SECONDARY KINETIC DEUTERIUM ISOTOPE EFFECTS IN THE BASE HYDROLYSIS OF ALKYL α-NAPHTHOATES

Thesis for the Degree of Ph. D.
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Robert Lawrence Turner

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ABSTRACT

SECONDARY KINETIC DEUTERIUM ISOTOPE EFFECTS

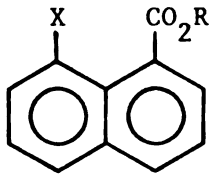
IN THE BASE HYDROLYSIS OF ALKYL α-NAPHTHOATES

by

Robert Lawrence Turner

Since Bartell (1) first proposed that non-bonded interactions may be important in secondary kinetic isotope effects, many efforts have been directed toward elucidating the nature and significance of these effects. In order to further investigate the role of non-bonded interactions in secondary kinetic deuterium isotope effects, we undertook a study of the temperature and solvent dependence of the base hydrolysis of the methyl 1-naphthoates I and II. The results obtained from this study dictated a further investigation of the isotope effects resulting from deuteration of the alcohol portion of methyl 1-naphthoate (Ic) and 2,2-dimethylpropyl 1-naphthoate (III).

The surprisingly small isotope effects observed for Ib (k_H/k_D = .979 ± .006 at 26°) and IIb (k_H/k_D = .971 ± .009 at 85°)



Ia: R = CH_3; X = H
Ib: R = CH_3; X = D
Ic: R = CD_3; X = H

IIa: R = CH_3; X = CH_3
IIb: R = CH_3; X = CD_3

IIIa: R = $CH_2C(CH_3)_3$; X = H
IIIb: R = $CD_2C(CH_3)_3$; X = H
IIIc: R = $CD_2C(CD_3)_3$; X = H
IIId: R = $CH_2C(CH_3)_3$; X = D

in 48.1% aqueous methanol indicated that secondary kinetic deuterium isotope effects arising from non-bonded interactions are insignificant when other electronic factors are operating. The thermodynamic parameters calculated from the temperature dependence of k_H/k_D demonstrated that the steric factors affected both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. These opposing effects resulted in a very small value of $\Delta\Delta G^{\ddagger}$. Explanations for these isotope effects in terms of competing steric effects are offered.

The large difference in the isotope effects for the base hydrolysis of Ic (k_H/k_D = 1.030 ± .008) and IIIb (k_H/k_D = 1.099 ± .010) in 54.1% aqueous dioxane at 25° indicated a change in the rate determining step for the hydrolysis of the neopentyl ester. The normal isotope effect for the hydrolysis of IIIb was explained in terms of an inductive effect on the relative stabilities of the developing alkoxide ion in the second step.

References

1. a. L. S. Bartell, J. Am. Chem. Soc., 83, 3567 (1961).
   b. L. S. Bartell, Iowa State Journal of Science, 36, 137 (1961).

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by

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To Beth

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INTRODUCTION

Secondary kinetic isotope effects resulting from deuterium substitution are believed to arise from differences in vibrational force constant changes in going from ground state to transition state. The electronic structure and hence the forces which bind atoms together are independent of the changes in atomic mass of nuclei caused by deuterium substitution. Therefore, the potential energy surfaces for X-H and X-D are invariant, i.e., the force constants are the same. Kinetic isotope effects are then the result of differences in nuclear mass on the motion of the nuclei within the same potential energy surface.

The difference in the anharmonic vibrational energies of X-H and X-D bonds is illustrated in Figure 1. From this figure we conclude that both the zero-point vibrational energy and the mean vibrational amplitude are greater for X-H than for X-D. This leads to different average bond lengths and angles in deuterated molecules.

The relation of force constant changes to the isotopic rate ratio, k_H/k_D, is illustrated in Figure 2. If the force constant decreases, the ZPE difference decreases, and a normal isotope effect is observed, $k_H/k_D > 1$. If the force constant increases, the ZPE difference increases, and an inverse isotope effect is observed, $k_H/k_D < 1$. The direction of the force constant change can be determined experimentally. The problem, however, is

