TEMPERATURE DEPENDENCE OF SOME SECONDARY KINETIC DEUTERIUM ISOTOPE EFFECTS

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This is to certify that the

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Temperature Dependence of some Secondary Kinetic Deuterium Isotope Effects

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Uan Gen KANG

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ABSTRACT

TEMPERATURE DEPENDENCE OF SOME SECONDARY KINETIC DEUTERIUM ISOTOPE EFFECTS

By

Uan Gen Kang

In an effort to understand the origin of isotope effects, Karabatsos and his coworkers[1] measured several isotope effects as functions of temperature. They found that both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ contribute to the isotope effects. They usually have the same sign, which results in smaller isotope effects due to cancellation. Their preliminary results indicated that in correlating isotope effects and reaction mechanisms the $\Delta\Delta H^{\ddagger}$ term is more significant than the $\Delta\Delta G^{\ddagger}$ term. Furthermore, within the limits of accuracy imposed by the assumptions of Bartell's procedure,[2] a comparison of calculated isotope effects ($\Delta\Delta E$), due only to nonbonded interactions, with experimental values of $\Delta\Delta H^{\ddagger}$ indicates that in ordinary systems with hyperconjugation possible, hyperconjugation is the dominant contributor to $\Delta\Delta H^{\ddagger}$.

In the nucleophilic hydrolyses of acid chlorides and esters,[1b] the isotope effects due to $\Delta\Delta G^{\ddagger}$ are nearly unity. However, in the activation process the force constants

should increase, because the demand for hyperconjugation decreases and nonbonded interactions increase. Therefore, an inverse isotope effect ($k_H/k_D < 1$) is expected. Indeed, the $\Delta\Delta H^{\ddagger}$ term is reasonably large and positive leading to an inverse isotope effect. The experimental isotope effect is only near unity because of cancelling contributions to $\Delta\Delta G^{\ddagger}$ from $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$.

From the results of the present study, the negative $\Delta\Delta H^{\ddagger}$ value (-123 cal/mole in 65% acetone-water and -114 ± 6 cal/mole in 70% acetone-water) is reasonable in view of the near limiting character of the solvolysis of the 8-methyl-1-naphthoyl chloride in 65% and 70% acetone-water. The much less negative values in 75%, 80% and 85% acetone-water (-23 ± 14, -27 ± 58 and -10 ± 18 cal/mole respectively) are consistent with the borderline character of acid chloride solvolysis and indicate less limiting character in these solvents. However, the isotope effects due to $\Delta\Delta G^{\ddagger}$ (k_H/k_D = 1.014 ± .003 in 85% A/W -20.60°; and 1.023 ± .006 in 70% A/W, -20.60°) show their insensitivity to changes in reaction mechanism. They result from the cancelling contributions of the $T\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ terms ($\Delta\Delta H^{\ddagger}$ = -114 ± 6 cal/mole and $\Delta\Delta S^{\ddagger}$ = -0.4 ± .0 e.u. in 70% A/W; $\Delta\Delta H^{\ddagger}$ = -10 ± 18 cal/mole, $\Delta\Delta S^{\ddagger}$ = 0.0 ± .0 e.u. in 85% A/W) to $\Delta\Delta G^{\ddagger}$.

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[ii] G. J. Karabatsos and C. G. Papaioannou, Tetrahedron Lett., 22, 2629 (1968).

(b) G. J. Karabatsos and coworkers; unpublished results.
[i] T. A. Evans (Ph.D. Thesis, 1968);
[ii] U. G. Kang (M.S. Thesis, 1969);
[iii] A. A. Effio Leon (Ph.D. Thesis, 1971);
[iv] W. C. Sass (Ph.D. Thesis, 1970);
[v] V. F. Smith, Jr. (Ph.D. Thesis, 1972);
[vi] U. G. Kang (Ph.D. Thesis, 1972 present work).

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By

Uan Gen Kang

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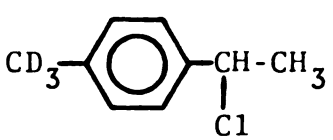
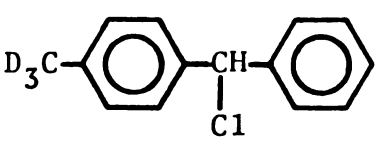
INTRODUCTION

Secondary kinetic isotope effects have been explained in terms of hyperconjugation, nonbonded interactions and inductive effects.[1]

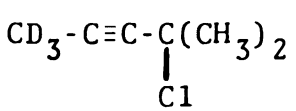
Solvolysis studies of compounds with remote hyperconjugating methyl-$\underline{d}_3$ groups support the importance of hyperconjugation to the secondary isotope effects.[2] For example, if the isotope effect caused by deuterium substitution at such remote positions is due to hyperconjugation, then a decrease in the demand for hyper-



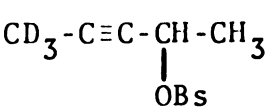
k_H/k_D = 1.10
(HOAc, 50°)[3]



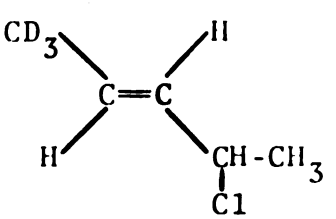
k_H/k_D = 1.058
(80% Acetone, 25°)[4]



k_H/k_D = 1.092
(80% EtOH, 25°)[5]



k_H/k_D = 1.109
(60% EtOH, 25°)[6]



k_{II}/k_D = 1.132
(95% EtOH, 25°)[7]

conjugation should decrease the β-secondary isotope effects. The results of Shiner and his coworkers[8] confirm this prediction (Table 1). All α-isotope effects for the solvolysis of a series of substituted 1-phenylethyl halides are about 1.154 ± .003, 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 effects (k_H/k_D = 1.154) support the conclusion that the mechanism of the reaction is mainly limiting.[9] 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.

Nuclear quadrupole coupling constant,[10] nuclear magnetic resonance chemical shift,[11] and dipole moment studies[12] have established that deuterium is more electropositive than hydrogen. The effect of deuterium substitution on acid strength (Table 2) has been interpreted in terms of the differences in the inductive effects of deuterium and hydrogen. In all cases deuteration decreases the acid strength. On the other hand, as expected, deuteration increases the basicity[13] of benzyl-α,α-d_2-amine (K_H/K_D = 0.88.

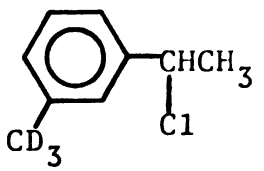
Table 1. Isotope Effects for 1-Phenylethyl Chlorides Corrected to 50% Ethanol at 25°.[8]

Substituent	k_H/k_D (α)	k_H/k_D (β)
p-methoxy	1.157	1.113
p-phenoxy	1.157	1.164
p-methyl	1.157	1.200
p-fluoro	1.152	1.211
m-methyl	1.151	1.222
none	1.153	1.224
m-bromo	1.133	1.221
p-nitro	1.098	1.151

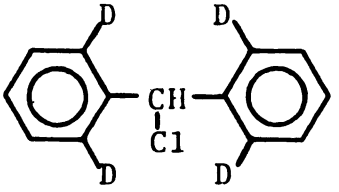
Table 2. Deuterium Isotope Effects in Acidity.

Acid	K_H/K_D	Reference
DCOOH	1.035 ± .002	14
CD_3COOH	1.032 ± .002	15
$(CD_3)_3COOH$	1.042 ± .003	15
C_6D_5COOH	1.024 ± .006	15
$C_6H_5CD_2COOH$	1.12 ± .02	13

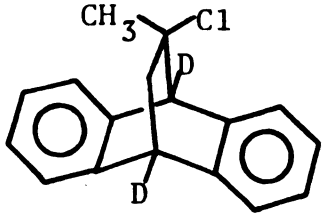
Solvolysis of the following compounds shows that kinetic isotope effects due to the inductive effect are small and opposite in direction from those due to hyperconjugation and nonbonded interactions.



k_H/k_D = 0.976
(80% Acetone, 62°)[3]



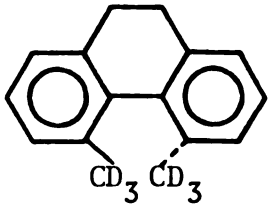
k_H/k_D = 0.981 per D
(80% Acetone, 25°)[15]



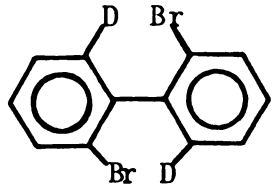
k_H/k_D = 0.986 ± .001
(60% EtOH, 45°)[16]

Bartell[17] has explained secondary isotope effects in terms of nonbonded interactions. His argument is as follows: The vibrational amplitudes of the C-H bond are larger than those of the C-D bond. Therefore, in the activation process from a crowded ground state to a less crowded transition state, there is greater relief of nonbonded interactions for the unlabeled than for the deuterium labeled compound. Consequently, a normal isotope effect should be observed. An inverse isotope effect should be observed in cases where the transition state is more crowded than the ground state.

