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

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ABSTRACT

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By

Uan Gen Kang

The rates of solvolysis of propionyl-$\underline{d}_0$, -2,2-$\underline{d}_2$ and -3,3,3-$\underline{d}_3$ chlorides were measured in 75%, 80% and 85% acetone-water and different temperatures.

The observed β-isotope effects are consistent with a dual mechanism, i.e. simultaneous hydrolysis by both limiting and nucleophilic mechanisms. For example, as the water concentration and temperature increase, the contribution of limiting mechanism gradually increases to lead to greater isotope effects, such as: $k_H/k_D(80\%) = 0.989 \pm .007(-30.58°)$, $1.008 \pm .005(-10.56°)$; $k_H/k_D(85\%) = 0.961 \pm .004(-26.17°)$, and $k_H/k_D(75\%) = 1.008 \pm .007(-25.55°)$. The finding that the β-isotope effects are near one has been taken as an indication that the hydrolysis of propionyl chloride proceeds predominantly by a nucleophilic mechanism.

Leffek and his co-workers (1) found that the temperature insensitive β-isotope effects in the hydrolysis of isopropyl esters were the result of $\Delta\Delta H^{\ddagger}$ being zero, with

$\Delta\Delta S^{\ddagger}$ apparently controlling them. They have suggested that the observed isotope effects are due to the rotatinal barrier difference in the ground state between methyl- and methyl-$\underline{d}_3$. Halevi (2) has explained their results in terms of differences in the solvation of the protium compound and its deuterium analog.

We find that the γ-isotope effects, in contrast to the β-isotope effects, in the solvolysis of propionly chloride are also temperature insensitive. For example, k_H/k_D(80%) = 0.976 ± .005(-25.41°), 0.976 ± .010(-30.58°). k_H/k_D(85%) = 0.977 ± .007(-10.57°), 0.976 ± .005(-15.54°), 0.973 ±.005(-20.47°). This temperature insensitivity, however, does not appear to arise from differences in the entropies of activation. The $\Delta\Delta S^{\ddagger}$ contribution to the isotope effect is zero in 80% and 85% acetone-water solutions. The temperature insensitive isotope effects appear to be solely controlled by differences in the enthalpies of activation. Thus, these results may be taken as support of the ideas of Wolfsberg and Stern (3), who have suggested that temperature independent isotope effects may result from compensating changes in force constants.

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

(2) E. A. Halevi, "Secondary Isotope Effects," Progress in Physical Organic Chemistry, Vol. 1, S. G. Cohen, A. Streitwieser, and R. W. Taft, ed., John Wiley and Sons, New York, 1963.

(3) M. Wolfsberg and M. J. Stern, Pure Appl. Chem., 8, 225, 325 (1964).

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By

Uan Gen Kang

A THESIS

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To my wife

Jung Ja

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TABLE OF CONTENTS

LIST OF TABLES

Table | Page

LIST OF FIGURES

INTRODUCTION

Secondary deuterium isotope effects on the rates of reactions have been explained in terms of hyperconjugation, nonbonded interactions and inductive effects (1).

In an effort to prove the importance of hyperconjugation, which has been controversial (2), Shiner and his group have investigated several solvolytic reactions. For example, they found (3) k_H/k_D for the solvolysis of 1 to be 1.092 ± .001. Since the triple bond "insulates" the nonbonded interactions between the reaction center and the site of isotopic substitution, it is reasonable to explain the isotope effect in terms of hyperconjugation.

1

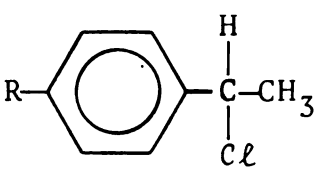
If the demand for hyperconjugation in the transition state is partly responsible for secondary isotope effects, then the β-isotope effect should decrease by reducing this demand. The results of Shiner and his coworkers (1a) on the solvolysis rates of a series of substituted 1-phenylethyl halides confirm this prediction (Table 1). All α-isotope effects given in Table 1 are within ±.003 of

Table 1.--Rates and isotope effects for 1-phenylethyl chlorides corrected to 50% ethanol, 25° (1a).

Substituent	Relative Rate	$k_H/k_D(\alpha)$	$k_H/k_D(\beta)$
p-Methoxy	$11.4 - 7.6 \times 10^5$	1.157	1.113
p-Phenoxy	$3.0 - 2.0 \times 10^3$	1.157	1.164
p-Methyl	59.0	1.157	1.200
p-Fluoro	3.0	1.152	1.211
m-Methyl	2.0	1.151	1.222
None	1.0	1.153	1.224
m-Bromo	6.6×10^{-3}	1.133	1.221
p-Nitro	2.9×10^{-5}	1.098	1.151

1.154, except those of the m-bromo (k_H/k_D = 1.133) and p-nitro (k_H/k_D = 1.098) compounds. The large α-isotope effect (k_H/k_D = 1.154) is strong evidence that the mechanism of the reaction is limiting. The smaller α-isotope effects for the m-bromo and p-nitro compounds indicate some nucleophilic participation in the transition state. The observed β-isotope effects show that the reduction of the demand for hyperconjugation, whether due to electron-releasing para substituents (p-methoxy and p-phenoxy), or to nucleophilic participation in the transition state (m-bromo and p-nitro), decreases the β-isotope effect.

Rate studies on the acetolysis of 2 (k_H/k_D = 1.011) by Lewis and coworkers (4) and on the solvolysis of 3 (k_H/k_D = 1.04) by Shiner and Verbanic (5) offer further convincing evidence for the importance of hyperconjugation. The isotope effect caused by deuterium substitution at such remote position is most likely due to hyperconjugation.



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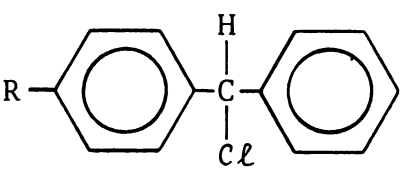


3

R = CH_3 or CD_3

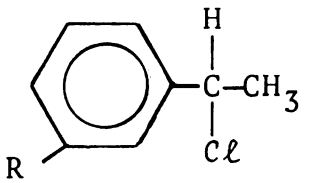
Nuclear quadrupole coupling constant studies (6), nuclear magnetic resonance chemical shift studies (7) and dipole moment studies (8) have established that deuterium

is more electropositive than hydrogen. Halevi and his coworkers (9) and Streitwieser and Klein (10) have studied the effect of deuterium substitution on acid strength (Table 2) and have interpreted their results in terms of the differences in the inductive effect of deuterium and hydrogen. In all cases deuteration decreases the acid strength. On the other hand, as expected, deuteration increases the basicity (9b) of benzyl-α,α-$\underline{d}_2$-amine (K_H/K_D = 1.13).

Table 2.--Deuterium isotope effects on acidity.

Acid	K_H/K_D	Reference
DCOOH	1.035 ± .002	11
CD_3COOH	1.032 ± .002	10
$(CD_3)_3CCOOH$	1.042 ± .003	10
C_6D_5COOH	1.024 ± .006	10
$C_6H_5CD_2COOH$	1.12 ± .02	9

Lewis and his coworkers (4b) have interpreted the inverse isotope effect (k_H/k_D = 0.988 ± .005) observed in the solvolysis of $\underline{4}$ in terms of more effective stabilization of the transition state by the ring methyl-$\underline{d}_3$ group, as a result of its being a better electron releasing group than the methyl.



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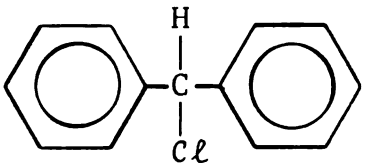


5

R = CH_3 or CD_3

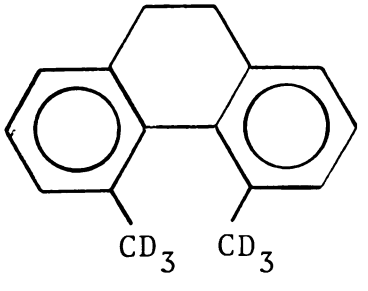
Streitwieser and Klein's (12) solvolytic studies of 5 support further the notion that deuterium is a better electron donor than hydrogen. Indeed, deuteration on the ring accelerates the reaction. However, the relative magnitude of acceleration per deuterium (ortho 1.9%, meta 1.5%, and para 1.0%) is difficult to explain. The magnitude from the meta position relative to that from the ortho position is as expected, but that from the para position is quite low. We might have expected a larger value from the para position, because of the greater positive charge at the para than at the meta position. This unusual positional effect has been discussed and working hypotheses have been given (12).