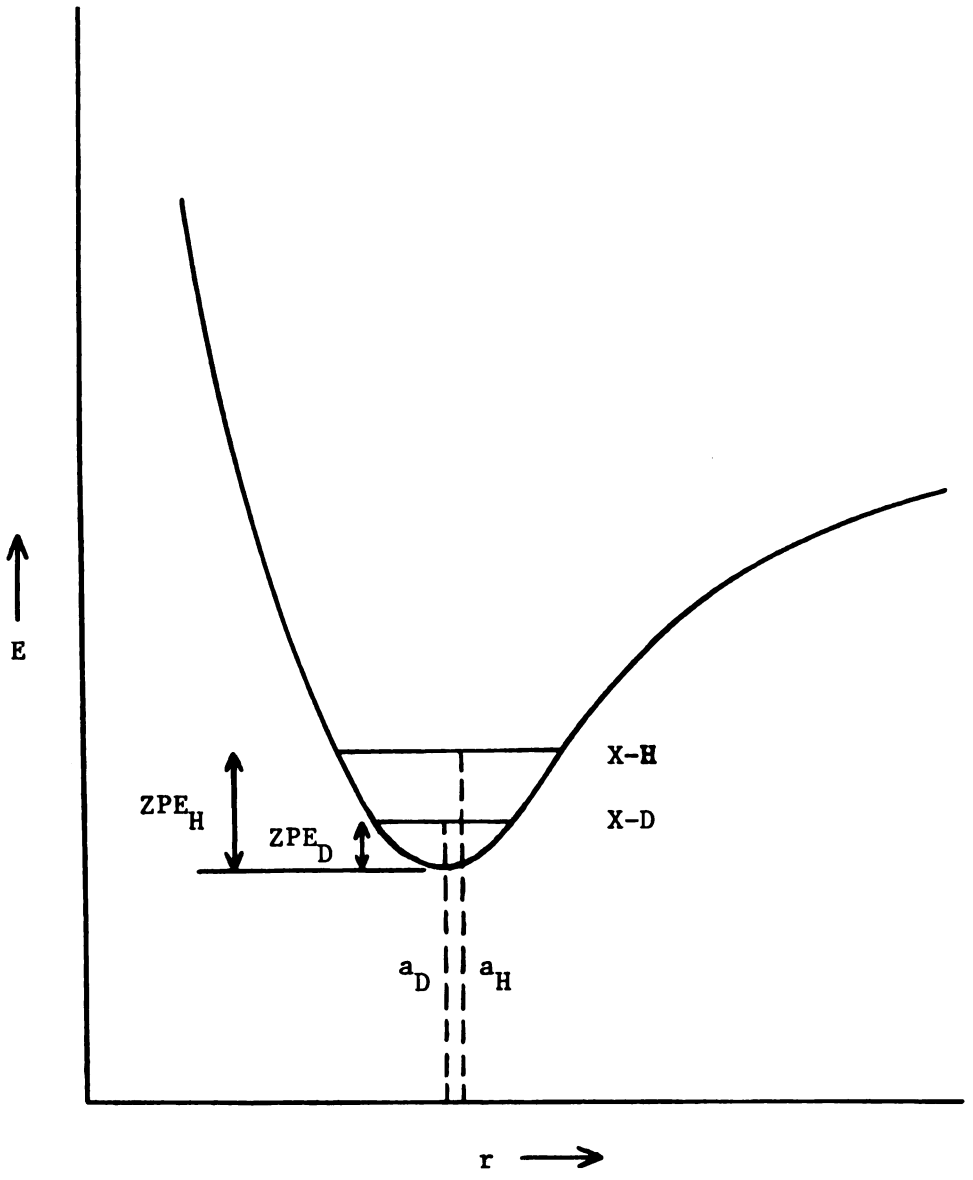
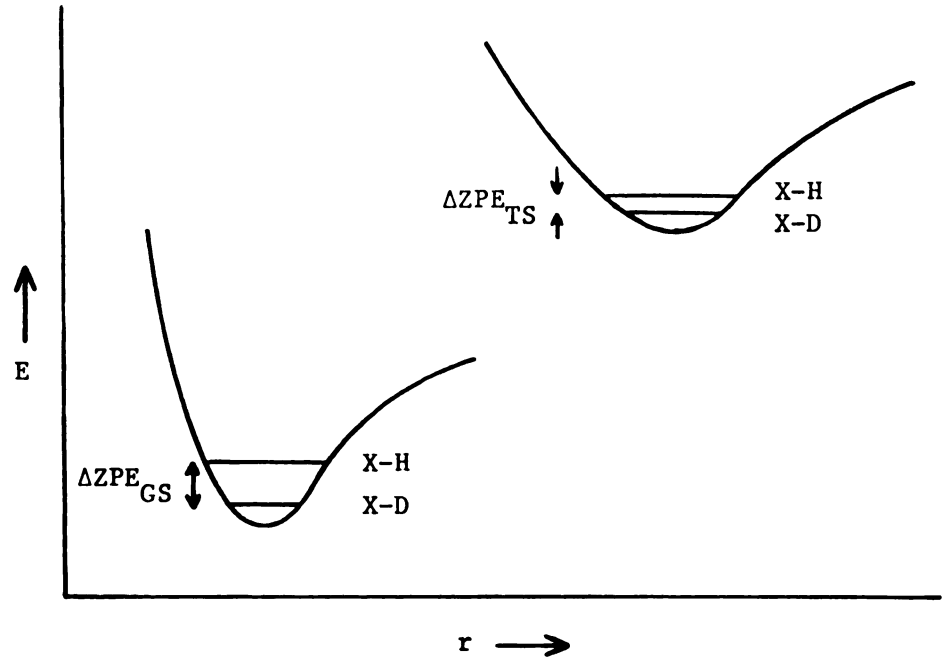


Figure 1: Vibrational potential energy function for X-H and X-D bonds (2).