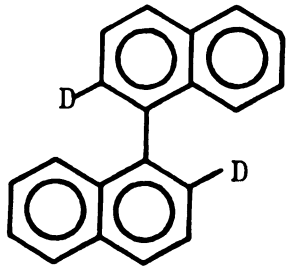
The following conformational studies have shown that the effective steric requirement for the C-D bond is less than that for the C-H bond. Since the racemization (a, b, and c) and ring flipping (d) are purely conformational changes, it is reasonable to explain the observed isotope effects in terms of nonbonded interactions.

a 

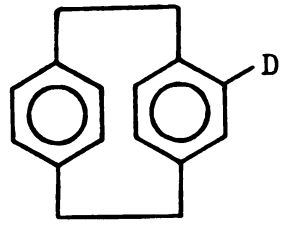
k_H/k_D = 0.83
(benzene, 42°)[18]

b 

k_H/k_D = 0.85
(EtOH, -20°)[19]

c 

k_H/k_D = 0.83 to 0.88
($HCON(CH_3)_3$, 20° and 65°)[20]

d 

k_H/k_D = 0.83 ± .004
($CDCl_3$, 35°)[21]

Brown and his coworkers[1,22] studied the reactions of methyl-$\underline{d}_3$-pyridines with Lewis acids and alkyl iodides. They found small or no isotope effects with the <u>meta</u> and <u>para</u> 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 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 in these cases are caused mainly by nonbonded interactions.

There seems to be little question that hyperconjugation, nonbonded interactions and inductive effects all contribute to secondary deuterium isotope effects. In general, if effective hyperconjugation is possible it dominates the inductive effect. However, the relative contributions of hyperconjugation and nonbonded interactions are not well understood.[1]

Although secondary isotope effects are interpreted in terms of hyperconjugation, nonbonded interactions and inductive effects, molecular force constant changes[56] on activation are generally accepted as the origin of isotope effects. Wolfsberg and Stern[23] have calculated isotope effects from molecular geometries, atomic masses, and assigned force constants for initial and transition states. 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, the temperature dependence of these effects should depend mainly on the differences in the corresponding enthalpies of activation ($\Delta\Delta H^{\ddagger}$), and not on differences in the entropies of activation ($\Delta\Delta S^{\ddagger}$).

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

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

Hakka and coworkers[24] have shown that in the hydrolysis of t-butyl chloride and its d_9 analog $\Delta\Delta H^{\ddagger}$ = -520 cal/mole $\cong$ $\Delta\Delta G^{\ddagger}$ with no apparent contribution from $\Delta\Delta S^{\ddagger}$ (= -0.2 e.u.). These results support the idea that force constant changes are the origin of the isotope effects.

However, Shiner and Verbanic's results[4] on the solvolysis of p-methyl-d_3-benzhydryl chlorides (ΔE_a = -106 ± 20 cal/mole per C-D bond, $\ln A_H/A_D$ = -0.075 ± 0.0015 per C-D bond), Shiner's studies[25] on the solvolysis of 2,3-dimethyl-2-chlorobutane-3-d (ΔE_a = -580 ± 70 cal/mole, $\ln A_H/A_D$ = -0.32 ± 0.03) and Lewis and Coppinger's results[3] on the solvolysis of p-methyl-d_3-α-phenylethyl chloride (ΔE_a = -154.5 cal/mole per D, $\ln A_H/A_D$ = -0.084 per D) show that the isotope effects depend on both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. Shiner and Hartshoron's studies[26] on β-isotope effects of phenylethyl-d_3 chloride ($\Delta\Delta G^{\ddagger}$ = -120

cal/mole, ΔE_a = -77.2 cal/mole and A_H/A_D = 1.075) and p-methyl-phenylethyl-$\underline{d}_3$ chloride ($\Delta\Delta G^{\ddagger}$ = -108.0 cal/mole, ΔE_a = -39.3 cal/mole and A_H/A_D = 1.123) show clearly the dependence of isotope effects on both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$.

Mislow and coworkers' study of the racemization of 9,10-dihydro-4,5-bis (methyl-$\underline{d}_3$) phenanthrene[18] gave similar results ($\Delta\Delta H^{\ddagger}$ = 240 cal/mole and $\Delta\Delta S^{\ddagger}$ = 0.53 e.u.) Carter and Dahlgren[20] also found, for the racemization of 1,1'-binaphthyl-2,2'-$\underline{d}_2$, $\Delta\Delta H$ = 270 ± 140 cal/mole and $\Delta\Delta S^{\ddagger}$ = 0.54 ± 0.43 e.u. (errors are three times the standard deviation).

The results obtained by Leffek and coworkers on the solvolysis of isoproyl-β-$\underline{d}_6$ derivatives[27] are the most unusual. The $\Delta\Delta H^{\ddagger}$ was approximately zero and the temperature independent isotope effect was due entirely to $\Delta\Delta S^{\ddagger}$ (Table 3). Five explanations have been given for the temperature independent isotope effect of this system. 1) Leffek and coworkers[27] have suggested that the observed isotope effect is due to the rotational barrier difference in the ground state between methyl and methyl-$\underline{d}_3$, which results from the larger steric requirement of the protium compound. In the transition state the barrier to internal rotation is reduced considerably and leads to favorable acceleration of the protium analog. The negligible contribution to the isotope effect from the $\Delta\Delta H^{\ddagger}$ was explained by a cancellation of the effect from the rotational barrier difference and the one

Table 3. Solvolysis of Isopropyl-β-$\underline{d}_6$ Derivatives in Water[27]

Compound	Solvent	k_H/k_D(T°)	k_H/k_D(T°)	$\Delta\Delta G^{\ddagger}$(25°) cal/mole	$\Delta\Delta H^{\ddagger}$ cal/mole	$\Delta\Delta S^{\ddagger}$ e.u.
i-pro-$\underline{d}_6$-OTs	H_2O	1.555(5°)	1.547(30°)	260	-7 + 28	.84 + .1
i-pro-$\underline{d}_6$-OMs	H_2O	1.542(6°)	1.545(30°)	255	21 + 14	.93 + .05
i-pro-$\underline{d}_6$-Br	H_2O	1.317(40°)	1.324(70°)	179	35 + 15	.65 + .05

from the zero-point energy difference. 2) Halevi[1b] has explained the data in terms of differences in the solvation of the protium compound and its deuterated analog. He assumed that charge dispersal is more effective in the deuterium compound, thus reducing the degree of solvation of the deuterio compound with respect to that of the protio compound. Consequently, the more effective solvation of the protio compound reduces its $\Delta H^{\ddagger}$ with respect to that of the deuterio analog. However, this solvation energy gain for the protio compound is counterbalanced by the energy loss due to breaking the hydrogen bonds among the water molecules. Thus, the net effect is an entropy gain due to the breaking of the quasicrystalline water structure. 3) Wolfsberg and Stern[23] have shown that it is possible to obtain reasonably large temperature-independent isotope effects over the usual temperature range by compensating changes in various force constants. Thus, if the C-D stretching force constant of the transition state was reduced relative to the reactant from 4.8 to 3.5 mdyn/Å and the torsion and H-C-C bending force constants were increased from 0.15 to 1.0 mdyn/Å and from 0.68 to 1.0 mdyn/Å, respectively, then the calculated isotope effects were reasonably constant at 1.41 ± 0.01 from 250° to 380° K. Shiner (2.p150) has suggested two possible explanations for this unusual temperature independent isotope effect:

4) The force constants of the transition state might be affected by solvation which is temperature dependent. Thus, if a reasonably large isotope effect was caused by lowering of a force constant in the transition state and if solvation were to increase this force constant, a smaller isotope effect would be obtained as a result of solvation. An increase in temperature would tend to lessen the solvation and, therefore, increase the isotope effect. This increase might be sufficient to cancel the usual decrease in isotope effect caused by the temperature increase. 5) With reservations due to inconsistancies with the α-isotope effect, the temperature independence of the isotope effect could be explained in terms of changes in mechanism, i.e., on the basis that the solvolysis of the i-propyl compounds is borderline in character. Thus, as the temperature is raised, a more dissociative transition state could cause an increase in the β-effect which may balance the normal decrease expected from the zero-point energy term.

All the data cited above show clearly the important influence that $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ might have on secondary isotope effects.

In order to understand further the origin of secondary isotope effects, we undertook to study the temperature and solvent dependence of isotope effects in the hydrolysis of 8-methyl-1-naphthoyl chloride and its 8-methyl-d_3 analog.

EXPERIMENTAL

KINETICS

Preparation of Solvents

Conductivity Water. -- Conductivity water was prepared by passing distilled water through a 5 x 80 cm column containing alternate layers of Dowex 1-X8 (anion exchange resin) and Dowex 50W-X8 (cation exchange resin). Water treated in this manner had a specific conductance of less than 2×10^{-6} mho/cm.

Conductivity Acetone. -- Three liters of acetone (Baker Analyzed Reagent) was refluxed with 80 g of potassium permanganate and 10 pellets of sodium hydroxide for three hours and distilled. The acetone obtained in this manner had a specific conductance of less than 1×10^{-8} mho/cm.