Bartell (13) has explained secondary isotope effects in terms of nonbonded interactions. It is intuitively very appealing to explain all secondary isotope effects by the following simple argument: The amplitudes of vibration of hydrogen atoms are larger than those of the deuterium atoms. Since the tetrahedral ground state is more crowded than the trigonal carbonium ion in the transition state, there is greater relief of nonbonded interactions for the

hydrogen than for the deuterium compound in the activation process. The net effect is, therefore, faster reaction of the hydrogen compound.

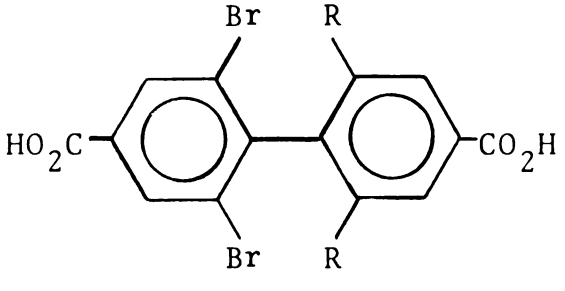
Bartell's results calculated on the basis of his model are sensitive to the assumed molecular structures. The order of magnitude, however, of the isotope effects is comparable with the experimental values (13).

Mislow and coworkers (14) and Melander and Carter (15) have shown that the effective steric requirement for deuterium is less than that for hydrogen in the rate of racemization of compounds 6 and 7. Since the racemizations are purely conformational changes, the observed isotope effects must be steric in origin.



k_D/k_H = 1.13

6



R = H or D

k_D/k_H = 1.19

7

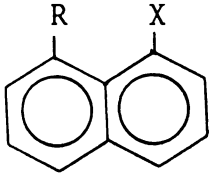
Brown and his coworkers (1c,16) have studied the reactions of methyl-d_3-pyridines with Lewis acids and alkyl iodides. They found small or no isotope effects with the

meta and para methyl-$\underline{d}_3$ substituted pyridines, but inverse isotope effects with the ortho substituted ones. The inverse isotope effects increased as the steric requirement of the alkyl iodide and the Lewis acid became larger. For example, the isotope effects in the reaction of 2-methyl-$\underline{d}_3$-pyridine are k_H/k_D = 0.97 with methyl iodide, k_H/k_D = 0.96 with ethyl iodide, and k_H/k_D = 0.935 with isopropyl iodide. For 2,6-dimethyl-$\underline{d}_6$-pyridine a k_H/k_D of 0.92 was observed with boron trifluoride. On the other hand, the much smaller boron hydride (BH_3) gave no isotope effect. These results are consistent with the view that the secondary deuterium isotope effects are caused mainly by nonbonded interactions.

There seems to be little question that hyperconjugation, inductive effects and nonbonded interactions all contribute to secondary deuterium isotope effects. In general, if in a system effective hyperconjugation is possible, it dominates over the inductive effect. For example, the solvolysis of t-butyl-$\underline{d}_9$ chloride in water gives a large normal isotope effect of 2.387, which is consistent with the predictions of nonbonded interactions and hyperconjugation, but contrary to the prediction of the inductive effect.

Karabatsos and his coworkers (17) has examined the question of the relative contributions of hyperconjugation and nonbonded interactions to secondary deuterium isotope effects. For the 1,8-disubstituted naphthalene system 8,

in which there are strong steric interactions but no formal hyperconjugation between the site of isotopic substitution and the reaction center, the steric isotope effects calculated by Bartell's method were generally higher than the experimental effects. However, where hyperconjugation is possible, e.g. acetyl chloride and t-butyl-d_9 chloride, the calculated steric isotope effects were less than 10% of the experimental isotope effects. The authors concluded that in cases where hyperconjugation is possible the isotope effect is primarily due to hyperconjugation.



8

R = D, CD_3

X = $CH_2C\ell$, $COC\ell$, CO_2CH_3

Secondary isotope effects, whether interpreted in terms of hyperconjugation, inductive effects or nonbonded interactions, arise from changes in the force constants between reactants and transition states. Wolfsberg and Stern (18) have calculated isotope effects from molecular geometries, atomic masses, and force constants. Their results agree reasonably well with the magnitude of the experimental values. In general, lower force constants in the transition state than in the reactant cause normal isotope effects, $k_H/k_D > 1$, while higher force constants in the transition state cause inverse isotope effects, $k_H/k_D < 1$.

If force constant changes determine secondary isotope effects, then the temperature dependence of these effects should depend on the differences in the corresponding enthalpies of activation ($\Delta\Delta H^{\ddagger}$), not on those in the entropies of activation ($\Delta\Delta S^{\ddagger}$). The relationship between the temperature dependence of isotope effects on the enthalpies ($\Delta\Delta H^{\ddagger}$) and entropies of activation ($\Delta\Delta S^{\ddagger}$) can be derived from either the Arrhenius (eq. 1) or the transition state theory (eq. 2).

$$\ln(k_H/k_D) = -\Delta E_a/RT + \ln A_H/A_D \qquad (1)$$

$$\ln(k_H/k_D) = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R \qquad (2)$$

Hakka and his coworkers (19) have shown that in the solvolysis of t-butyl chloride and its d_9 analog the enthalpy of activation difference ($\Delta\Delta H^{\ddagger}$) is approximately equal to that of the free energy ($\Delta\Delta F^{\ddagger}$), with no apparent contribution from the entropy of activation difference ($\Delta\Delta S^{\ddagger}$). This result supports the assumption that the force constant changes are the origin of the isotope effect.

Shiner and Verbanic's results (5) on the solvolysis of p-methyl-d_3-benzhydryl chlorides ($\Delta\Delta H^{\ddagger}$ = -318 cal/mole, $\Delta\Delta S^{\ddagger}$ = -1.03 e.u.), Shiner's studies (20) on the solvolysis of 2,3-dimethyl-3-α-2-chlorobutane ($\Delta\Delta H^{\ddagger}$ = -580 cal/mole, $\Delta\Delta S^{\ddagger}$ = -1.46 e.u.) and Lewis and Coppinger's results (4a) on the solvolysis of p-methyl-d_3-α-phenyl chloride

($\Delta\Delta H^{\ddagger}$ = 465 cal/mole, $\Delta\Delta S^{\ddagger}$ = -1.15 e.u.) show that the isotope effect depends both on $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$.

Leffek and his co-workers (21) studied the solvolysis of isopropyl halides and sulfonates at a single temperature. Their results could be explained by either hyperconjugation or nonbonded interactions. But their results (22) on the temperature dependence of these isotope effects were very unusual. The $\Delta\Delta H^{\ddagger}$ was approximately zero and the temperature independent isotope effect was due entirely to $\Delta\Delta S^{\ddagger}$. Their results are summarized in Table 3. Three explanations have been given for the temperature independent isotope effect of this system.

(a) Leffek and his co-workers have suggested that the observed isotope effect is due to the rotational barrier difference in the ground state between methyl and methyl-$\underline{d}_3$ because of the larger steric requirement for the protium analog. In the transition state the barrier to internal rotation is reduced considerably. Thus, the net effect is favorable acceleration of the protium analog. The negligible contribution to the isotope effect from $\Delta\Delta H^{\ddagger}$ was explained by a cancellation of an effect from the rotational barrier difference and the one from the zero-point energy difference.

(b) Halevi (1b) has explained the isotope effect due entirely to $\Delta\Delta S^{\ddagger}$ by differences in the solvation of the protium compound and its deuterium analog. He assumed

Table 3.--Temperature dependence of the β-deuterium isotope effect for the solvolysis of isopropyl compounds in water (22).

Isopropyl Methanesulfonate		Isopropyl Toluenesulfonate		Isopropyl Bromide	
Temp. °C	k_H/k_D	Temp. °C	k_H/k_D	Temp. °C	k_H/k_D
30.001	1.547	30.017	1.545	69.994	1.324
25.000	1.551	30.001	1.548	69.993	1.317
20.002	1.551	25.005	1.539	65.002	1.322
12.514	1.547	24.999	1.542	60.000	1.318
12.501	1.540	20.005	1.543	59.933	1.315
5.000	1.555	15.003	1.545	55.005	1.313
		10.003	1.537	40.005	1.312
		6.008	1.542	40.005	1.317

Compound	($\Delta\Delta H^{\ddagger}$ cal/mole)	($\Delta\Delta S^{\ddagger}$ e.u.)
Isopropyl Methanesulfonate	7 ± 28	-0.84 ± 0.1
Isopropyl p-toluenesulfonate	-21 ± 14	-0.93 ± 0.05
Isopropyl bromide	-35 ± 15	-0.65 ± 0.05

that charge dispersal is more effective in the deuterated compound, thus reducing the degree of solvation of the deuterio compound with respect to that of the protio compound. The more effective solvation of the protio compound reduces its $\Delta H^{\ddagger}$ with respect to that of the deuterio analog. But in this water solvolysis system, this solvation energy gain for the protio compound is counterbalanced by the energy loss in breaking the hydrogen bonds among the water molecules. Thus, the net effect is the entropy gain due to the breaking of the quasi-crystalline water structure.