A. Decrease in force constant; $\Delta\Delta ZPE < 0$, $k_H/k_D > 1$



B. Increase in force constant; $\Delta\Delta ZPE > 0$, $k_H/k_D < 1$

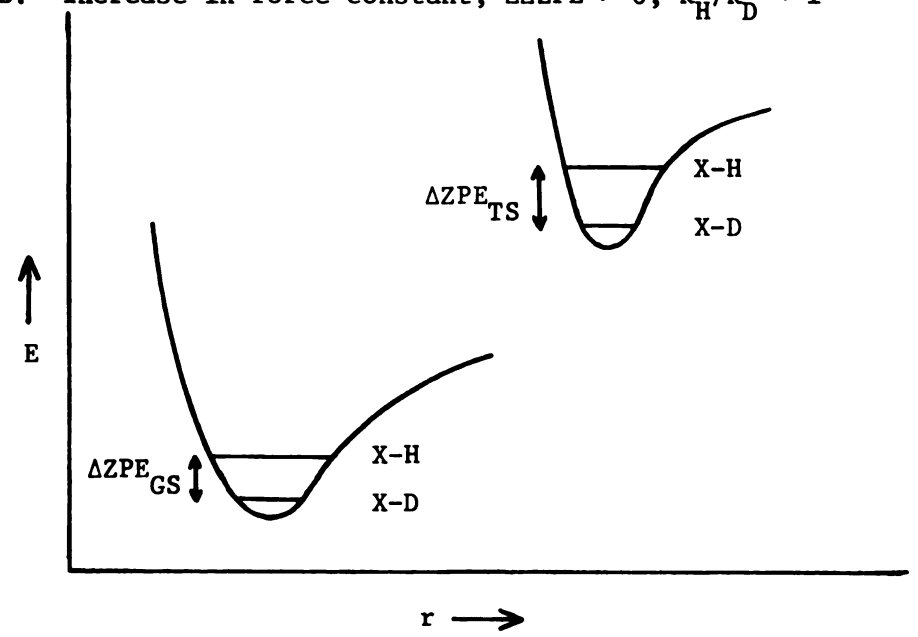


Figure 2: Relation of force constant changes to ZPE differences (2).

interpreting the observed force constant changes in physical organic terms.

The main reason for this difficulty is our inability to determine the exact geometry of the transition state for a given reaction by extrakinetic methods. Since many factors are involved in the determination of a kinetic isotope effect, e.g., induction, hyperconjugation, non-bonded interactions, hybridization, and solvation, these factors are normally impossible to separate from one another. The correlation of a kinetic isotope effect with a reaction mechanism is, therefore, a rather complex problem. As a result, there is little agreement as to the origin of force constant changes observed in secondary kinetic isotope effects. The factors generally applied in interpreting secondary kinetic isotope effects are induction, hyperconjugation, and non-bonded interactions. These factors can be related in a qualitative fashion to changes in the force constants.

Measurements of dipole moments (3) and NMR studies (4,5) have shown that deuterium is more electropositive than hydrogen. Molecular refraction (6) and optical activity data (7) have also demonstrated that C-D is less polarizable than C-H. The principal factors involved appear to be the anharmonicity of the vibrations and the difference in average bond lengths and angles between deuterated and undeuterated molecules. From these data on the physical properties of deuterated compounds one concludes that the electron density about carbon is greater in the C-D bond than in the C-H bond. Therefore, if a positive charge is produced near the site

of deuteration, C-D should stabilize it better than C-H. Consequently, an inverse isotope effect should be observed.

The most pertinent chemical evidence for the greater inductive effect of deuterium arises from isotope effects on the acidities of deuterated acids. These results are summarized in Table 1. It should be pointed out however, that although the observation of

Table 1: Isotope effects on the acidities of organic acids in water.

Acid	K_H/K_D
DCO_2H	$1.070 \pm .008$[a], 1.084[e]
CD_3CO_2H	$1.032 \pm .002$[a]
$(CD_3)_3CCO_2H$	$1.042 \pm .003$[b]
$CH_3CD_2CO_2H$	1.08[c]
$CD_3CH_2CO_2H$	1.01[c]
$C_6H_5CD_2CO_2H$	1.12[c]
$C_6D_5CO_2H$	$1.024 \pm .006$[a,b]
C_6D_5OH	$1.12 \pm .02$[b]
$C_6D_5NH_3^+$	$1.06 \pm .02$[d]
$2,4,6\text{-}C_6H_2D_3NH_3^+$	$1.04 \pm .02$[d]
$3,5\text{-}C_6H_3D_2NH_3^+$	$.99 \pm .02$[d]

[a]Reference 8. [b]Reference 9. [c]Reference 10. [d]Reference 1. [e]Reference 13.

normal isotope effects for these dissociation reactions confirm the greater inductive effect of deuterium, any quantitative application of these effects is meaningless, since substituent effects on weak carboxylic acids operate through changes in entropy, i.e., $\Delta\Delta H^{o} \simeq 0$. Also, pK_a differences are known to be quite sensitive to both solvent polarity and temperature (12).

Since the inductive effect of deuterium located at least one carbon atom removed from the reaction center is very small and inseparable from other factors, inductive effects are seldom applied in correlating secondary kinetic isotope effects and reaction mechanisms.