Mixed Solvents. -- Mixtures of acetone and water were prepared by weighing the water and acetone for the desired volume/volume ratios. The densities and ratios used are given in Table 4. A Torbal balance (model PL-12, Torsion Balance Co.) with a capacity of 2000 g and a stated accuracy of 0.1 g was used.

Table 4. Binary Solvents

V/V (%A/W)	85	80	75	70	65
W/W (%A/W)	81.67	75.89	70.24	64.74	59.37

Density of water at 25° = 0.997044.
Density of acetone at 25° = 0.7844.

Conductance Apparatus

The conductance was measured by means of a Wayne-Kerr conductance bridge, accurate to ±0.1% (model B 221, Wayne-Kerr Co., Ltd.), equipped with a Wayne-Kerr Autobalance Adaptor (model AA 221) with a PS109 power supply unit.

Conductance Cell

The two conductance cells used are essentially the same as described by Papaioannou.[34] The cells were stored with used reaction solvent at least two hours before use to avoid adsorbtion of ions during a kinetic run. They were rinsed three times with conductance water and twice with conductance acetone before use.

Measurement of Time

A precision Scientific Electronic Digital Timer (accurate to 1/100th of a minute) was used.

Constant Temperature Bath

A geared-drive stirrer (model 382-66 Lapine Co.) with two small eleven-blade propellers and a large eight-blade propeller was placed in the upper center of the bath. The heating knife (125W, Central Scientific Co.) was placed at a distance of 9 cm from the stirrer. The precision thermo-regulator (micro-set Lapine Co.) and the Beckmann differential thermometer (Sargent & Co.) were placed side by side 4 cm from the heater. The conductivity cell on the submersible magnetic stirrer (Troemner Co.) was placed at a distance of 12 cm from the thermometer. The stirrer and the electronic relay (Precision Scientific Co.) were supported by plexiglas covering the bath. The bath was surrounded with styrofoam 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 styrofoam cover which fitted the cell very well. The temperature control with this bath was better than ±0.003° over a temperature range from -20 to +40°.

Measurement of Temperature

The temperature was determined by means of a quartz thermometer (2801A Hewlett-Packard) accurate to ±0.01° and a platinum resistance thermometer (Portametric PVB 300 Electro Scientific Industries). The temperature was measured more than three times at each temperature. The quartz- and platinum-thermometer probes were attached

side-by-side in the ice point measurement and in the temperature bath to the Beckmann-thermometer. From each thermometer, ten readings were taken over a one hour period and the average temperature was corrected for linearity and for the deviation of the ice point for the quartz thermometer. The average resistance reading obtained was converted to temperature using the Werner and Frazer method.[28] Results from the quartz and platinum thermometers agreed to better than ±0.005°. During each kinetic run the temperature was monitored regularly by the quartz or the Beckmann thermometer and adjusted if necessary.

Rate Determination

After the conductance cell was filled with 260 ml of solvent, it was immersed in the temperature bath and allowed to completely equilibrate for about 30 minutes. The solvent conductance, which was generally less than 5×10^{-8} mho, was recorded. About 20 mg (2.6×10^{-4} molar) of acid chloride was dissolved in precisely one ml of conductivity acetone and injected into the cell with a one ml syringe. At the same time, the timer was started and the solution was stirred for at least two minutes. Conductance readings, four per minute for fast reactions and usually two per minute and one per two minutes for slow reactions, 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 expression, using the program RATE (Tables 5-9).

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

C_∞ = conductance at thirteen half-lives

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 under the same conditions, the observed slight deviations would not lead to appreciable error.

The reported average rates are the mean average of the independent determinations. The uncertainty indicated is the standard error. The average rates and standard errors were calculated using program DEV written by the author (Appendix One).

$$\sigma = \left(1/(N-1) \sum_{i=1}^{N} (x_i - \bar{x})^2\right)^{\frac{1}{2}}$$

x_i = observed rate

$\bar{x}$ = mean rate.

Table 5. Rates and Isotope Effects of the Solvolysis of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-1-naphthoyl Chloride in 65% Acetone-water (V/V).

Isotope	k x $10^3 sec^{-1}$	k x $10^3 sec^{-1}$	k_H/k_D	Temp.,°C
$\underline{d}_0$	18.948 18.983 19.006	18.979 ± .029	1.018 ± .005	-15.45
$\underline{d}_3$	18.602 18.737 18.578	18.639 ± .086		
$\underline{d}_0$	9.613 9.636 9.604	9.618 ± .017	1.023 ± .002	-20.60
$\underline{d}_3$	9.397 9.399	9.398 ± .001		

Table 6. Rates and Isotope Effects of the Solvolysis of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-1-naphthoyl Chloride in 70% Acetone-water (V/V).

Isotope	$k \times 10^3 sec^{-1}$	$\bar{k} \times 10^3 sec^{-1}$	k_H/k_D	Temp., °C
$\underline{d}_0$	14.914 14.764 14.784	14.821 ± .081	1.014 ± .006	-10.39
$\underline{d}_3$	14.597 14.596 14.636	14.610 ± .023		
$\underline{d}_0$	7.840 7.824 7.892	7.852 ± .036	1.018 ± .010	-15.45
$\underline{d}_3$	7.663 7.703 7.784	7.717 ± .062		
$\underline{d}_0$	4.135 4.122 4.150	4.136 ± .014	1.023 ± .006	-20.60
$\underline{d}_3$	4.038 4.026 4.060	4.041 ± .017		

Table 7. Rates and Isotope Effects of the Solvolysis of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-1-naphthoyl Chloride in 75% Acetone-water (V/V).

Isotope	k x 10^3 sec^{-1}	$\bar{k}$ x 10^3 sec^{-1}	k_H/k_D	Temp.,°C
$\underline{d}_0$	20.667 20.572 20.727	20.655 ± .078	1.015 ± .009	- 0.46
$\underline{d}_3$	20.390 20.487 20.175	20.351 ± .160		
$\underline{d}_0$	6.386 6.408 6.434	6.409 ± .024	1.015 ± .005	-10.39
$\underline{d}_3$	6.292 6.321 6.340	6.318 ± .024		
$\underline{d}_0$	3.199 3.202 3.210	3.203 ± .006	1.018 ± .002	-15.45
$\underline{d}_3$	3.146 3.141 3.149	3.145 ± .005		
$\underline{d}_0$	1.629 1.687 1.680	1.686 ± .006	1.018 ± .008	-20.60
$\underline{d}_3$	1.648 1.653 1.669	1.657 ± .011		

Table 8. Rates and Isotope Effects of the Solvolysis of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-1-naphthoyl Chloride in 80% Acetone-water (V/V).

Isotope	k x 10^3 sec^{-1}	$\bar{k}$ x 10^3 sec^{-1}	k_H/k_D	Temp.,°C
$\underline{d}_0$	7.439 7.450 7.463 7.509 7.429 7.477 7.443 7.442	7.456 ± .026	1.014 ± .007	- 0.46
$\underline{d}_3$	7.304 7.385 7.376 7.390 7.451 7.396 7.396 7.355	7.380 ± .045		
$\underline{d}_0$	2.349 2.355 2.354 2.375	2.358 ± .011	1.008 ± .009	-10.39
$\underline{d}_3$	2.351 2.347 2.318	2.339 ± .018		
$\underline{d}_0$	1.146 1.142 1.147	1.145 ± .002	1.016 ± .005	-15.45
$\underline{d}_3$	1.128 1.121 1.131	1.127 ± .005		
$\underline{d}_0$	0.6063 0.6086 0.6078 0.6086	0.6078 ± .0011	1.017 ± .002	-20.60
$\underline{d}_3$	0.5986 0.5972 0.5968	0.5975 ± .0009		

Table 9. Rates and Isotope Effects of the Solvolysis of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-1-naphthoyl Chloride in 85% Acetone-water (V/V).

Isotope	k x 10^3sec^{-1}	$\bar{k}$ x 10^3sec^{-1}	k_H/k_D	Temp.,°C
$\underline{d}_0$	2.811 2.820	2.815 ± .006	1.012 ± .004	- 0.46
$\underline{d}_3$	2.787 2.787 2.772	2.782 ± .008		
$\underline{d}_0$	0.9254 0.9257 0.9275	0.9262 ± .0011	1.015 ± .002	-10.39
$\underline{d}_3$	0.9124 0.9134 0.9108	0.9122 ± .0013		
$\underline{d}_0$	0.4348 0.4339 0.4282	0.4345 ± .0005	1.013 ± .002	-15.45
$\underline{d}_3$	0.4289 0.4292 0.4282	0.4288 ± .0006		
$\underline{d}_0$	0.2181 0.2184 0.2184	0.2183 ± .0002	1.014 ± .003	-20.60
$\underline{d}_3$	0.2158 0.2146 0.2152	0.2152 ± .0006		

Two rate determinations which deviated from the mean of the remaining rate constants by more than ten times the standard deviation were discarded. All rate constants used were determined with the same batch of solvent, except for the runs in 80% A/W at 0°.