(c) Wolfsberg and Stern (18) have interpreted the temperature independent isotope effect by using force constant changes. They showed that it is possible to obtain large temperature independent isotope effects, if some force constants which give rise to small frequencies increase in the transition state, while others that give rise to large frequencies, such as stretching frequencies, decrease. The results of a model calculation are shown in Table 4.

Whatever the real answer may be, it is clear that in order to define better the origin of secondary isotope effects, we need more experimental data, especially on the temperature and solvent dependence of these effects. The work described in this thesis deals with this problem in the solvolysis of propionyl chloride.

Table 4.--"Temperature independent" secondary hydrogen isotope effect.

$(CD_3)_2CHX \longrightarrow [(CD_3)_2CD\cdots\cdots X]^{\ddagger a}$

T(°K)	k_H/k_D
100	1.4678
250	1.4088
280	1.4110
300	1.4130
320	1.4151
340	1.4170
360	1.4188
380	1.4200

[a]The following force constant changes were assumed: f_{CH_o} in CH_3, 4.8 —> 3.5 millidyne/Å; $f_{torsion}$, 0.15 —> 1.0 md-A and f_{HCC} in CH_3, 0.68 —> 1.0 md-Å. One HCCC torsion coordinate was employed per methyl group.

EXPERIMENTAL

Kinetics

Preparation of Solvents

Conductivity Water.--Conductivity water was prepared by passing distilled water through a column filled with alternate layers of "Baker Analyzed" reagent Dowex 1-X8 anion exchange resin and "Baker Analyzed" reagent Dowex 50 W-X8 (cation exchange resin). The Dowex 1-X8 was converted to the hydroxide form by treating it with concentrated potasium hydroxide solution and then washing it with distilled water. The conductivity water prepared in this way had a specific conductance of about 2×10^{-6} mho/cm. It was regularly checked by measuring the conductance before preparation for mixed solvents.

Conductivity Acetone.--The Conant-Kirner method (23) was used to prepare conductivity acetone. Acetone (Fisher certified A-18), 1.5ℓ, was refluxed with 80 g. of potassium permanganate and five pellets of potassium hydroxide for three hours. It was distilled as described by Papaioannou (17b). The acetone obtained in this way had a specific conductance less than 1×10^{-8} mho/cm.

Mixed Solvents.--Mixtures of acetone and water were prepared by weighing the water and acetone to the nearest 0.5g. with a Torbal balance as described by Evans (24).

Conductance Apparatus

The conductance was measured by means of a Wayne-Kerr Conductance bridge (model B 221, Wayne-Kerr Co. Ltd.) equipped with a Wayne-Kerr Autobalance Adaptor (model AA 221).

Conductance Cell

For the kinetic studies of the hydrolysis of the acid chlorides two cells were used; one of them was made of a 250 ml Erlenmeyer flask and the other of a 500 ml Erlenmeyer flask. The rest of the cell was the same as described by Papaioannou (17b). With the 250 ml cell one drop of acid chloride was used, whereas with the 500 ml cell two drops of acid chloride were used. The obtained rate constants were essentially the same from both of them. The cells were stored with used reaction solvent at least 3 hr. before use to avoid adsorption of ions during a kinetic run. They were rinsed five times with conductance water and twice with conductance acetone before use.

Measurement of Time

A precision Scientific electronic digital timer (no. 69237, Precision Scientific Co.) accurate to 1/100th

of a minute was used.

Constant Temperature Bath

The bath used is described by Papaioannou (17b). A Beckman Differential Thermometer (Arthur H. Thomas Co.) was used to monitor the bath temperature. The bath was covered all around with Styroform so as to be insulated from room temperature changes. After immersing the cell, the inside of the bath was insulated from the outside with a Styroform cover fitting the cell very well. The temperature control with this bath was better than 0.003° over a temperature range from -30° to -10°. The bath was equipped with a submersible magnetic stirrer (model 700, Henry Troemner, Inc.).

Calibration of the Beckmann Thermometer

The Beckmann differential thermometer was calibrated by means of a platinum resistance thermometer (no. 8163, Leads Northrup Co.) as described by Evans (24), and by means of a quartz thermometer (2801 A, Hewlett-Packard).

The temperature sensing part of the quartz thermometer was cycled between temperature bath and water near room temperature until the ice-point reading became constant. Ten readings were taken from the quartz thermometer in °C *vs.* the Beckmann Thermometer. The average of readings from the quartz thermometer was corrected against the

provided chart at each temperature and for the deviation from the ice point. The corrected temperature was equated with the average of the Beckmann differential thermometer readings, so that the Beckmann readings could be converted directly to centigrade.

Rate Determination

After the conductance cell was filled with solvent, about 200 ml for the small cell and about 400 ml for the large, it was immersed into the temperature bath and allowed to completely equilibrate for about one hour. The solvent conductance, which was generally less than 0.1×10^{-6} mho, was recorded. One or two drops of acid chloride were added, depending on whether the small or the large cell was used. At the same time, the timer was started and the solution was stirred at least for one minute. The initial reading was taken when the capacitance had become fairly constant. Conductance readings, two per minute, were taken over the first three half-lives. The infinite value was obtained after 13 half-lives and exactly at the same time for all deuterated and undeuterated compounds.

Treatment of Data

The first order rate constants were determined by a least squares solution of the integrated first order rate expression.

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

C_∞ = conductance at infinite time

C_t = conductance at time t.

Conductance was taken as directly proportional to the concentration of hydrochloric acid formed. However, slight temperature independent deviations were observed in all solvents. Since we are mainly interested in the relative rate constants between deuterated and undeuterated acid chlorides measured under the same conditions, the observed slight deviations would not lead to appreciable error.

A rate constant obtained from a typical kinetic run is shown in Table 5. The reported average rates are the mean of at least three independent runs, which were alternated usually in the order $\underline{d}_0$, $\underline{d}_2$ and $\underline{d}_3$. The uncertainty indicated is the standard error σ.

$$\sigma = \sum_i \left[(x_i - \bar{x}_i)^2/n\right]^{1/2}$$

x_i = observed rate

$\bar{x}_i$ = mean.

Rate ratios, k_H/k_D, are the ratios of the corresponding means. The uncertainty indicated is the standard error obtained from the following relation:

Table 5.--Run number 228, propionyl chloride, 75% acetone/ water, 253°K. Conductance at infinity = 6.56800-004.

Time	Conductance	Calculated k	R
3.02	3.79800-004	4.72148-003	-4.12048-003
3.55	4.18800-004	4.72901-003	-3.24000-003
4.03	4.49800-004	4.74289-003	-3.21792-004
4.56	4.78800-004	4.74330-003	-2.52899-004
5.07	5.03200-004	4.75082-003	2.00555-003
5.55	5.22800-004	4.74988-003	1.88390-003
6.02	5.39800-004	4.75464-003	3.76262-003
6.54	5.55800-004	4.75135-003	2.79622-003
7.04	5.69200-004	4.75087-003	2.80900-003
7.55	5.81000-004	4.74934-003	2.31842-003
8.04	5.90800-004	4.74688-003	1.28176-003
8.55	5.99600-004	4.74268-003	-7.90676-004
9.06	6.07200-004	4.73797-003	-3.40089-003
9.55	6.13600-004	4.73397-003	-4.73076-003

Rate Constant = 4.74422-003

Std. Dev. of k = 6.08859-006

$$\sigma_{k_H/k_D} = \left[\left(\frac{\sigma_H}{\bar{k}_H}\right)^2 + \left(\frac{\sigma_D}{\bar{k}_D}\right)^2\right]^{1/2} k_H/k_D$$

The average rate constants at the different temperatures were used to determine the thermodynamic activation parameters $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ from the following equation:

$$\log(\bar{k}/T) = \frac{-\Delta H^{\ddagger}}{2.3026R}(1/T) + \frac{\Delta S^{\ddagger}}{2.3026R} + \log(k/h)$$

where $\bar{k}$ is the average rate constant, T is the absolute temperature, R is the gas constant, k is Boltzmann's constant and h is Plank's constant. Two computer programs were used to calculate the activation parameters; one by an iterative least square method (Acteng Program), in which the deviations from the "best" line were weighed, and the other by a single least squares solution (Active Program) of $\log(\bar{k}/T)$ *vs.* 1/T. The isotope effects (k_H/k_D) obtained at different temperatures were used to calculate the difference in enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$) of activation from the following equation and by a single least squares solution of ln k_H/k_D *vs.* 1/T by the Program Hand:

$$\ln(k_H/k_D) = -\frac{\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R}$$

All manual calculations were performed on a Wang calculator (Model 320 K).