Halevi has stated that hyperconjugation with C-D is less effective than with C-H due to C-D being less polarizable (11). However, Streitweiser and coworkers (16c) have pointed out that an increase in hyperconjugation in the transition state results in a weakening of the C-H force constant. Therefore, a normal isotope effect would be predicted, Figure 2, without invoking differential hyperconjugation for C-H and C-D.

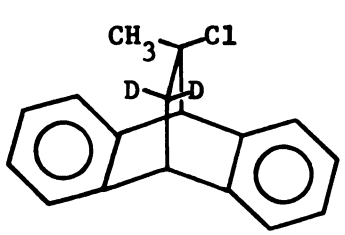
Although the role of hyperconjugation in secondary kinetic isotope effects has been questioned, substantial evidence has been accumulated which makes this role quite prominent. Shiner and coworkers (14) have reported significant rate retardations for the solvolysis of deuterated t-butyl chlorides. Their results are summarized in Table 2. The variation of k_H/k_D with the amount of deuterium substitution supports the contention that hyperconjugation is important in this mechanistically limiting reaction. Furthermore, the slight increase in k_H/k_D per deuterium atom is also consistent

Table 2: Isotope effects for the solvolysis of t-butyl chloride in 60% aqueous ethanol at 25° (14).

Compound	k_H/k_D	k_H/k_D per D
$(CH_3)_2CClCH_2D$	1.092	1.092
$(CH_3)_2CClCHD_2$	1.202	1.096
$(CH_3)_2CClCD_3$	1.330	1.100
$(CD_3)_2CClCH_3$	1.710	1.102
$(CD_3)_3CCl$	2.327	1.103

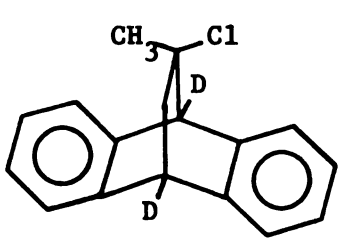
with the conformational dependence of hyperconjugation.

The dependence of hyperconjugation on the spatial orientation of the C-H bond was elegantly demonstrated by Shiner and Humphrey (15) in the solvolysis of the deuterated bicyclooctane derivatives I and II in 60% aqueous ethanol at 45°. The normal isotope effect



I

k_H/k_D = 1.14 ± .01



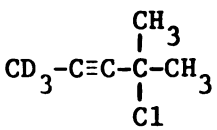
II

k_H/k_D = .986 ± .01

for compound I is consistent with hyperconjugative stabilization in the transition state. Since such stabilization is impossible

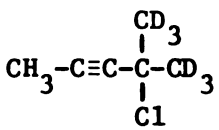
when the C-H bond is in the nodal plane of the developing vacant p orbital, no normal isotope effect is observed for II. The small inverse isotope effect presumably arises from the greater inductive effect of the C-D bond over the C-H bond (16).

Shiner and Kriz (19) have also shown that hyperconjugation can be transmitted through an unsaturated linkage. In the solvolysis of the unsaturated compound III, the site of isotopic substitution is too far removed from the reaction center for inductive or steric effects to be important. Consequently, the observed normal isotope effect is ascribed to hyperconjugation through the π-orbitals of the acetylenic bond.



III

$k_H/k_D = 1.092 \pm .001$



IV

$k_H/k_D = 1.655 \pm .004$

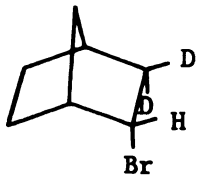
Shiner and coworkers (20) found rather large variations in the β-isotope effect for the solvolysis of <u>para</u>-substituted 1-phenylethyl chlorides, Table 3. The large α-isotope effect is characteristic of reactions whose mechanisms are limiting. Although the α-isotope effect remains essentially constant throughout the series of substituents, indicating no change in the mechanism of the reaction, the β-isotope effect varies considerably. As the electron releasing ability of the substituent increases, the amount of positive charge present at the reaction center decreases, thus

the need for hyperconjugative stabilization from the methyl group is lowered. Consequently, k_H/k_D decreases.

Table 3: Isotope effects for the solvolysis of <u>para</u>-substituted 1-phenylethyl chlorides in 50% aqueous ethanol at 25° (20).

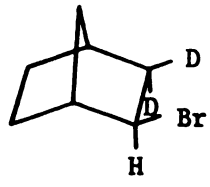
Substituent	k_H/k_D (α)	k_H/k_D (β)
p-OCH_3	1.157	1.113
p-OC_6H_5	1.157	1.164
p-CH_3	1.157	1.200
p-F	1.152	1.211
m-CH_3	1.151	1.222
p-H	1.153	1.224

This dependence of hyperconjugation on electron demand has been used to support the nonclassical norbornyl cation (23). The smaller isotope effect for the solvolysis of the <u>exo</u>-bromide, VI,



V

k_H/k_D = 1.16



VI

k_H/k_D = 1.04

over that of the endo-bromide, V, was attributed to charge delocalization by σ-participation which lowers the requirement for C-H hyperconjugation from the 3-position. Similar results were obtained for the solvolysis of the 3,3-dideuterio-2-norbornyl brosylates (24).