Rate ratios, k_H/k_D, (Tables 17) are the ratios of the corresponding means. The uncertainty indicated is the standard error obtained from the following relation:

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

Rate ratios and the standard errors were calculated by using program RRD (Appendix Two) written by the author.

The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table 13) were calculated by using program AKTIVE by a single least squares solution from the following equation:

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

The difference in enthalpy ($\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$) and entropy ($\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$) of activation were calculated by using the following equation:

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

In using the least squares curve-fitting program KINFIT (Table 18), written and provided by Professor Dye of this Department,[29] the errors in the k_H/k_D determinations were weighted in calculating $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. Program HAND calculates $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ (Table 18) by a single least squares solution of $\ln k_H/k_D$ *vs.* 1/T.

Program RATE, AKTIVE and HANDS were written by Dr. Sonnichsen and program HAF (Appendix Three) was written by the author to calculate the half-live, and three- and thirteen half-lives.

SYNTHESIS

The deuterated and undeuterated compounds were synthesized by the procedure summarized in Figure 1.[30]

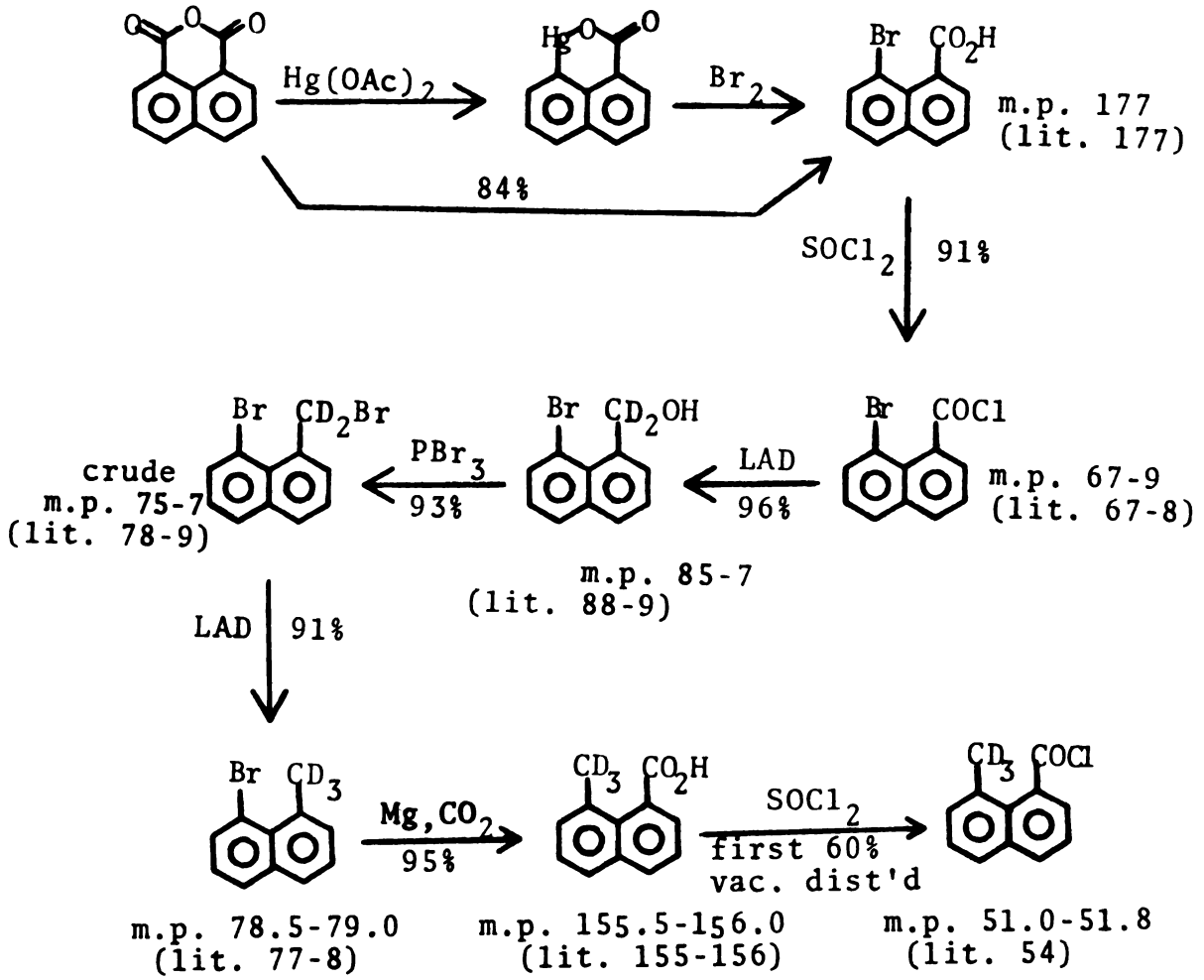


Figure 1. Synthetic scheme.

Preparation of Anhydro-8-hydroxymercuri-1-naphthoic Acid

The procedure of Whitmore et al.[31] was applied. In each of four 5-liter round-bottomed flasks, 49.5 g (0.25 mole) of 1,8-naphthalic anhydride was suspended in a solution of 35 g (0.875 mole) of sodium hydroxide in 1500 ml of water. As each flask was heated, the color turned dark brown. After 30 min. of reflux all solid material had dissolved completely. When 87.5 g (0.275 mole) of mercuric acetate dissolved in 50 ml of glacial acetic acid and 250 ml of water was poured slowly into each flask, the color turned orange. By adding 75 ml of glacial acetic acid each solution was made acidic (pH 5). After 24 hrs. reflux, the solid was filtered and washed with two liters of water, one liter of ethanol and one liter of ether. Without further purification, the solid from the four reactions was used in the next step.

Preparation of 8-Bromo-1-naphthoic Acid

The procedure of Rule et al.[32] was applied. Assuming a quantitative yield of anhydro-8-hydroxymercuri-1-naphthoic acid (1 mole, 371 g) in the previous step, we suspended the impure material in 1500 ml of glacial acetic acid and 250 ml of water in a 5-liter three-necked round-bottomed flask. The mixture was vigorously stirred with a mechanical stirrer and cooled in an ice-bath. A bromine-sodium bromide aqueous solution (680 g sodium bromide in 1250 ml of water and 56.6 ml of bromine) was added slowly from two dropping funnels so as to disperse as soon as

possible. The slurry formed was heated slowly to 100° and poured into a mixture of 2500 ml of water and 2500 g of ice with stirring. The white precipitate was suction filtered and washed with two liters of water. After drying in the hood, it yielded 84% of 8-bromo-1-naphthoic acid. Careful recrystallization gave acid which melted at 177° (lit.[32] m.p. 177°). It was found that recrystallization was not necessary to get good yields in the next step.

All the reaction apparatus described in the following sections was oven-dried overnight at 130° prior to use.

Preparation of 8-Bromo-1-naphthoyl Chloride

The thionyl chloride used was purified by Fieser's method.[33] A mixture of 79 g (0.32 moles) of 8-bromo-1-naphthoic acid and 38.4 ml (0.48 moles) of thionyl chloride was refluxed in a 250 ml round-bottomed flask for two hours until evolution of hydrogen chloride and sulfur dioxide stopped. The reflux condenser was fitted with a barium oxide drying tube. The dark solution was kept overnight and then twice distilled under vacuum through a distilling head which was heated with electric heating tape to prevent crystallization. To protect the vacuum pump a drying tower filled with a mixture of barium oxide, potassium hydroxide and drierite and a liquid nitrogen vacuum trap were used. B.p. 143-5°/0.06 mm, m.p. 67-9° (lit.[34] m.p. 67-8°), yield 90.5%.

In all the syntheses that follow dry ether means ether distilled from lithium aluminum hydride immediately before use.

Preparation of 8-Bromo-1-naphthylcarbinol-α,α-$\underline{d}_2$

In a 2-liter round-bottomed flask, 9.7 g (0.23 moles) of lithium aluminum deuteride (LAD) was suspended in 230 ml of dry ether. A solution of 76.7 g (0.285 moles) of acid chloride in 900 ml of dry ether was added slowly over a one hour period with stirring while maintaining gentle reflux. After addition was finished, the mixture was further refluxed for 5 hours, cooled in an ice-bath for 30 min. and carefully quenched under stirring, with 16 ml of water and 16 ml of 5% sodium hydroxide. The suspension was stirred overnight at room temperature and filtered. The ether layer, to which was added the ether used to wash the solid, was washed three times with 16 ml of water and dried over anhydrous magnesium sulfate. After rotary evaporation of the ether, a 96% yield of the alcohol was obtained. After recrystallization from cyclohexane the alcohol melted at 85-7° (lit.[30] m.p. 86.8°,[35a] m.p. 88-9°,[35b] m.p. 87-88.5°).