Preparation of Propionyl Chlorides

All propionyl chlorides were prepared by the method of Brown (25). To a round-bottomed flask equipped with a vigeaux fractionating column and standard distillation head was added 5 g. of propionic acid and 40 g. of benzoyl chloride. The reaction mixture was heated very rapidly so that the propionyl chloride could be distilled as soon as possible into a receiver which was cooled with a dry ice-acetone mixture. The acid chloride boiled somewhat low due to dissolved hydrochloric acid. The distillate was refluxed for 30 minutes to degas the hydrochloric acid. The distillation was repeated twice. Overall yield was about 70%.

The purity of the propionyl chloride was checked by comparison of its infrared spectrum with that appearing in the Sadtler Index (26) and by nmr. Nmr was used to detect the presence of benzoyl chloride and the extent of the deuteration. Both deuterated compounds were nmr pure. The extent of deuteration of the -3,3,3-$\underline{d}_3$ chloride was assumed to be the same as that of its precursor propionic-3,3,3-$\underline{d}_3$ acid (98%).

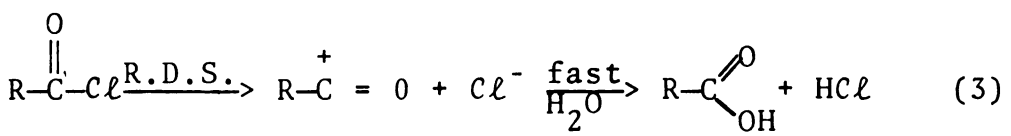
The propionyl chlorides were stored in glass vials with polyethylene stoppers which were sealed with "parafilm" plastic. They were kept inside a desiccator.

RESULTS AND DISCUSSION

Mechanism of Acid Chloride Solvolysis

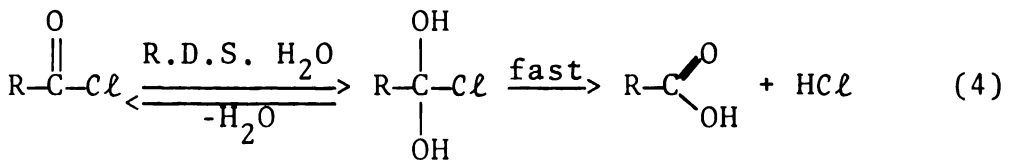
Acid chlorides may react with nucleophiles either by a limiting (S_n1), or/and by a nuchleophilic mechanism, depending on the reaction conditions. The nucleophilic mehcanism may be either an S_n2 or an addition-elimination (AE) mechanism. The AE mechanism is favored over the S_n2, because it can explain the observed carbonyl oxygen exchange with the oxygen of the solvent water in the hydrolysis reaction (27).

In highly polar solvents and high temperatures the limiting mechanism, eq. 3, tends to predominate.



$$R-\overset{\overset{O}{\|}}{C}-Cl \xrightarrow{R.D.S.} R-\overset{+}{C}=O + Cl^- \xrightarrow[H_2O]{fast} R-C(=O)-OH + HCl \qquad (3)$$

On the other hand, in non-polar solvents and low temperatures, the nuchleophilic mechanism, eq. 4, tends to predominate.



$$R-\overset{\overset{O}{\|}}{C}-Cl \underset{-H_2O}{\overset{R.D.S.\ H_2O}{\rightleftharpoons}} R-\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{C}}-Cl \xrightarrow{fast} R-C(=O)-OH + HCl \qquad (4)$$

The observed isotope effects during the solvolysis of propionyl chloride (Tables 6-8) are consistent with a dual-mechanism, i.e. simultaneous hydrolysis by both limiting and nucleophilic mechanisms. The reasons on which this statement is based will be discussed in the next section. First, evidence from other investigations will be presented, which supports such dual mechanisms.

The Effect of Solvent Changes on Mechanism

Duality of the acid chloride mechanism has been demonstrated by Hudson and Berger (28). In 5% water-95% acetone (v/v) the hydrolysis of p-substituted benzoyl chlorides proceeds almost exclusively by a nucleophilic mechanism with the following rate order: NO_2>Br>H>CH_3<CH_3O (Fig. 1). The rate acceleration of the p-methoxy compound has been attributed to a change in mechanism. However, in 50% water-50% acetone the rate order is reversed, as shown in Figure 2. Only the p-nitro compound appears to react by a nuchleophilic mechanism. The methoxy compound clearly proceeds by a limiting mechanism. Thus, as the ionizing power of the solvent increases, the reaction mechanism changes from a predominantly nuchleophilic to a predominantly limiting.

From rate-product studies of the hydrolysis of benzoyl chloride in aqueous solutions containing different

Table 6.--Rates of solvolysis of propionyl -d_0, -2,2-d_2 and -3,3,3-d_3 chlorides in 75% acetone-water.

Run No.	Isotope	$k \times 10^{-3}$ sec^{-1}	$\bar{k} \times 10^{-3}$ sec^{-1}	k_H/k_D	Temp. °C
222	d_0	4.690	4.706 ± .016		-20.55
225	d_0	4.683			
228	d_0	4.744			
223	d_2	4.647	4.655 ± .019	1.011 ± .005	-20.55
226	d_2	4.619			
229	d_2	4.698			
224	d_3	4.892	4.916 ± .017	0.957 ± .005	-20.55
227	d_3	4.898			
230	d_3	4.957			
206	d_0	2.683	2.646 ± .012		-25.55
210	d_0	2.681			
215	d_0	2.612			
217	d_0	2.607			
219	d_0	2.672			
220	d_0	2.648			
221	d_0	2.616			
207	d_2	2.613	2.626 ± .015	1.008 ± .007	-25.55
211	d_2	2.687			
213	d_2	2.628			
216	d_2	2.590			
218	d_2	2.610			
208	d_3	2.755	2.758 ± .004	0.960 ± .005	-25.55
212	d_3	2.767			
214	d_3	2.752			
189	d_0	1.415	1.404 ± .005		-30.58
191	d_0	1.394			
194	d_0	1.404			
190	d_2	1.414	1.422 ± .004	0.988 ± .004	-30.58
192	d_2	1.429			
196	d_2	1.422			
193	d_3	1.502	1.495 ± .004	0.939 ± .004	-30.58
195	d_3	1.486			
197	d_3	1.505			
198	d_3	1.490			

Table 7.--Rates of solvolysis of propionyl -d_0, -2,2-d_2 and -3,3,3-d_3 chlorides in 80% acetone-water.

Run No.	Isotope	$k \times 10^{-3}$ sec^{-1}	$\bar{k} \times 10^{-3}$ sec^{-1}	k_H/k_D	Temp. °C
152	d_0	6.433	6.436 ± .021		-10.56
153	d_0	6.544			
154	d_0	6.385			
155	d_0	6.414			
164	d_0	6.611			
166	d_0	6.162			
168	d_0	6.452			
170	d_0	6.365			
173	d_0	6.473			
174	d_0	6.451			
175	d_0	6.437			
177	d_0	6.501			
157	d_2	6.275	6.381 ± .022	1.088 ± .005	-10.56
167	d_2	6.412			
169	d_2	6.439			
171	d_2	6.413			
172	d_2	6.366			
176	d_2	6.384			
113	d_0	3.906	3.908 ± .023		-15.54
116	d_0	3.976			
119	d_0	3.818			
121	d_0	3.934			
123	d_0	3.906			
112	d_2	3.856	3.904 ± .016	1.001 ± .007	-15.54
115	d_2	3.927			
118	d_2	3.888			
120	d_2	3.900			
120	d_2	3.883			
122	d_2	3.978			
111	d_3	3.966	3.981 ± .007	0.982 ± .006	-15.54
114	d_3	3.996			
117	d_3	3.983			
102	d_0	2.251	2.241 ± .004		-20.47
105	d_0	2.237			
108	d_0	2.245			
101	d_2	2.217	2.239 ± .012	1.001 ± .007	-20.47
104	d_2	2.240			
106	d_2	2.276			
110	d_2	2.223			
100	d_3	2.322	2.318 ± .009	0.967 ± .021	-20.47
103	d_3	2.321			
109	d_3	2.341			

Table 7 (Continued)