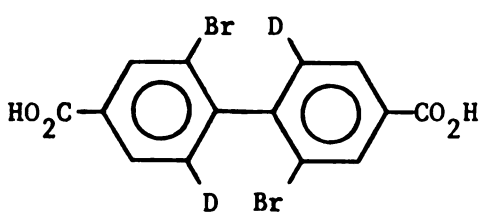
Brown and McDonald (26) have reported inverse isotope effects for the reaction of alkyl iodides with methylpyridines, Table 4. Since no effect was observed for 3-methyl-$\underline{d}_3$-pyridine or 4-methyl-$\underline{d}_3$-pyridine, the authors concluded that the inverse isotope effect for 2-methyl-$\underline{d}_3$-pyridine was steric in origin. This conclusion was supported by the observation of an increase in k_D/k_H with the size of the alkyl iodide and an increase in k_D/k_H for 2,6-dimethyl-$\underline{d}_6$-pyridine.

Table 4: Isotope effects for the reaction of alkyl iodides with methylpyridines in nitrobenzene (26).

Compound	Alkyl iodide	Temp.(°C)	k_D/k_H
4-Methyl-$\underline{d}_3$-pyridine	CH_3I	25	1.001 ± .003
3-Methyl-$\underline{d}_3$-pyridine	CH_3I	25	1.009 ± .002
2-Methyl-$\underline{d}_3$-pyridine	CH_3I	25	1.030 ± .003
	CH_3CH_2I	75	1.036
	$(CH_3)_2CHI$	100	1.058
2,6-Dimethyl-$\underline{d}_6$-pyridine	CH_3I	25	1.095 ± .003
	CH_3CH_2I	75	1.072
	CH_3CH_2I	100	1.070

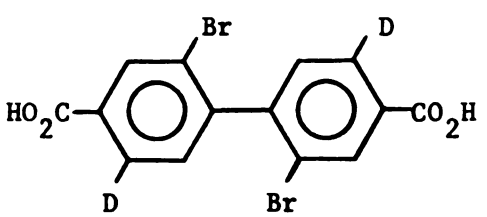
Bartell, like Brown, has stated that secondary isotope effects can be explained in terms of non-bonded interactions (28). The basis for this argument is that repulsions involving deuterium atoms are smaller than those for hydrogen due to the smaller mean-square amplitude of vibration of C-D. The effective size of deuterium is, therefore, smaller than that of hydrogen. Consequently, a release of steric compression in the transition state will yield a normal isotope effect, while an increase in steric compression will result in an inverse effect. Although Bartell has demonstrated that non-bonded interactions cannot be ignored when correlating secondary kinetic isotope effects, it is often not known whether these interactions are repulsive or attractive. Quantitative predictions are, therefore, unjustified. This is particularly true in view of our lack of knowledge concerning the geometry of the transition states. Bartell, himself, has noted that it is impossible to separate steric effects from other electronic factors.

The inverse isotope effect reported by Melander and Carter (29) for the racemization of 2,2'-dibromo-4,4'-dicarboxy-6,6'-biphenyl-$\underline{d}_2$, VII, in ethanol was attributed to non-bonded interactions. The



VII

$k_D/k_H = 1.18 \pm .03$



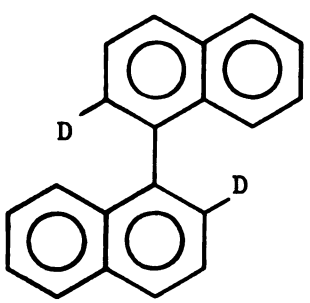
VIII

$k_D/k_H = 1.02 \pm .02$

possibility of the isotope effect originating partially from the greater inductive effect of deuterium on π-orbital overlap was negated with the observation of no isotope effect outside of experimental error for the racemization of the 5,5'-dideuterio derivative, VIII.

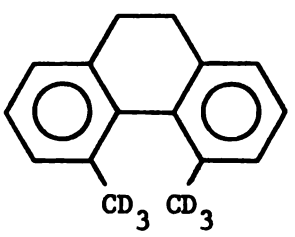
Another example of the importance of steric interactions was reported by Carter and Dahlgren (30) for the racemization of 2,2'-binaphthyl-$\underline{d}_2$, IX. The increase in rate resulting from deuterium substitution was ascribed to an increase in the force constant for the in-plane C-H bending vibration. Mislow and coworkers (31), having found a large inverse isotope effect for the racemization of the sterically non-planar ring system X, concluded:

> It does not seem likely that steric factors are responsible to a major extent for deuterium isotope effects observed in S_N1 reactions . . . since the hydrogens are far less compressed than in these systems studied . . . therefore, non-bonded interactions are operative only under conditions of severe crowding.



IX

k_D/k_H = 1.186; 36°



X

k_D/k_H = 1.137; 42°

A similar conclusion was drawn by Karabatsos and coworkers (32) in the comparison of calculated and experimental isotope effects for some limiting solvolysis reactions. Their results are summarized in Table 5. Using the potential functions of Scott and Scheraga (33), the authors employed Bartell's procedure (28) to calculate isotope effects based on non-bonded repulsions. In those systems where hyperconjugation was possible, their calculations greatly underestimated the experimental isotope effects. They concluded that less than 10% of the observed isotope effect is due to non-bonded interactions when hyperconjugation is possible.