Preparation of 8-Bromo-1-bromomethylnaphthalene-α,α-$\underline{d}_2$

A solution of 58.2 g (0.244 moles) of 8-bromo-1-naphthylcarbinol-α,α-$\underline{d}_2$ in 1500 ml of dry ether and 20 ml (0.25 moles) of pyridine dried over barium oxide[36] was placed in a 5-liter three-necked round-bottomed flask fitted

with a mechanical stirrer and a condenser with an anhydrous barium oxide drying tube. To it was added with stirring 200 g (0.738 moles) of freshly opened phosphorus tribromide. The mixture was refluxed for 13 hours, cooled to room temperature and poured into 500 ml of water. The ether layer, to which was added the ether used to wash the water layer, was washed with 2 x 30 ml of water, 30 ml of saturated sodium bicarbonate and 30 ml of water. It was treated over anhydrous magnesium sulfate with norit, filtered and rotary evaporated. Yield: 93.2%, crude m.p. 75-7° (lit.[34] m.p. 78-9°). The nmr spectrum in carbon tetrachloride showed only an aromatic multiplet at τ = 2.08-2.96. The product was used without further purification in the next step.

Preparation of 1-Methyl-$\underline{d}_3$-8-bromonaphthalene

In a 5-liter three-necked round-bottomed flask fitted with a mechanical stirrer and condenser with anhydrous barium oxide drying tube was suspended 10 g (0.238 moles) of lithium aluminum deuteride in 600 ml of dry ether. To it was added over a 20-minute period, with stirring, 104.5 g (0.344 moles) of 1-bromomethyl-8-bromonaphthalene-α,α-$\underline{d}_2$ dissolved in 1300 ml of dry ether. After being refluxed for 8 hours, the mixture was cooled in an ice bath for one hour. It was very carefully quenched with 16 ml of water and 16 ml of 5% sodium hydroxide and stirred overnight. The solid was filtered and washed with ether. The filtrate was

washed with 2 x 16 ml of water, decolorized with norit and dried with anhydrous magnesium sulfate. After removal of the ether by rotary evaporation, a 90.5% yield of product was obtained. Careful recrystallization led to a product melting at 78.5-79.0° (lit.[37] m.p. 77-8°,[34] m.p. 76-7°). The nmr spectrum in carbon tetrachloride showed only an aromatic multiplet at τ = 2.17-3.08.

Preparation of 8-Methyl-$\underline{d}_3$-1-naphthoic Acid

In a 2-liter three-necked round-bottomed flask equipped with a mechanical stirrer and a condenser with anhydrous barium oxide drying tube was placed a suspension of 21.3 g (0.875 moles) Domal high purity magnesium granules, previously heated in an oven for 30 minutes, in 32 ml of dry ether. To it was added slowly over a 20 minute period 40 g (0.178 moles) of 1-methyl-$\underline{d}_3$-8-bromo-naphthalene dissolved in 65 ml of dry ether and 5 ml of ethyl bromide (dried over barium oxide). The mixture was refluxed and formed a greenish-milky suspension. To it was added dropwise 26 ml of dry ethyl bromide mixed with 175 ml dry ether at such a rate as to keep the mixture refluxing. After the mixture was heated at reflux for an additional 15 hrs., 180 g of dry ice was added slowly, followed by 450 ml of ether and an additional 180 g of dry ice. Stirring was continued until the excess dry ice was evaporated. Then 230 ml of 20% hydrochloric acid was added and the resulting solution was stirred overnight. The

ether layer was washed with 3 x 250 ml of water. After that, 40 g of norit and 10g magnesium sulfate was added to it. The solid was filtered and the ether was removed by rotary evaporation. Yield: 94.5%. After careful recrystallization the solid melted at 154-5° (lit.[30] m.p. 155-6°,[34] m.p. 152-3°,[38] m.p. 153°). The nmr spectrum in carbon tetrachloride showed an aromatic multiplet at τ = 1.90-2.39, a singlet at τ = -2.70 and no methyl peak at τ = 7.2. The mass spectrum had a peak at m/e 189 (96 ± 3% labeled). The melting point of the relevant X-1-naphthoic acids (Table 10) confirm the conclusion that the compounds synthesized in this work have the substituent (bromo and methyl group) in the 8-position.[39]

Table 10. Melting Points of X-1-naphthoic Acids[39]

Position of X	3	4	5	6	7	8[57]
m.p. for X = Br	233-4	219-20	258-9	185-6	235-6	177
m.p. for X = CH_3	---	176-7	188-9	178-9	146-7	154-5

Preparation of 8-Methyl-$\underline{d}_3$-1-naphthoyl Chloride

About 5 g of 8-methyl-$\underline{d}_3$-1-naphthoic acid was refluxed with 16 ml of purified thionyl chloride for one hour and kept at room temperature overnight. The excess thionyl chloride was distilled under vacuum, first at room temperature and then be heating to 60° (30 mm Hg) for three hours. The product acid chloride was distilled under vacuum (0.04 mm Hg) twice through a 15 cm glass spiral column with a distilling head that was heated to 60° with an electric heating tape, to prevent crystallization. The vacuum pump was protected with a drying tower containing a mixture of drierite, potassium hydroxide and barium oxide and a vacuum trap cooled with liquid nitrogen. The first 60% of the product which distilled was collected in three fractions. Of these, only the second and third fraction were used in the kinetic runs. The product boiled at 83-4°/0.04 mm Hg and melted at 51.0-.8° (lit.[34] m.p. 54°). From the intensity of the mass spectrum peaks at m/e 205 (0.9%), 206 (2.8%) and 207 (96.3%) we concluded that the product contained about 96% of the $\underline{d}_3$ isomer. The nmr spectrum in carbon tetrachloride showed only an aromatic multiplet at τ = 1.95-2.63 and <u>no</u> methyl peak at τ = 7.3. The infrared spectrum in carbon tetrachloride showed strong absorption at 1775 cm^{-1}.

Analytical Instruments

The mass spectrometer was a Hitachi, Ltd. RMU-60. Infrared spectra were taken with a Perkin-Elmer 237 B model, Grating Infrared Spectrophotometer. For the nmr spectra, either a Varian Associates A 56/60 D Analytical NMR Spectrometer or a Varian T-60 NMR spectrometer was used. Melting points were determined with an electro-thermal melting point apparatus by using a calibrated thermometer.

RESULTS AND DISCUSSION

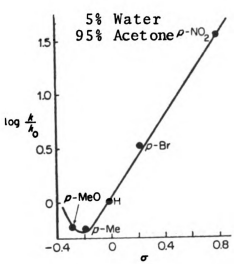
MECHANISM OF ACID CHLORIDE SOLVOLYSIS

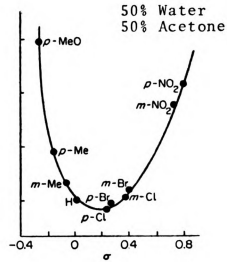
The evidence for the borderline mechanism of acid chloride hydrolysis will be presented along with the suggestion that 8-methyl-1-naphthoyl chloride solvolyzes by a limiting mechanism in 65% and 70% acetone-water.

Acid chloride solvolysis is typically borderline[40] in character; namely, depending on reactant structure, solvent, temperature or other reaction conditions, acid chlorides react with nucleophiles differently, in a manner that we may describe either by a mixture of simultaneous S_n1 and AE reactions (dual mechanism),[41] or by a unified mechanism[42] in which the transition state changes as a function of reaction conditions. Since acid chlorides might show also typical limiting or nucleophilic behavior, they are good systems to correlate various aspects of isotope effects ($\Delta\Delta G^{\ddagger}$, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) and reaction mechanisms.

The Effect of Solvent Changes on Mechanism

The borderline character of some acid chloride hydrolyses has been demonstrated by Hammett $\sigma\rho$ plots which are strongly solvent dependent (Figure 2). It was thought





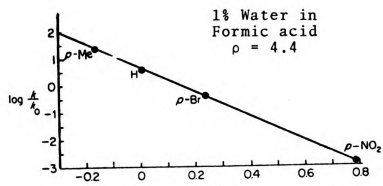


Figure 2. Plots of $\log (k/k_o)$ against σ for hydrolysis of substituted benzoyl chlorides in various solvent mixtures.

that the S_n1 mechanism takes over in an increasing number of cases as the solvent polarity increases.[43]

From rate-product studies of the hydrolysis of benzoyl chloride in aqueous solutions containing different amounts of o-nitroaniline, Gold and coworkers[41c] have suggested that benzoyl chloride reacts by a nucleophilic mechanism in 80% acetone-20% water (w/w) and by about 50% limiting mechanism in 50% acetone-50% water (w/w) solution.

As steric hinderance to AE reaction increases, acid chlorides tend to react via an S_n1 mechanism. Bender and Chen[44] have studied the hydrolysis of p-substituted 2,6-dimethylbenzoyl chlorides in 99% acetonitrile-1% water solvents. The neutral (Hammett ρ = -3.85) and acid-catalyzed hydrolysis (Hammett ρ = -3.73) of these compounds proceed by a limiting mechanism, as supported by a common ion effect, salt effect, the large negative Hammett ρ values correlated with σ^+ and by no carbonyl oxygen exchange. In 95% dioxane-5% water solvent, which has a lower dielectric constant, Bunton and coworkers[41a] have found that the carbonyl oxygen of the mesitoyl chloride does exchange with water. This indicates that this sterically hindered acid chloride hydrolyzes, at least partially, by an AE mechanism.