Run No.	Isotope	$k \times 10^{-3}$ sec^{-1}	$\bar{k} \times 10^{-3}$ sec^{-1}	k_H/k_D	Temp. °C
41	d_0	1.265	1.248 ± .003		-25.41
42	d_0	1.242			
43	d_0	1.261			
47	d_0	1.245			
52	d_0	1.228			
55	d_0	1.245			
59	d_0	1.249			
62	d_0	1.242			
65	d_0	1.257			
68	d_0	1.244			
44	d_2	1.278	1.262 ± .003	0.988 ± .010	-25.41
46	d_2	1.261			
50	d_2	1.267			
54	d_2	1.254			
58	d_2	1.263			
61	d_2	1.254			
64	d_2	1.270			
66	d_2	1.253			
48	d_3	1.285	1.278 ± .005	0.976 ± .005	-25.41
49	d_3	1.288			
51	d_3	1.276			
53	d_3	1.245			
57	d_3	1.280			
60	d_3	1.298			
63	d_3	1.281			
65	d_3	1.273			
179	d_0	0.6681	0.678 ± .004		-30.58
182	d_0	0.6687			
184	d_0	0.6885			
186	d_0	0.6912			
188	d_0	0.6771			
204	d_0	0.6727			
180	d_2	0.6823	0.685 ± .003	0.989 ± .007	-30.58
181	d_2	0.6760			
183	d_2	0.6960			
185	d_2	0.6858			
187	d_2	0.6950			
202	d_2	0.6769			
201	d_3	0.6880	0.694 ± .006	0.976 ± .010	-30.58
203	d_3	0.6850			
205	d_3	0.7096			

Table 8.--Rates of solvolysis of propionyl -$\underline{d}_0$, -2,2-$\underline{d}_2$ and -3,3,3-$\underline{d}_3$ chloride in 85% acetone-water.[2]

Run No.	Isotope	$k \times 10^{-3}$ sec^{-1}	$\bar{k} \times 10^{-3}$ sec^{-1}	k_H/k_D	Temp. °C
138	d_0	3.140	3.163 ± .006		-10.57
141	d_0	3.160			
144	d_0	3.178			
147	d_0	3.163			
162	$\underline{d}_0$	3.175			
137	d_2	3.254	3.211 ± .012	0.985 ± .004	-10.57
140	d_2	3.200			
143	d_2	3.126			
146	d_2	3.175			
156	d_2	3.218			
158	d_2	3.245			
159	d_2	3.257			
160	d_2	3.204			
161	d_2	3.225			
163	$\underline{d}_2$	3.208			
136	d_3	3.321	3.237 ± .023	0.977 ± .007	-10.57
139	d_3	3.213			
142	d_3	3.165			
145	d_3	3.249			
148	$\underline{d}_3$	3.235			
126	d_0	1.924	1.927 ± .004		-15.54
128	d_0	1.935			
130	d_0	1.913			
132	$\underline{d}_0$	1.937			
125	d_2	1.942	1.971 ± .010	0.978 ± .005	-15.54
127	d_2	1.972			
129	d_2	1.999			
131	$\underline{d}_2$	1.972			
124	d_3	1.969	1.975 ± .010	0.976 ± .005	-15.54
133	d_3	1.973			
134	d_3	1.967			
135	$\underline{d}_3$	1.993			
89	d_0	1.098	1.115 ± .005		-20.47
92	d_0	1.118			
95	d_0	1.120			
98	$\underline{d}_0$	1.124			

Table 8 (Continued)

Run No.	Isotope	$k \times 10^{-3}$ sec^{-1}	$\bar{k} \times 10^{-3}$ sec^{-1}	k_H/k_D	Temp. °C
88	d_2	1.053	1.120 ± .020	0.995 ± 0.18	-20.47
91	d_2	1.140			
94	d_2	1.141			
97	d_2	1.149			
87	d_3	1.134	1.146 ± .003	0.973 ± .005	-20.47
90	d_3	1.142			
93	d_3	1.150			
96	d_3	1.155			
99	d_3	1.148			
76	d_0	0.5841	0.581 ± .017		-26.17
79	d_0	0.5827			
82	d_0	0.5818			
86	d_0	0.5751			
75	d_2	0.6021	0.604 ± .002	0.961 ± .004	-26.17
78	d_2	0.6011			
81	d_2	0.5997			
84	d_2	0.6091			
85	d_2	0.6103			
74	d_3	0.5982	0.595 ± .003	0.976 ± .039	-26.17
77	d_3	0.5914			
80	d_3	0.5868			
83	d_3	0.6050			

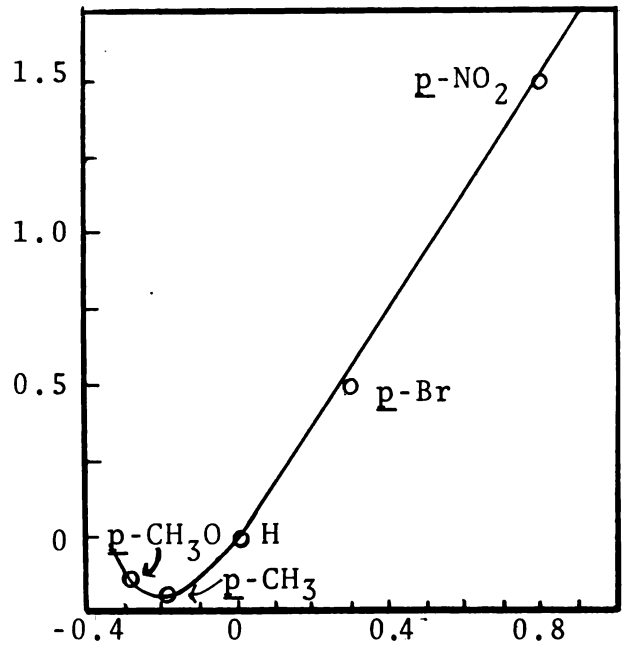


Figure 1.--The Hammett relations for p-substituted benzoyl chlorides in 5% water and 95% (v/v) acetone.(29)

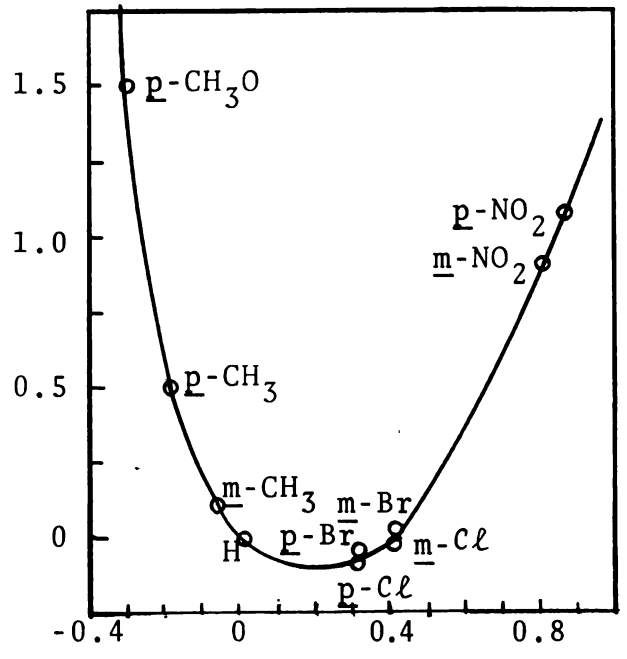


Figure 2.--The Hammett relations for p-substituted benzoyl chlorides in 50% water and 50% (v/v) acetone.(29)

amounts of o-nitroaniline, Gold and his co-workers (30) have shown that benzoyl chloride reacts by a nuchleophilic mechanism in 80% acetone-20% water (w/w). However, it does react about 50% by a limiting mechanism in 50% acetone-50% water (w/w) solution.

Bender and Chen (31) have studied the hydrolysis of p-substituted 2,6-dimethylbenzoyl chlorides in 99% acetonitrile-1% water solvents. The neutral and acid-catalyzed hydrolyses of these compounds proceed by a limiting mechanism, as supported by a common ion effect, salt effect, the large negative Hammett ρ value correlated with σ^+, and by no carbonyl oxygen exchange. In 95% dioxane-5% water solvent, which has a lower dielectric constant, Bunton and his co-workers (27) have found that the carbonyl oxygen of the mesitoyl chloride does exchange with water. This indicates that this sterically hindered acid chloride hydrolizes, at least partially, by an AE nucleophilic mechanism. The tetrahedral intermediate was even more clearly demonstrated in the alkaline solvolysis of mesitoyl chloride (21). For example, in the presence of catalytic amounts of hydroxide ion, the order of the relative rate of p-substituted compounds is the reverse of that of the acid or neutral hydrolysis. It is now accelerated by electron-withdrawing groups and retarded by electron-donating groups. The Hammett correlation has a $\rho = 1.2$ (31).