Table 5: Comparison of calculated and experimental isotope effects for some limiting solvolysis reactions (32).

Compound	k_H/k_D (calc.)	k_H/k_D (exp.)
α-naphthylcarbinyl-α,α-$\underline{d}_2$ chloride	1.30	1.30
acetyl-$\underline{d}_3$ chloride	.98	1.68
$\underline{t}$-butyl-$\underline{d}_9$ chloride	1.10	2.39

Hakka and coworkers (34) demonstrated that the isotope effect for the solvolysis of $\underline{t}$-butyl-$\underline{d}_9$ chloride, Table 6, was solvent independent. They concluded that there was no significant interaction of solvent with the developing cation in this solvolysis reaction. These findings were confirmed by Frisone and Thornton (35) who studied the effect of a series of solvents with the same ionizing power.

Table 6: Solvent and temperature dependence of the isotope effects for the solvolysis of t-butyl-d_9 chloride (34).

Temp.(°C)	k_H/k_D (water)	k_H/k_D (50% ethanol)
5	2.55	2.542
10	2.53	2.505
15	2.48	2.465
20	2.45	2.419
25		2.387
30		2.345

In the solvolysis of p-alkylbenzhydryl chlorides, Shiner and Verbanic (21) have reported significant changes in the isotope effects with solvent, Table 7. The observed normal isotope effect was attributed to hyperconjugation through the phenyl ring. They suggested that the decrease in k_H/k_D with increasing solvent polarity was due to a greater dispersal of the developing charge through solvation, resulting in a decrease in the effectiveness of hyperconjugation. Similarly, the decrease in k_H/k_D with greater chain branching was ascribed to an increase in steric hindrance to solvent participation at the site of isotopic substitution.

Schubert prefers to explain these results in terms of steric hindrance to solvation at the para-position of the phenyl ring (22). The decrease in k_H/k_D with increasing solvent polarity is ascribed to an increase in solvent stabilization of the delocalized charge,

thereby, lowering the demand for hyperconjugative stabilization.

Table 7: Solvent dependence of the isotope effects for the solvolysis of p-alkylbenzhydryl chlorides (21).

Compound	90% Ethanol	80% Acetone	70% Acetone	67% Acetone
$p\text{-}CD_3C_6H_4CH\phi Cl$	1.025	1.058	1.038	1.021
$p\text{-}CH_3CD_2C_6H_4CH\phi Cl$	1.009	1.025	1.019	1.012
$p\text{-}(CH_3)_2CDC_6H_4CH\phi Cl$	.998	1.006		

Evans (2) found that the β-isotope effect for the solvolysis of acetyl-$\underline{d}_3$ chloride depended strongly on solvent, Table 8. Although the change in k_H/k_D with solvent composition may be related to a change in mechanism, the data definitely indicate that solvent may play an important role in determining the magnitude of a secondary kinetic isotope effect.

The role of solvation in secondary kinetic isotope effects is still generally ignored. This is not due to the unimportance of solvation, but to the lack of quantitative data on this subject. It is, therefore, important that the possible dependence of an isotope effect on solvation be considered when interpreting isotope effects. In Halevi's words (11): "It is an oversimplification to disregard solvent when dealing with small effects in highly polar solutions."

Table 8: Solvent dependence of the β-isotope effect for the solvolysis of acetyl-$\underline{d}_3$ chloride (2).

Solvent (% Acetone/Water)	Temp.(°C)	k_H/k_D
75	-31.0	1.135 ± .020
80	-31.0	1.122 ± .010
85	-31.0	1.122 ± .013
90	-28.9	1.044 ± .009
95	-25.5	1.004 ± .004

The temperature dependence of the isotope effect for the solvolysis of $\underline{t}$-butyl-$\underline{d}_9$ chloride reported by Hakka and coworkers, Table 6, conforms closely to the normal approximation that $\Delta\Delta G^{\ddagger} = \Delta\Delta H^{\ddagger}$. Leffek and coworkers (36), however, found an unusual temperature independence of the isotope effect for the solvolysis of isopropyl tosylate, isopropyl methanesulfonate, and isopropyl bromide, Table 9. This temperature independence was found to arise entirely from entropy differences dominating $\Delta\Delta G^{\ddagger}$ and, therefore, could not be explained in terms of zero-point energy differences alone. Calculations indicated that differences in the six-fold barriers to internal rotation between deuterated and undeuterated substrates would tend to cancel the enthalpy difference and create an entropy difference of the magnitude observed. The temperature independence was then attributed to a fortuitous cancellation of the $\Delta\Delta H^{\ddagger}$ arising from zero-point energy sources and internal

rotation effects. This type of rationalization is supported by the theoretical analysis of Wolfsberg and Stern (37) who demonstrated that compensating effects in force constant changes may lead to temperature independent k_H/k_D values.

Table 9: Temperature independence of the isotope effects for the solvolysis of isopropyl compounds in water (36).