Thus, it is reasonable to assume that the sterically hindered[45] 8-methyl-1-naphthoyl chloride hydrolyzes mainly by a near limiting mechanism in polar media.

Correlation of Activation Parameters and Reaction Mechanism

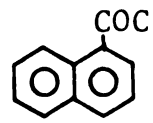
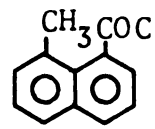
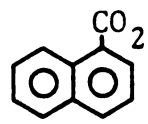
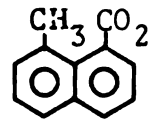
Long and coworkers[46] have suggested that the entropy of activation ($\Delta S^{\ddagger}$) might serve as a convenient criterion of mechanism. Since in a nucleophilic hydrolysis a water molecule participates in the bond formation with loss of its translational freedom, they predicted that reactions proceeding by nucleophilic mechanisms will have lower entropies of activation relative to those of reactions which proceed by limiting mechanisms. Experimental results summarized in Table 11 are consistent with their prediction. However, Long suggested that the entropy criterion must be used with caution and with other evidence. In view of the complex behavior of entropy of activation in solvolysis reactions[48] Long's caution is fully justified. These cautious comments notwithstanding, we conclude that the entropy of activation ($\Delta S^{\ddagger}$) data summarized in Table 12 are consistent with a borderline behavior of the solvolysis of the acid chlorides with decreasing solvent polarity, as $\Delta S^{\ddagger}$ becomes always more negative.

The small negative values ($\Delta S^{\ddagger}$ = -2 e.u. in 65% acetone; $\Delta S^{\ddagger}$ = -6 e.u. in 70% acetone) for 8-methyl-1-naphthoyl chloride (Table 13) are consistent with a limiting mechanism in these solvents, which becomes less limiting as the solvent polarity decreases. The large negative values ($\Delta S^{\ddagger}$ = -26 e.u. in 48% MeOH; $\Delta S^{\ddagger}$ = -30 e.u. in 54% dioxane) for the nucleophilic base hydrolysis of methyl 8-methyl-1-naphthoate further support this view.

Table 11. Entropies of Activation for Limiting and Nucleophilic Solvolyses in Aqueous-acetone at 50°[47]

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
$MeOC_6H_4CH_2Cl$	70	-11.99
	80	-14.21
$MeOC_6H_4CH_2OTs$	85	-10.29
Ph_2CHCl	70	-10.26
	80	-12.96
$NO_2C_6H_4CHPhCl$	70	- 9.96
$NO_2C_6H_4CHPhBr$	70	- 8.38
$NO_2C_6H_4CHPhOTs$	85	- 8.12
(b) Nucleophilic Mechanism		
$PhCH_2Cl$	70	-23.96
$PhCH_2Br$	70	-23.75
$PhCH_2OTs$	85	-19.62
$PhCH_2OTs$	70	-16.64

Table 12. Entropies of Activation (ΔS^{*}) in e.u. for Some Acid Chlorides and Esters[b]

Compound	65A[a]	70A	75A	80A	85A	90A	Ref.
CH_3COCl				-12.2±0.4	-16.6±0.8	-17.6±0.8	34,42[a]
CH_3CH_2COCl			-12.7±1.4	-15.7±0.6	-18.2±0.4	-23.8±1.0	57
$(CH_3)_2CHCOCl$			-16.5±1.6	-21.1±1.0	-18.2±0.4	-23.8±1.0	58
$(CH_3)_3CCOCl$			-20.8±1.6	-22.2±0.8	-24.8±0.8	-28.6±0.8	58
		-9.2±0.2					59
	-1.8	-5.8±1.0	-5.2±1.3	- 7.0±2.0	- 7.8±3.1		60
	10 M[a]	30 M	48 M	80 M	54 D[a]		Ref.
	-29.6±.5	-26.1±.9	-21 ±1	-19 ±1	-30.37±.01		61b
			-25.8±.7		-30.3±.4		61b

[a]65A indicates 65% V acetone-35% water, 10M; 10% W methanol-90% water 54D; 54% W dioxane-50% water.

[b]Calculated from program AKTIVE and quoted errors are two times the standard deviation (2σ).

Table 13. Activation Parameters[a] for the Hydrolysis of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-naphthoyl Chlorides

Solvent (%A/W)	Isotope	$\Delta H^{\ddagger}$ (cal/mole)	$\Delta S^{\ddagger}$ (e.u.)
65	$\underline{d}_0$	16,584	-1.8
	$\underline{d}_3$	16,712	-1.3
70	$\underline{d}_0$	15,982±255	-5.8±1.0
	$\underline{d}_3$	16,094±234	-5.4±0.9
75	$\underline{d}_0$	16,601±343	-5.2±1.3
	$\underline{d}_3$	16,626±362	-5.1±1.4
80	$\underline{d}_0$	16,651±519	-7.0±2.0
	$\underline{d}_3$	16,704±558	-6.8±2.1
85	$\underline{d}_0$	16,958±805	-7.8±3.1
	$\underline{d}_3$	16,972±798	-7.7±3.1

[a]Calculated from program AKTIVE and quoted errors are two times the standard deviation (2σ).

Isotope Effects as Criteria of Mechanism

An excellent review on this subect was written recently by Shiner,[2,9] Schleyer[9] and Scheppele.[1d]

Since the first observation of larger isotope effects in near limiting solvolyses and smaller effects in near nucleophilic displacements, intensive efforts have been made to use the observed isotope effects as criteria of reaction mechanisms. In general, for S_n2 reactions typical observed values are in the range 0.95-1.06 per α-deuterium at 25°, with variation in a systematic way as a function of the leaving group, nucleophile and substrate reactivity. For limiting mechanisms, the observed α-isotope effects are larger, with an upper limit that depends on the leaving group; about 1.15 for chloride and 1.22 for sulfonate groups,[49] at 25°.

The benzyl derivatives are very good examples by which to show this correlation, because substituent effects on solvolysis rates have shown that this series of compounds belong to the classical borderline region[50] that might exhibit typical S_n1 and S_n2 behavior at the extremes of reactivity. Shiner and Rapp[2] measured the α-d effects of p-methylbenzyl chloride in 70% and 97% trifluoroethanol-water mixtures (Table 14). These solvolyses were assumed to be largely limiting, because the observed α-isotope effects per D were reasonably constant [1.143(97% TFE) and 1.140(70% TFE)]. However, in 50% (V/V) ethanol-water

(Y-value = 1.655 at 25°) at 45°, p-methylbenzyl chloride showed an α-effect per D of 1.086. The authors explained it by a significant amount of nucleophilic attack by solvent. It is interesting to compare these results with that of Karabatsos and his coworkers[51,52] from the solvolysis of 8-methyl-1-naphthylcarbinyl-α,α-d_2- chloride. In a much less polar solvent (67% acetone-water, Y = 0.2) and at a lower temperature (25°) this isotope effect already shows the upper limit of the limiting mechanism (k_H/k_D = 1.15 per D). The reason lies in the sterically hindered nature of the compound, a feature that is also present in 8-methyl-1-naphthoyl chloride. Furthermore, 8-methyl-1-naphthoyl chloride solvolyzes about 10 times faster than 1-naphthoyl chloride,[51] whereas methyl 8-methyl-1-naphthoate reacts 5000 times slower than methyl-1-naphthoate.[61b]

All the above data provide good evidence to support a near limiting mechanism for the solvolysis of 8-methyl-1-naphthoyl chloride.

THE ORIGIN OF THE ISOTOPE EFFECTS

Karabatsos and his coworkers[51,53] have used two approaches in efforts to understand the origin of secondary deuterium isotope effects and to assess the relative contributions of hyperconjugation and nonbonded interactions to them.

Table 14. α-Deuterium Effects (per D)[a] on Rates of Solvolysis of Some Benzyl Derivatives at 25°[2]

Leaving group	Cl	OBs[b]	OBs[b]	OBs[b]
Substituent	p-CH_3	none	p-CF_3	P-NO_2
Solvents				
97T[c]	1.143	1.173	----	1.026[d]
80T	----	1.161	----	----
70T	1.140	----	1.042	1.011[d]
50E	1.086[d]	----	----	----
70E	----	----	1.019	1.006
80E	----	1.074	1.016	1.005
90E	----	1.060	1.014	1.002
95E	----	1.053	1.014	----

[a] $(k_H/k_{D2})^{\frac{1}{2}}$

[b] p-bromobenzenesulfonate

[c] 97T indicates 97 wt% 2,2,2-trifluoroethanol-3% water; 70E indicates 70 vol% ethanol-30% water etc.

[d] Estimated from observed values at 45°, assuming normal temperature dependence.

They measured isotope effects as functions of temperature so as to calculate the relative contributions of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. This is important, in view of the demonstration by previous studies that the contribution of $\Delta\Delta S^{\ddagger}$ is in some cases not only significant, but even dominant. Such a $\Delta\Delta S^{\ddagger}$ contribution to isotope effects is not surprising in view of the importance of entropy in equilibria and kinetics in general.[54] One useful result of the temperature studies is to separate the better understood $\Delta\Delta H^{\ddagger}$ term, which can be interpreted in terms of hyperconjugation, inductive effects and nonbonded interactions, from the more complex $\Delta\Delta S^{\ddagger}$ term.