The Effect of Temperature Change on Mechanism

Kelly and Watson (32) have studied the hydrolysis of benzoyl chloride at high water concentrations in acetone-water solution at various temperatures. Their results, along with those of other investigators, are shown in Figure 3.

The results shown in Figure 3 are consistent with a dual mechanism. In low water concentrations, benzoyl chloride hydrolizes by a nucleophilic mechanism. As the ionizing power of the solvent increases, the mechanism shifts from a nucleophilic to a limiting, as shown by the changes in the slope of the curves in Figure 3. At 0° and 10 mole/liter $[H_2O]$ the mechanism has partly changed from nucleophilic to limiting. By using the dual-mechanism the authors have derived eq. 5.

$$k_{obs.} = k_2[H_2O]^{(0.00920T - 1.14)} + k_1[H_2O]^8 \qquad (5)$$

The calculated rate constant $k_{obs.}$ agrees within ±10% with all the observed experimental data that have been included here. The calculated relative contributions by k_1 (unimolecular) and k_2 (bimolecular) to the hydrolysis rate at various temperatures are shown in Table 9.

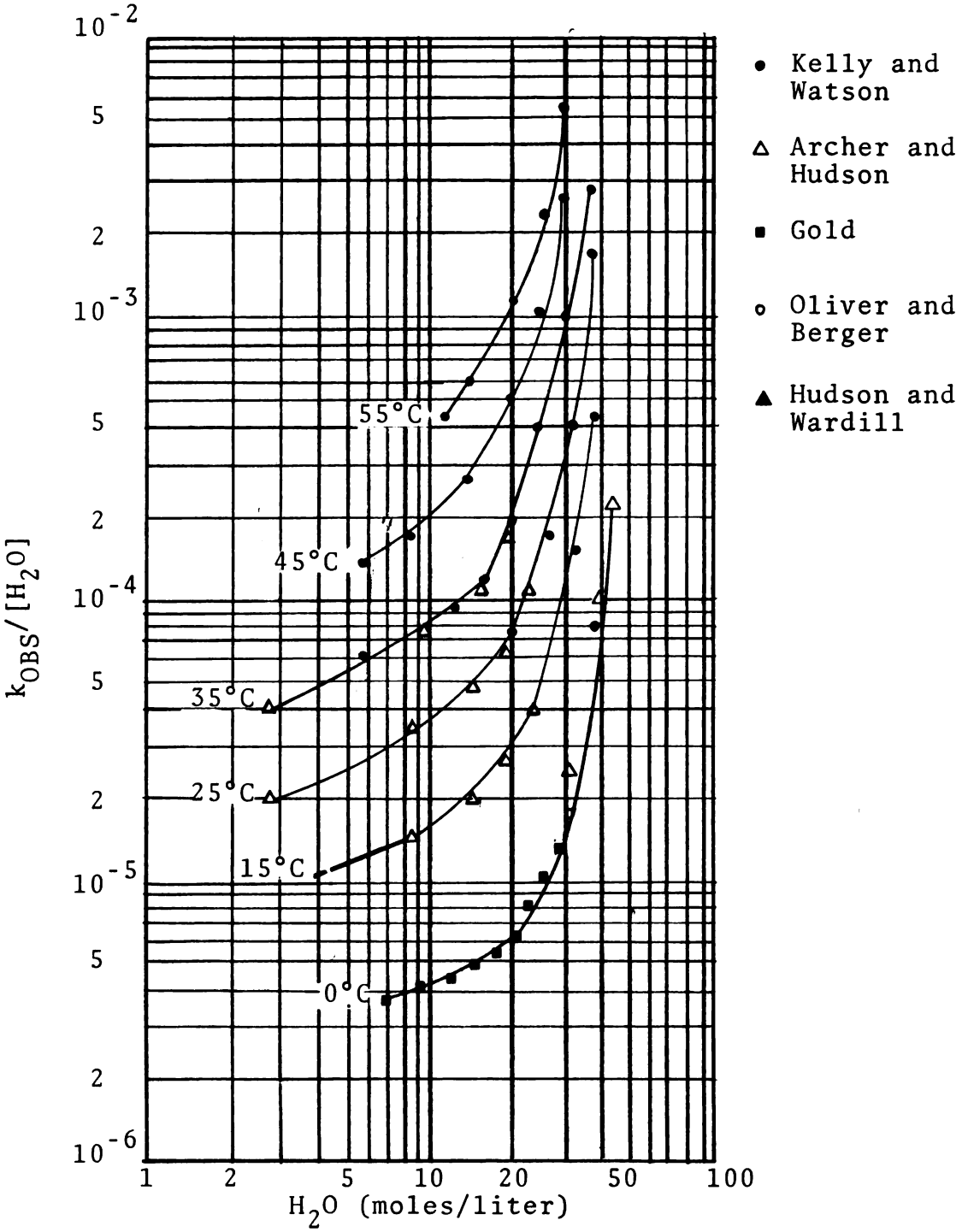


Figure 3.--Observed reaction rate constants vs. water concentration for the hydrolysis of benzoyl chloride.

Table 9.--Relative contributions by unimolecular (k_1) and by bimolecular (k_2) mechanism to the rate of the benzoyl chloride hydrolysis.

Temp. 0°C	$k_2 \times 10^6$	$k_1 \times 10^{16}$
0	1.81	6.90
15	5.32	38.9
25	10.3	112
35	19.0	300
45	33.4	880
55	56.6	2100

Isotope Effects and Mechanism

Isotope Effects as Criteria of Mechanism

Llewellyn and his co-workers (34) investigated the secondary hydrogen isotope effects of a series of alkyl esters in water. Some of their data are summarized in Tables 10 and 11.

Shiner and his co-workers (1a) have suggested that, in general, the α- and β-secondary isotope effects are near one, or inverse, for nucleophilic reactions and much larger for limiting reactions. Thus, secondary isotope effects may be used as criteria for deciding the mechanism of a reaction.

The observed β-isotope effects near one indicate that the hydrolysis of propionyl chloride proceeds predominantly by a nucleophilic mechanism. They are consistent with the dual mechanism. For example, as the water concentration and temperature increase, the contribution of the limiting mechanism gradually increases to lead to greater isotope effects (Table 12). The results are also consistent with the unified mechanism suggested by Evans (24).

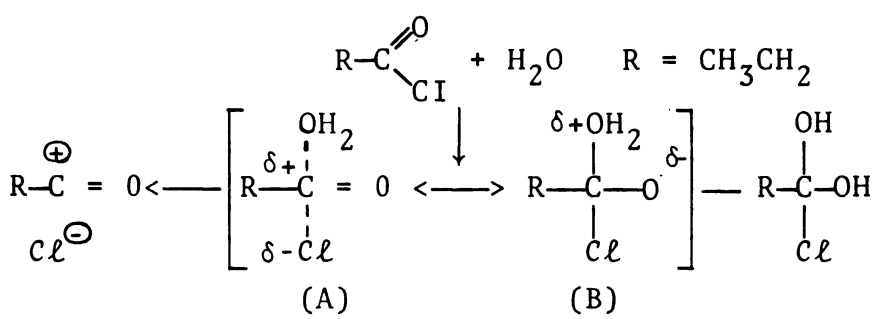


Table 10.--Isotope effects, k_H/k_D, for the solvolysis of α-deuterated alkyl esters (RX) in water.

Leaving Group	Methyl-$\underline{d}_3$	Ethyl-$\underline{d}_2$	Isopropyl-$\underline{d}_1$
Tosylate	0.96	1.038	1.134
Methanesulfonate	0.96	1.037	1.143
Iodide	0.87	0.968	1.050
Bromide	0.90	0.983	1.069
Chloride	0.92		
Reference	34(a)	34(b)	34(b)

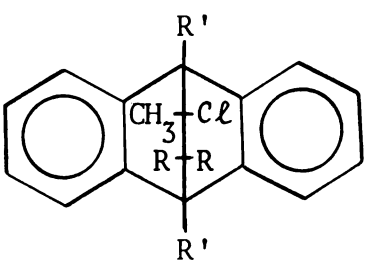
Table 11.--Isotope effects, k_H/k_D, for the solvolysis of β-deuterated alkyl esters (RX) in water.

Leaving Group	Ethyl-$\underline{d}_3$	Isopropyl-$\underline{d}_6$	$\underline{t}$-Butyl-$\underline{d}_9$
Tosylate	1.018	1.551	
Methanesulfonate	1.028	1.545	
Iodide	1.033	1.313	
Bromide	1.031	1.336	
Chloride			2.530
Reference	21	21	19

Table 12.--Temperature and solvent dependence of the β- and γ-isotope effects in the hydrolysis of propionyl-$\underline{d}_0$, 2,2-$\underline{d}_2$ and -3,3,3-$\underline{d}_3$ chlorides.

