nucleophilic Catalysis", *Advances in Physical Organic Chemistry*, Vol. 5, V. Gold, ed. Academic Press, London, 1967.

50. G. E. Branch and A. C. Nixon, *J. Amer. Chem. Soc.*, **58**, 2499 (1936).

51. E. W. Grunden and R. F. Hudson, *J. Chem. Soc.*, 501 (1956).

52. S. I. Miller, *J. Phys. Chem.*, **66**, 978 (1962).

53. W. H. Saunders, Jr., S. Aspenger and D. H. Edison, *J. Amer. Chem. Soc.*, **80**, 2421 (1958).

54. J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

55. J. E. Leffler and E. Grunwald, "*Rates and Equilibria of Organic Reactions*", John Wiley and Sons, Inc., New York, N.Y., 1964, Chap. 9.

56. C. D. Ritchie and W. F. Sager, "An Examination of Structure-Reactivity Relationship", *Progress in Physical Organic Chemistry*, **Vol. 3**, A. Streitweiser Jr., and R. W. Taft, ed., Interscience, 1965, p. 323.

57. R. C. Peterson, *J. Org. Chem.*, **29**, 3133 (1964).

58. O. Exner, *Nature*, **201**, 488 (1964).

59. S. Winstein and A. H. Fainberg, *J. Amer. Chem. Soc.*, **79**, 5937 (1957).

60. E. Tomila, *Acta Chem. Scand.*, **9**, 975 (1955).

61. a) J. B. Hyne, *J. Amer. Chem. Soc.*, **82**, 5129 (1960).

    b) J. B. Hyde, R. Wills and R. E. Wonka, *ibid.*, **84**, 2914 (1962).

    c) J. B. Hyne and H. S. Golinkin, *Can. J. Chem.*, **46**, 125 (1968).

62. K. T. Leffek and A. F. Matheson, ibid., **49**, 439 (1971).

63. E. D. Kaplan and E. R. Thornton, *J. Amer. Chem. Soc.*, **89**, 6644 (1967).

64. L. L. Schlager and F. A. Long, "Entropies of Activation and Mechanisms of Reactions in Solutions", *Adv. in Phys. Org. Chem.*, **Vol. 1**, V. Gold, ed., Academic Press, London, 1963, p. 1.

MICHIGAN STATE UNIVERSITY LIBRARIES
3 1293 03196 5860