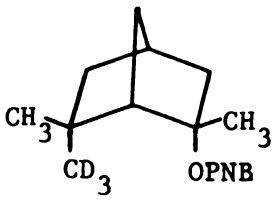
Compound	Temp. Range	k_H/k_D
Isopropyl-$\underline{d}_6$ tosylate	6° to 30°	1.54
Isopropyl-$\underline{d}_6$ methanesulfonate	5° to 30°	1.55
Isopropyl-$\underline{d}_6$ bromide	40° to 70°	1.32

An unusual temperature dependence was reported by Evans (2) for the solvolysis of acetyl-$\underline{d}_3$ chloride in 90% aqueous acetone.

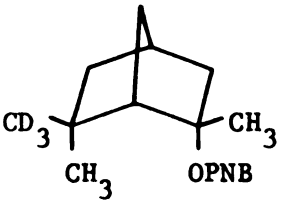
Table 10: Temperature dependence of the isotope effect for the solvolysis of acetyl-$\underline{d}_3$ chloride in 90% aqueous acetone (2).

Temperature (°C)	k_H/k_D
- 9.54	1.070 ± .010
-15.72	1.072 ± .015
-22.01	1.059 ± .002
-28.88	1.044 ± .009
-33.68	1.026 ± .010

This temperature dependence, an increase in k_H/k_D with increasing temperature, was found to be solvent dependent, since it was absent in more polar solvents, Table 10. A similar temperature dependence was reported by Smith (38) for the solvolysis of the endo-norbornyl p-nitrobenzoates, XI and XII, in 80% aqueous ethanol. This temperature dependence, which predicts an inversion in k_H/k_D at lower temperatures, was attributed to large entropy contributions to $\Delta\Delta G^{\ddagger}$.



XI



XII

Temp.(°C)	k_H/k_D (XI)	k_H/k_D (XII)
100	.997 ± .015	1.011 ± .013
125	1.003 ± .014	1.017 ± .014
142	1.027 ± .013	1.043 ± .013
150	1.026 ± .010	1.049 ± .011

It would appear that a precise evaluation of secondary kinetic isotope effects demands an accurate identification of the force constant changes in the activation process. Furthermore, any such evaluation must include both the temperature and solvent dependence of the isotope effects measured.

In order to further investigate the role of non-bonded interactions in secondary kinetic isotope effects, we undertook to study

the temperature and solvent dependence of the base hydrolysis of methyl 1-naphthoate, methyl 8-methyl-1-naphthoate, and their 8-deuterated analogs. The results obtained from this study dictated a further investigation of the isotope effects resulting from deuteration of the alcohol portion of methyl 1-naphthoate and 2,2-dimethylpropyl 1-naphthoate.

EXPERIMENTAL

I. Kinetics

A. Preparation of Solvents

Methanol: Methanol was purified in two steps. First, three liters of methanol (Baker Reagent Grade) was refluxed for 12 hours with a mixture of 150 ml furfural and 375 ml 10% aqueous sodium hydroxide. The resulting solution was fractionally distilled through a 30 cm Vigreaux column. Of the distilled methanol, 150 ml was reacted with 30 g of powdered magnesium until all of the magnesium had dissolved. Then, two liters methanol was added, refluxed for four hours, and fractionally distilled through a 50 cm Vigreaux column (39).

Water: Water was refluxed for 12 hours while bubbling nitrogen through the liquid and fractionally distilled through a 30 cm Vigreaux column.

1,4-Dioxane: Dioxane was purified according to the procedure outlined by L. F. Fieser in Experiments in Organic Chemistry (39).

Solvent Mixtures: The various solvent mixtures were prepared by weight ratios using a Torbal balance (Torsion Balance Co., Model PL-2). Sodium hydroxide (Baker Reagent Grade) was added to the solvent mixtures and the base concentrations determined by

titration against Fisher Primary Standard potassium hydrogen phthalate by using phenolphthalein as indicator. The concentrations of sodium hydroxide in the various solvent mixtures are reported in Table 11.

Table 11: Solvent mixtures used in the kinetic studies.

Solvent (w/w)	Mole fraction water	[NaOH] (moles/liter)
10.0% Methanol/Water	.947	.1990 ± .0004
30.0% Methanol/Water	.806	.2029 ± .0004
48.1% Methanol/Water	.659	.2031 ± .0004
48.1% Methanol/Water[a]	.659	.1980 ± .0008
80.0% Methanol/Water	.308	.2007 ± .0008
54.1% Dioxane/Water	.806	.1943 ± .0003

[a]Solvent used for the base hydrolysis of methyl 8-methyl-1-naphthoates.

B. Kinetic Apparatus

A Unicam SP.800 ultraviolet spectrophotometer equipped with an SP.825 program controller, a mains relay, and a Sargent Recorder (Model SR) was used for all absorbance measurements. Except for the hydrolyses of the methyl 8-methyl-1-naphthoates, all kinetic runs were followed continuously by using the automatic program controller.

C. Measurement of Time

A Precision Scientific electric digital timer (Model No. 69235) accurate to 0.01 minute was used for the measurement of time.