Solvent (% Acetone/Water)	Temp. °C	k_{H_2}/k_{D_2}	k_{H_3}/k_{D_3}
85	-26.17	0.961 ± .004	0.976 ± .039
	-20.47	0.995 ± .018	0.973 ± .005
	-15.54	0.978 ± .005	0.976 ± .005
	-10.57	0.985 ± .004	0.977 ± .007
80	-30.58	0.989 ± .007	0.976 ± .010
	-25.41	0.998 ± .010	0.976 ± .005
	-20.47	1.001 ± .007	0.967 ± .021
	-15.54	1.001 ± .007	0.982 ± .006
	-10.56	1.008 ± .005	
75	-30.58	0.988 ± .004	0.939 ± .004
	-25.55	1.008 ± .007	0.960 ± .005
	-20.55	1.011 ± .005	0.957 ± .005

As the ionizing power of the solvent and the temperature increase, the transition state shifts toward (A), i.e. one where the carbon-chlorine bond has been extensively broken (more limiting like). It should be emphasized that the above argument will be invalid in special cases. For example, Shiner and Humphrey (35) have shown that the isotope effect for the solvolysis of compound 9b, where effective hyperconjugation is possible, is 1.14. Such an isotope effect is consistent with the expected limiting mechanism of the reaction. On the other hand, the k_H/k_D for compound 9c, where the bridgehead C–H (or C–D) bond is in the nodal plane of the carbonium ion, is 0.986.



9a R = R' = H
9b R = D, R' = H
9c R = H, R' = D

Entropy of Activation and Mechanism

Long and co-workers (36a) and Schaleger and Long (36b) have suggested that the entropy of activation might serve as a convenient criterion of mechanism. Since in a nucleophilic hydrolysis a water molecule participates in

the bond formation with loss of its translational and rotational freedom, they predicted that reactions proceeding by nucleophilic mechanisms will have lower entropies of activation relative to those of reactions proceeding by limiting mechanisms.

Experimental results summarized in Table 13 are consistent with their prediction.

The entropies of activation for the hydrolysis of the propionyl chloride (Table 14) are consistent with a dual mechanism for this reaction. As the water content increases, the entropies of activation become less negative, an indication that the contribution of the limiting mechanism is increasing.

The Origin of the Isotope Effects

As pointed out in the introduction, isotope effects have been assumed to arise from changes in force constants. These changes have been attributed to hyperconjugation, nonbonded interactions and inductive effects. The present results may be interpreted in terms of either hyperconjugation or nonbonded interactions.

Hyperconjugation.--On the basis of infrared studies, Katon and Feairheller (38) have assigned two stable conformations, 10a and 10b, for priopionyl chloride in the ground state. Stiefvater and Wilson have proved that propionyl fluoride exists in two analogous stable conformations, the

Table 13.--Entropies of activation for limiting and nucleophilic solvolyses in aqueous-acetone at 50°C (37).

Substrate	Solvent (%Acetone-Water)	$\Delta S^{\ddagger}$ (e.u.)
(a) Limiting Mechanism		
t-BuCℓ	70	-10.89
	80	-12.41
t-BuBr	70	-10.20
	80	-11.23
$MeOC_6H_4CH_2C\ell$	70	-11.99
	80	-14.21
$MeOC_6H_4CH_2OTs$	85	-10.29
$Ph_2CHC\ell$	70	-10.26
	80	-12.96
$NO_2C_6H_4CHPhC\ell$	70	- 9.96
$NO_2C_6H_4CHPhBr$	70	- 8.38
$NO_2C_6H_4CHPhOTs$	85	- 8.12
(b) Nucleophilic Mechanism		
$PhCH_2C\ell$	70	-23.96
$PhCH_2Br$	70	-23.75
$PhCH_2OTs$	85	-19.62
$PhCH_2OTs$	70	-16.64

Table 14.--Transition state activation parameters[a] for the hydrolysis of propionyl-$\underline{d}_0$, -2,2-$\underline{d}_2$ and -3,3,3-$\underline{d}_3$ chlorides.

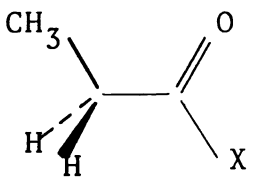
Solvent (% A/W)	Isotope	$\Delta S^{\ddagger}$(b) (e.u.)	$\Delta H^{\ddagger}$(b) (cal/mole)	$\Delta S^{\ddagger}$(c) (e.u.)	$\Delta H^{\ddagger}$(c) (cal/mole)
75	$\underline{d}_0$	-12.7 ± .7	14,193 ± 171	-12.7 ± .5	14,169 ± 122
	$\underline{d}_2$	-13.9 ± .7	13,904 ± 172	-13.9 ± .2	13,881 ± 55
	$\underline{d}_3$	-13.5 ± .7	13,959 ± 172	-13.6 ± .1	13,935 ± 29
80	$\underline{d}_0$	-15.7 ± .3	13,822 ± 80	-15.7 ± .4	13,798 ± 91
	$\underline{d}_2$	-16.2 ± .3	13,693 ± 80	-16.2 ± .4	13,670 ± 91
	$\underline{d}_3$	-15.0 ± .4	13,984 ± 111	-15.0 ± .3	13,962 ± 84
85	$\underline{d}_0$	-18.2 ± .4	13,536 ± 111	-18.2 ± .4	13,515 ± 102
	$\underline{d}_2$	-18.7 ± .4	13,380 ± 111	-18.7 ± .6	13,364 ± 150
	$\underline{d}_3$	-18.2 ± .4	13,525 ± 111	-18.2 ± .4	13,499 ± 109

(a) Calculated from the data in Tables 6 through 8.

(b) Calculated from Acteng.

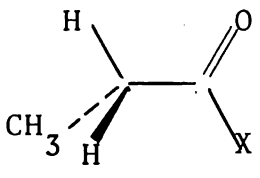
(c) Calculated from Active.

cis one being favored over the gauche by 1290 ± 50 cal/mole (39). In the ground state, therefore, effective hyperconjugation involving the α-hydrogens is possible.



10a

X = Cℓ or F



10b

According to the unified or dual mechanism proposed for the hydrolysis of the propionyl chloride the demand for hyperconjugation is reduced in the transition state of the nucleophilic mechanism due to a decrease in the partial positive charge on the carbonyl carbon. Consequently, the difference in the zero point energy (ΔZPE) increases in the transition state. The observed isotope effect should thus be inverse ($k_H/k_D < 1$). On the contrary, in the limiting mechanism the hyperconjugative demand increases in the transition state. Accordingly, the difference in zero point energy in the transition state decreases and should lead to a normal isotope effect ($k_H/k_D > 1$).

Nonbonded Interactions.--The results may also be rationalized in terms of nonbonded interactions. When the transition state is more crowded than the ground state, the force constant associated with the isotopic bond increases. Consequently, the difference in the zero point energy becomes larger in the transition state than in the ground state and leads to an inverse isotope effect. The nucleophilic

mechanism of the hydrolysis of propionyl chloride falls in this category. The limiting mechanism on the other hand would fit the case where the transition state is less crowded than the ground state.

γ-Isotope Effects in the Solvolysis of Propionyl Chloride.--Leffek and his co-workers (40) observed inverse isotope effects in the hydrolysis of various n-propyl esters in water (Table 15). They interpreted the observed 5-8% inverse γ-isotope effects in terms of increased nonbonded interactions in the transition state. Halevi (1b) gave an alternate explanation in terms of inductive effects. A much smaller effect (k_H/k_D = 0.990 ± 0.006) was obtained by Leffek (41) in the hydrolysis of n-propyl-3,3,3-d_3 bromide in 50% (v/v) ethanol-water solvent mixture.

Table 15.--γ-isotope effects for the hydrolysis in water of n-propyl compounds.

Compound	T°C	k_H/k_D(±.006)
Benzenesulfonate	54.183	0.947
Methanesulfonate	60.004	0.943
Bromide	80.009	0.921
Iodide	90.003	0.924

Jewett and Dunlap (42) have interpreted the inverse isotope effect (k_H/k_D = 0.983) in the aqueous alcoholysis of 11 and the normal isotope effect (k_H/k_D = 1.132) in the solvolysis of 12 in terms of inductive and hyperconjugative effects, respectively.

$R_3CCH_2C(CH_3)_2C\ell$

11

R = CH_3 or CD_3

trans RCH = $CHCHC\ell CH_3$

12

The observed 2-4% inverse γ-isotope effects in the solvolysis of propionyl chloride and its deuterated analog (Table 16) can be explained in terms of both inductive and nonbonded interactions. They are consistent with a dual mechanism, provided the contribution of the nucleophilic path is greater than that of the limiting path.