2) They chose two types of systems in which to estimate the relative importance of hyperconjugation and nonbonded interactions: first, systems in which nonbonded interactions are predominant and hyperconjugation is negligible, and second, systems in which nonbonded interactions and hyperconjugation both contribute to the $\Delta\Delta H^{\ddagger}$ term. By comparing the experimental $\Delta\Delta H^{\ddagger}$ values obtained from both systems with the theoretically calculated $\Delta\Delta E$ term due only to nonbonded interactions, they expected to be able to estimate the relative contributions of hyperconjugation and nonbonded interactions in systems in which both effects are operating.

Relative Importance of Enthalpy ($\Delta\Delta H^{\ddagger}$) and Entropy ($\Delta\Delta S^{\ddagger}$) Term to Isotope Effects

From the data summarized in Tables 15-16, it appears that both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ contribute to the observed isotope effects and that both terms have the same sign. In the discussion that follows we will try to show that isotope effects based on $\Delta\Delta H^{\ddagger}$ may be better mechanistic criteria than those based on $\Delta\Delta G^{\ddagger}$. We wish to make the following pertinent comments with respect to the data summarized in Tables 15-20.

(a) The β-$\underline{D}_3$ isotope effects for the hydrolysis of acetyl chloride in 85% acetone-water (Table 15) are: from $\Delta\Delta H^{\ddagger}$, $k_H/k_D = 1.21$ and from $\Delta\Delta G^{\ddagger}$, $k_H/k_D = 1.11$.[42a] Both isotope effects indicate some limiting character in the reaction mechanism and qualitatively agree with the theory of force constant changes.

(b) In the nucleophilic hydrolyses of the acid chlorides and esters (Table 15), the isotope effects k_H/k_D due to $\Delta\Delta G^{\ddagger}$ are near unity. However, in the activation process the force constants should increase, because the demand for hyperconjugation decreases and nonbonded interactions increase. Therefore, an inverse isotope effect ($k_H/k_D < 1$) is expected. Indeed, the $\Delta\Delta H^{\ddagger}$ term is reasonably large and positive leading to an inverse isotope effect. The experimental isotope effect is only near unity because of cancelling contributions from $T\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ to $\Delta\Delta G^{\ddagger}$.

Table 15. Hydrolysis of Compounds with Hyperconjugation, Nonbonded Interactions and Inductive Effects Possible.

Compound	solv.[a]	k_H/k_D	low T°C	k_H/k_D	high T°C	$\Delta\Delta H^{\ddagger b}$ cal/mole	$\Delta\Delta S^{\ddagger b}$	mech.	Ref
CD_3COCl	85A	1.11	-31	1.101	-21	-119±48	-0.3±.2	lim.	42a
	95A	1.004	-25	1.030	- 0	110±20	0.5±.2	AE	
CH_3CD_2COCl	75A	0.988	-31	1.011	-21	281±134	1.1±.6	AE	57
	80A	0.989	-31	1.008	-11	132± 40	0.5±.0	AE	
CD_3CH_2COCl	75A	0.939	-31	0.957	-21	232±184	0.8±.8	AE	
$(CH_3)_2CDCOCl$	75A	0.977	-29	0.988	-20	148± 72	0.6±.3	AE	58
	85A	0.953	-29	0.978	-10	163± 58	0.6±.2	AE	
	90A	0.955	-29	0.987	- 5	184± 64	0.6±.2	AE	
	95A	0.942	-18	0.978	- 5	308±104	1.1±.4	AE	
$CH_3CD_2CO_2Et$	base hydr.	0.936	20	0.946	30	276±134	0.8±.4	AE	61a

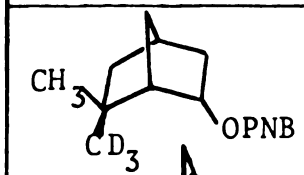
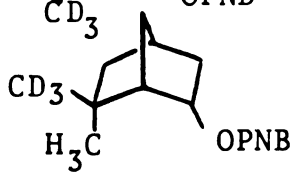
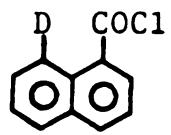
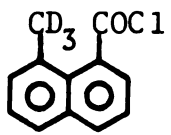
[a] 85A indicates 85V% acetone-15% water etc.

[b] Errors quoted are two times the standard deviation yielding 95% confidence limits.

(c) The remote isotope effects due to $\Delta\Delta G^{\ddagger}$ are not only insensitive to reaction mechanism, but also misleading (Table 16). For example, Brown and his coworkers[55] have suggested that the limiting activation process in the solvolysis of the 2,6,6-trimethyl-endo-2-norbornyl system is sterically hindered by the interaction between the leaving group and the endo-6-methyl group. On this basis, an inverse isotope effect is predicted. Contrary to expectation, the experimentally observed isotope effect[62] (Table 16) is normal. However, the large experimental positive $\Delta\Delta H^{\ddagger}$ value (endo-6-CD_3, $\Delta\Delta H^{\ddagger}$ = 204±82 cal/mole; exo-6-CD_3, $\Delta\Delta H^{\ddagger}$ = 244±96 cal/mole) gives a large inverse isotope effect (k_H/k_D = 0.70), as expected by the mechanism. The surprisingly small normal effect results from the slight domination of the $T\Delta\Delta S^{\ddagger}$ term over the $\Delta\Delta H^{\ddagger}$ term.

(d) From the results of the present study (Table 18), the negative $\Delta\Delta H^{\ddagger}$ [= -114±6 cal/mole, $(k_H/k_D)_H$ = 1.20 in 70% acetone-water] value is reasonable in view of the near limiting character of the solvolysis of the 8-methyl-1-naphthoyl chloride. The observed small isotope effect (k_H/k_D = 1.018) (Table 17) again results from the cancelling contribution of the $T\Delta\Delta S^{\ddagger}$ term ($\Delta\Delta S^{\ddagger}$ = -0.4±.0 e.u.) to the $\Delta\Delta G^{\ddagger}$ term.

Table 16. Hydrolysis of Compounds in Which Nonbonded Interactions are the Predominant Contributor to $\Delta\Delta H^{\ddagger}$ Term and Electronic Effects are Negligible

Compound	solv.[a]	k_H/k_D	low T°C	k_H/k_D	high T°C	$\Delta\Delta H^{\ddagger}$[b]	$\Delta\Delta S^{*}$[b]	mech.	ref.
	80E	1.00	100	1.03	150	204±82	0.5±.2	lim.	62
	80E	1.01	100	1.05	150	244±96	0.7±.2	lim.	62
	70A	1.024	- 12	1.02	20	-34	-0.1		59
	70A	1.023	- 21	1.014	- 10	-114±8	-0.4±.0	near lim.	60

[a] 70A indicates 70V% acetone-30% water; 80E indicates 80V% ethanol-20% water etc.

[b] Errors quoted are two times the standard deviation yielding 95% confidence limits.

Table 17. Temperature and Solvent Dependence of the Isotope Effect in the Hydrolysis of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-1-naphthoyl Chlorides

Solvent (% A/W)	Temp.°	k_H/k_D [a]
65	-15.45	1.018±.005
	-20.60	1.023±.002
70	-10.39	1.014±.006
	-15.45	1.018±.010
	-20.60	1.023±.006
75	- 0.46	1.015±.009
	-10.39	1.015±.005
	-15.45	1.018±.002
	-20.60	1.018±.008
80	- 0.46	1.014±.007
	-10.39	1.008±.009
	-15.45	1.016±.005
	-20.60	1.017±.002
85	- 0.46	1.012±.004
	-10.39	1.015±.002
	-15.45	1.013±.002
	-20.60	1.014±.003

[a]Calculated from program RATE and RRD. Quoted errors are the standard deviations.

Table 18. Activation Parameters[a] Determined from the Temperature Dependence of the Isotope Effect of 8-Methyl-$\underline{d}_0$- and -$\underline{d}_3$-1-naphthoyl Chloride Hydrolysis

Solvent (V% A/W)	$\Delta\Delta H^{\neq b}$ (cal/mole)	$\Delta\Delta H^{\neq c}$ (cal/mole)	$\Delta\Delta H^{\neq d}$ (cal/mole)	$\Delta\Delta S^{\neq b}$ (e.u.)	$\Delta\Delta S^{\neq c}$ (e.u.)	$\Delta\Delta S^{\neq d}$ (e.u.)
65	-123	-123	-123	-0.4	-0.4	-0.4
70	-114±6	-114±8	-102±2	-0.4±.0	-0.4±.0	-0.4±.0
75	- 23±14	- 28±28	- 57±16	-0.1±.1	-0.1±.2	-0.2±.1
80	- 27±58	- 32±60	- 43±66	-0.1±.1	-0.1±.2	-0.1±.3
85	- 10±18	- 7±30	+ 17±12	-0.0±.0	-0.0±.2	+0.1±.0

[a]Errors quoted are two times the standard deviation yielding 95% confidence limits.