Temperature Insensitivity of the γ-Isotope Effects.--As pointed out, Leffek and his co-workers (22) found that the temperature insensitive β-isotope effects in the hydrolysis of isopropyl esters were the result of $\Delta\Delta H^{\ddagger}$ being zero, with $\Delta\Delta S^{\ddagger}$ apparently controlling them. We find (Table 16) that the γ-isotope effects, in contrast to the β-isotope effects, in the solvolysis of propionyl chloride are also temperature insensitive. This temperature insensivity, however, does not appear to arise from differences in the entropies of activation.

Table 16.--Temperature and solvent dependence on the γ-isotope effect in the hydrolysis of propionyl -3,3,3-$\underline{d}_3$ chloride.

Solvent (%A/W)	Temp. °C	k_{H_3}/k_{D_3}
85	-26.17	0.976 ± .039
	-20.47	0.973 ± .005
	-15.54	0.976 ± .005
	-10.57	0.977 ± .007
80	-30.58	0.976 ± .010
	-25.41	0.976 ± .005
	-20.47	0.967 ± .021
	-15.54	0.982 ± .006
75	-30.58	0.939 ± .004
	-25.55	0.960 ± .005
	-20.55	0.957 ± .005

In Table 17 are summarized the differences in the entropies of activation ($\Delta\Delta S^{\ddagger}$) and the enthalpies of activation ($\Delta\Delta H^{\ddagger}$) which were calculated by using eq. 7.

$$\ln k_H/k_D = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R \qquad (7)$$

The results show that the $\Delta\Delta S^{\ddagger}$ contribution to the isotope effect is zero in 80% and 85% acetone-water solutions. The temperature insensitive isotope effects appear to be solely controlled by differences in the enthalpies of activation. Thus, these results may be taken as support of the ideas of Wolfsberg and Stern (18), who have suggested that temperature independent isotope effects may result from compensating changes in force constants.

Table 17.--Activation parameters[a] determined from the temperature dependence of the β- and γ-isotope effect of propionyl-$\underline{d}_0$, -2,2-$\underline{d}_2$ and 3,3,3-$\underline{d}_3$ chloride hydrolysis.

Solvent (% Acetone/Water)	Isotope	$\Delta\Delta H^{\ddagger}$ (cal/mole)	$\Delta\Delta S^{\ddagger}$ (e.u.)
75	$\underline{d}_2$	281 ± 67	1.1 ± .3
	$\underline{d}_3$	232 ± 92	0.8 ± .4
80	$\underline{d}_2$	132 ± 20	0.5 ± .0
	$\underline{d}_3$	21 ± 60	0.0 ± .2
85	$\underline{d}_2$	152 ± 119	0.6 ± .5
	$\underline{d}_3$	138 ± 157	0.0 ± .0

[a] Calculated from Hands.

REFERENCES

1. (a) V. J. Shiner, Jr., W. E. Buddenbaum, B. C. Murr and G. Lamaty, J. Am. Chem. Soc., 90, 418 (1968).

   (b) E. A. Halevi, "Secondary Isotope Effects," Progress in Phys. Org. Chem., Vol. 1, S. G. Cohen, A. Streitwieser, and R. W. Taft, ed., John Wiley and Sons, New York, 1963.

   (c) H. C. Brown, M. E. Azzaro, J. G. Kaelling and G. J. McDonald, J. Am. Chem. Soc., 88, 2514 (1966).

2. (a) M. J. S. Dewar, Hyperconjugation, Ronald Press Co., New York, 1962.

   (b) Tetrahedron, 5, 105-274 (1959).

3. V. J. Shiner, Jr., J. Am. Chem. Soc., 86, 2643 (1964).

4. (a) E. S. Lewis and G. M. Coppinger, ibid., 76, 4495 (1954).

   (b) E. S. Lewis, R. R. Johnson and G. M. Coppinger, ibid., 81, 3140 (1959).

5. V. J. Shiner, Jr. and C. J. Verbanic, ibid., 79, 373 (1957).

6. I. W. Simmons and J. H. Goldstein, J. Chem. Phys., 20, 1804 (1952).

7. V. D. Tiers, J. Am. Chem. Soc., 79, 5585 (1957).

8. D. R. Lide, J. Chem. Phys., 27, 343 (1957).

9. (a) E. A. Halevi, M. Nussim and A. Ron, J. Chem. Soc., 866 (1963).

   (b) E. A. Halevi and M. Nussim, Bull. Res. Council Israel, Sect. A5, 263 (1956).

10. A. Streitwieser, Jr. and H. S. Klein, J. Am. Chem. Soc., 85, 2759 (1963).

11. R. P. Bell and B. T. Miller, Trans. Faraday Soc., 59, 1147 (1963).

12. A. Streitwieser and H. S. Klein, J. Am. Chem. Soc., 86, 5170 (1964).

13. (a) L. S. Bartell, Tetrahedron Letters, 6, 13 (1960).

(b) L. S. Bartell, J. Am. Chem. Soc., 8, 3567 (1960).

14. K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., ibid., 86, 1733 (1964).

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

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

17. (a) G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaionnou, S. E. Scheppele, and R. L. Shone, ibid., 89, 463 (1967).

(b) C. G. Papaioannou, Ph.D. Thesis, Michigan State University, 1967.

(c) G. C. Sonnichsen, Ph.D. Thesis, Michigan State University, 1967.

18. M. Wolfsberg and M. J. Stern, Pure Appl. Chem., 8, 225, 325 (1964).

19. L. Hakka, A. Queen, and R. E. Robertson, J. Am. Chem. Soc., 87, 161 (1965).

20. V. J. Shiner, Jr., ibid., 76, 1603 (1954).

21. K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, Can. J. Chem., 38, 2171 (1960).

22. K. T. Leffek, R. E. Robertson, and S. E. Sugamori, ibid, 39, 1989 (1961).

23. J. B. Conant and W. R. Kirner, J. Am. Chem. Soc., 46, 245 (1924).

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

25. H. C. Brown, J. Am. Chem. Soc., 60, 1325 (1938).

26. Sadtler Standard Spectra, Sadtler Research Laboratories Philadelphia.

27. C. A. Bunton, T. A. Lewis and D. R. Llewellyn, Chem. Ind. (London), 1154 (1954).

28. (a) D. A. Brown and R. F. Hudson, J. Chem. Soc., 883 (1953).

(b) R. F. Hudson and J. E. Wardill, ibid., 1729 (1950).

(c) G. Berger and S. C. J. Oliver, Rec. Trav. Chim., 46, 516 (1927).

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

30. V. Gold, J. Hilton, and E. G. Jefferson, J. Chem. Soc., 2756 (1954).

31. M. L. Bender and M. C. Chen, J. Am. Chem. Soc., 85, 30 (1963).

32. M. J. Kelly and G. M. Watson, J. Phys. Chem., 62, 2624 (1958).

33. (a) B. L. Archer and R. F. Hudson, J. Chem. Soc., 3259 (1950).

(b) B. L. Archer, R. F. Hudson and J. E. Wardill, ibid., 888 (1953).

(c) G. E. K. Branch and A. C. Nixon, J. Am. Chem. Soc., 58, 2499 (1936).

(d) Ref. 28(c).

34. (a) J. A. Llewellyn, R. E. Robertson and J. M. W. Scott, Can. J. Chem., 38, 222 (1960).

(b) K. T. Leffek, J. A. Llewellyn and R. E. Robertson, ibid., 38, 1505 (1960).

35. V. J. Shiner, Jr., and J. S. Humphrey, Jr., J. Am. Chem. Soc., 85, 2416 (1963).

36. (a) F. A. Long, J. G. Pritchard and F. E. Stafford, ibid., 79, 2362 (1957).

(b) L. L. Schaleger and F. A. Long, "Entropies of Activation and Mechanisms of Reactions in Solution," Advances in Physical Organic Chemistry, Vol. 1, V. Gold, ed., Academic Press, London, 1963.

37. G. Konstam, "Heat Capacities of Activation and Their Uses in Mechanistic Studies," Advances in Physical Organic Chemistry, Vol. 5, V. Gold, ed., Academic Press, London, 1967.

38. J. E. Katon and W. R. Feairheller, Jr., J. Chem. Phys., 44, 144 (1966).

39. O. L. Stiefvater and E. B. Wilson, ibid., 50, 5385 (1969).

40. K. T. Leffek, J. A. Llewellyn and R. E. Robertson, J. Am. Chem. Soc., 82, 6315 (1960).

41. K. T. Leffek, Can. J. Chem., 42, 851 (1964).

42. J. G. Jewett and R. P. Dunlap, J. Am. Chem. Soc., 90, 809 (1968)