[b]Calculated from HANDS program.

[c]Calculated from KINFIT program; errors in k_H/k_D determinations were weighed.

[d]Calculated from data which include errors due to solvent preparation.

Relative Contribution of Hyperconjugation and Nonbonded Interactions to the Enthalpy Term ($\Delta\Delta H^{\ddagger}$)

It is interesting to compare the nonbonded isotope effects due to $\Delta\Delta H^{\ddagger}$ with those from $\Delta\Delta E$ values for the 8-methyl-1-naphthoyl chloride and its 8-methyl-$\underline{d}_3$ analog (Tables 19-20), which were calculated by using Bartell's procedure[17] and two different potential functions.[51,52] From the fact that the dihedral angles between the planes of the ring and the nitro group of 1,8-dinitronaphthalene[63] and 1,5-dinitronaphthalene[64] are 43° and 49°, it is reasonable to assume that the dihedral angle between the ring and COCl planes is between 45° and 60°. The calculated isotope effects for such angles are reasonably close to those observed experimentally. In Table 20 are summarized a few calculated and experimental isotope effects. Since the dihedral angles between the C-CO-C plane of the aromatic ring for 1-acetylnaphthalene is 42°, it is reasonable to assume a dihedral angle for 1-naphthoyl chloride of about 40°. Therefore, the calculated isotope effects are again reasonably close to the experimental ones. However, where hyperconjugation is possible, e.g. acetyl chloride and t-butyl chloride, the calculated nonbonded isotope effects ($\Delta\Delta E$) are much smaller than the experimental values. Therefore, within the limits of accuracy imposed by the assumptions of Bartell's procedure[66a] and the experimental values used (potential functions and geometry), our preliminary studies indicate that in ordinary systems with hyperconjugation possible, the dominant contributor to the $\Delta\Delta H^{\ddagger}$ term is hyperconjugation.

Table 19. Calculated Isotope Effects Due to Nonbonded Interactions for 8-Methyl-1-naphthoyl Chloride and 8-Methyl-$\underline{d}_3$ Analog[51]

deg.[c]	deg.[d]	$\Delta\Delta E$[a] cal/mole	k_H/k_D 25°	$\Delta\Delta E$[b] cal/mole	k_H/k_D 25°
0	0	-870	4.31	-530	2.43
15	7.5	-710	3.32	-520	2.03
30	14	-460	2.17	-230	1.48
45	18	-250	1.52	-100	1.18
60	20	-116	1.21	- 40	1.07
75	20	- 90	1.16	- 20	1.03
90	0	- 81	1.15	- 18	1.03

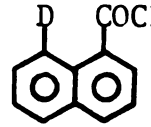
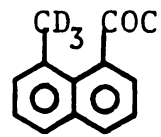
[a] $\Delta\Delta E = \Delta E_H - \Delta E_D$, potential function from ref. 66a.

[b] Potential function from ref. 66b.

[c] Dihedral angle between COCl and naphthalene ring.

[d] Dihedral angle between methyl group and naphthalene ring.

Table 20. Comparison of Calculated ($\Delta\Delta E$) and Experimental Isotope Effects ($\Delta\Delta H^{\ddagger}$) for Some Limiting Solvolyses

Compound	V(r)[a]	b	$\Delta\Delta E$ cald[c]	$\Delta\Delta H^{\ddagger}$ exp.[c]	solv.	T°C	mech.	ref.
CD_3COCl	S		8.1	-119±48[d]	85A	-25	near lim.	42a
	B		29					
$(CD_3)_3CCl$	S		-59	-520	H_2O	10	lim.	24
	B		-179					
	B		(-198)					
	S	15	-147	- 34	70A	15	border-line	59
	S	30	- 76					
	S	45	- 29					
	B	15	-254					
	B	30	-159					
	B	45	- 58					
	S	45	-100	-114± 6[d]	70A	-15	near lim.	60
	S	60	- 40					
	B	45	-250					
	B	60	-116					

[a]Potential function used for calculation comes from S; ref. 66b, B; ref. 66a.

[b]Dihedral angle between COCl and naphthalene ring.

[c]$\Delta\Delta E = \Delta E_H - \Delta E_D$, $\Delta\Delta H = \Delta H_H - \Delta H_D$.

[d]Errors quoted are two times the standard deviation yielding 95% confidence limits.

CONCLUSIONS

Our temperature studies indicate that both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ contribute to secondary deuterium isotope effects. It is suggested that more reasonable correlations might be achieved by relating the relative contributions of hyperconjugation, nonbonded interactions and inductive effects to the $\Delta\Delta H^{\ddagger}$ term rather than the $\Delta\Delta G^{\ddagger}$ term.

Isotope effect measurements as functions of temperature are important not only to the question of the origin of isotope effects but also to correlations between isotope effects and reaction mechanism.

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A P P E N D I C E S

APPENDIX ONE

```
      PROGRAM DEV (INPUT,OUTPUT,TAPE2=INPUT,TAPE3=OUTPUT)
      DIMENSION RT(20),AR(12),DD(20)
  200 FORMAT(12A6)
  202 FORMAT(I5)
  204 FORMAT(F12.5)
  206 FORMAT(* *,20(F10.5,/,* *))
  208 FORMAT(/,12X,7HAVRATE=,F10.5,12X,13HSTD DEV OF K=,F10.5,//)
  100 FORMAT(*1*)
      WRITE(3,100)
   10       READ(2,200)(AR(I),I=1,12)
      READ(2,202)N
      IF(N)99,99,12
   12 READ(2,204)(RT(I),I=1,N)
      FN=N
      SUMRT=0.
            DO 18 I=1,N
   18 SUMRT=RT(I)+SUMRT
      AV=SUMRT/N
      DO 19 I=1,N
   19 DD(I)=(RT(I)-AV)**2
      SUMDD=0
      DO 20 I=1,N
   20 SUMDD=(DD(I)+SUMDD)
      SDK=SQRT(SUMDD/(N-1))
      WRITE(3,200)(AR(I),I=1,12)
      WRITE(3,202)N
      WRITE(3,206)(RT(I),I=1,N)
      WRITE(3,208)AV,SDK
      GO TO 10
   99 STOP
      END
```

APPENDIX TWO

```
      PROGRAM RRD (INPUT,OUTPUT,TAPE2=INPUT,TAPE3=OUTPUT)
      DIMENSION RH(20),SH(20),RD(20),SD(20),RR(20),AB(20),S(20)
  200 FORMAT(12A6)
  202 FORMAT(I5)
  203 FORMAT(2F10.5)
  204 FORMAT(4F10.5)
  206 FORMAT(/,10X,4H RH=,F10.5,2X,F10.5)
  207 FORMAT(/,10X,4H RD=,F10.5,2X,F10.5)
  208 FORMAT(///,12X,12H RATE RATIO=,F10.5,///,12X,15H STD DEV OF RR=,F1
     10.5,////)
  100 FORMAT(*1*)
      WRITE(3,100)
   10 READ(2,200)(AB(I),I=1,20)
      READ(2,202)N
      IF(N) 99,99,12
   12 READ(2,204)(RH(I),SH(I),RD(I),SD(I),I=1,N)
      FN=N
      DO 13 I=1,N
   13 RR(I)=RH(I)/RD(I)
      DO 14 I=1,N
   14 S(I)=RR(I)*SQRT((SH(I)/RH(I))**2+(SD(I)/RD(I))**2)
      WRITE(3,200)(AB(I),I=1,20)
      WRITE(3,206)(RH(I),SH(I),I=1,N)
      WRITE(3,207)(RD(I),SD(I),I=1,N)
      WRITE(3,208)(RR(I),S(I),I=1,N)
      GO TO 10
   99 STOP
      END
```

APPENDIX THREE

```
      PROGRAM HAF (INPUT,OUTPUT,TAPE2=INPUT,TAPE3=OUTPUT)
      DIMENSION R(99),RH(99),RT(99),RI(99),AB(12)
  200 FORMAT(12A6)
  202 FORMAT(I5)
  204 FORMAT(E12.5)
  206 FORMAT(///,5X,6H RATE=,E12.5,5X,11H HALF-LIFE=,F10.1,5X,12H THREE-
     1HALF=,F10.1,5X,10H INFINITY=,F10.1,///)
  100 FORMAT(*1*)
      WRITE(3,100)
   10       READ(2,200)(AB(I),I=1,12)
      READ(2,202)N
      IF(N)99,99,12
   12 READ(2,204)(R(I),I=1,N)
      FN=N
            DO 18 I=1,N
   18 RH(I)=.693/(R(I)*60)
      DO 19 I=1,N
   19 RT(I)=3*RH(I)
      DO 20 I=1,N
   20 RI(I)=13*RH(I)
      WRITE(3,200)(AB(I),I=1,12)
      WRITE(3,202)N
      WRITE(3,206)(R(I),RH(I),RT(I),RI(I),I=1,N)
      GO TO 10
   99 STOP
      END
```