D. Temperature Control

The constant temperature bath consisted of a 16 liter glass jar insulated on the sides and bottom by at least one inch of vermilite packing supported within a plywood box. The top of the bath was covered with a sheet of 1/4 inch asbestos. The bath was equipped with a mechanical stirrer (Talboys Instrument Corp., Model No. 104), a Teel pump (Dayton Electrical Mfg. Co., Model No. 1P731), a Beckman differential thermometer, a 125 watt heating blade (Cenco), an electronic relay (Precision Scientific Co., Model No. 62690), and a mercury micro-set thermoregulator (Precision Scientific Co., Model No. 62541). At temperatures below 35°, cooling was provided by the circulation of cold tap water through two feet of 1/4 inch copper tubing supported in the bath. A continuous heating coil was used for temperatures above 35°. The continuous cooling or heating was regulated in conjunction with the intermittent heating provided by the electronic relay in order to obtain the desired temperature. Bath temperatures constant to ± .006° were obtained over the range of 15° to 69°. The temperatures of the cell compartment in the spectrophotometer were constant to ± .012°.

The constant temperature bath used for temperatures $\geq$ 70° was constructed in the same manner as outlined above except the Teel pump was excluded and a 3 x 5 inch hole was made in the asbestos

for the insertion of a wire basket to hold the quartz ampules.

E. Temperature Determination

The temperatures of the bath and cell compartment were measured by using a Hewlett Packard quartz thermometer (Model No. 2801A).

F. Rate Determinations

1. Methyl and 2,2-Dimethylpropyl 1-naphthoates:

Hydrogen and deuterium kinetic runs were performed randomly. Solvent (3.3 ml) was placed in the UV cell and allowed to thermally equilibrate within the cell compartment for two hours. Approximately 6 µl of a 0.10M ester solution was injected into the cell, shaken, and readings began immediately. Twenty five to sixty absorbance readings were made at 325 mµ over the first 2.5 to 3 half-lives, depending on the rate of the reaction. The infinite value was measured after ten half-lives. The absorbance range measured was .40 to .01 absorbance unit.

2. Methyl 8-methyl-1-naphthoates:

Hydrogen and deuterium kinetic runs were performed alternately. Approximately 3.8 ml of the reaction mixture was placed in each of eleven quartz ampules. The ampules were sealed and simultaneously placed in the constant temperature bath. After allowing seventy minutes for thermal equilibration, the ampules were removed at selected time intervals over a range of 0.6 half-life and cooled quickly in an ice bath. The ampules were stored at 0° until the

completion of each run (38).

Of each ampule, 3.00 ml was extracted with 10.00 ml cyclohexane (Baker GC-Spectrophotometric Quality Solvent). The cyclohexane solution was dried over anhydrous potassium carbonate (Mallinckrodt Analytical Reagent) and the absorbance measured against a blank solution at 310 mμ. There was no absorbance by a reaction mixture treated in this manner after sixteen half-lives. The absorbance range measured was .42 to .25 absorbance unit.

The absorbance was found to follow Beer's Law over the concentration ranges measured for all the esters studied. Examples of typical runs are illustrated in Figures 3 and 4.

G. Treatment of Data

First order rate constants were determined by solving the rate expression

$$(A_t - A_\infty) = A_o \exp(-kt) - A_\infty \exp(-kt)$$

A_t = absorbance at time t

A_∞ = absorbance at infinite time

by using a least squares curvefitting program, KINFIT (40).

The average rate constants reported are the mean average of the independent determinations. If an individual rate determination appeared questionable, then the 4d rule was applied. That is, if a given determination deviated from the mean by more than four times the mean deviation of the remaining determinations, it was discarded.

The rate ratios, k_H/k_D, are the ratios of the corresponding means. The reported deviations in k_H/k_D were calculated by using the

expression (41)

$$\sigma_{k_H/k_D} = [\sigma_H^2/k_D^2 + k_H^2\ \sigma_D^2/k_D^4]^{1/2}$$

Thermodynamic parameters were determined from a solution of ln k/T versus 1/T by using a least squares program, AKTIV. A solution of ln k_H/k_D versus 1/T with the least squares program HANDS and the least squares curvefitting program KINFIT yielded values for $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$.

II. Syntheses

A. Methyl 8-deuterio-1-naphthoate

1. Anhydro-8-hydroxymercuri-1-naphthoic acid (42)

To a five liter, three-necked round-bottomed flask (equipped with mechanical stirrer, reflux condenser, and addition funnel) was added 142.4 g (.72 mole) 1,8-naphthalic anhydride in a solution of 100.8 g (2.52 mole) sodium hydroxide and 3500 ml water. After heating the mixture slowly to reflux, a solution of 252.0 g (.79 mole) mercuric acetate, 108 ml glacial acetic acid, and 540 ml water was added dropwise. The resulting mixture was refluxed for forty hours. The hot mixture was filtered and the precipitate washed with six 1000 ml portions water, 1000 ml ethanol, and 500 ml ether. The white solid was dried in an oven to constant weight; yield = 265 g (99%).

2. 8-Bromo-1-naphthoic acid (42)

A mixture of 130.1 g (.35 mole) anhydro-8-hydroxymercuri-1-naphthoic acid, 565 ml glacial acetic acid, and 95 ml water was

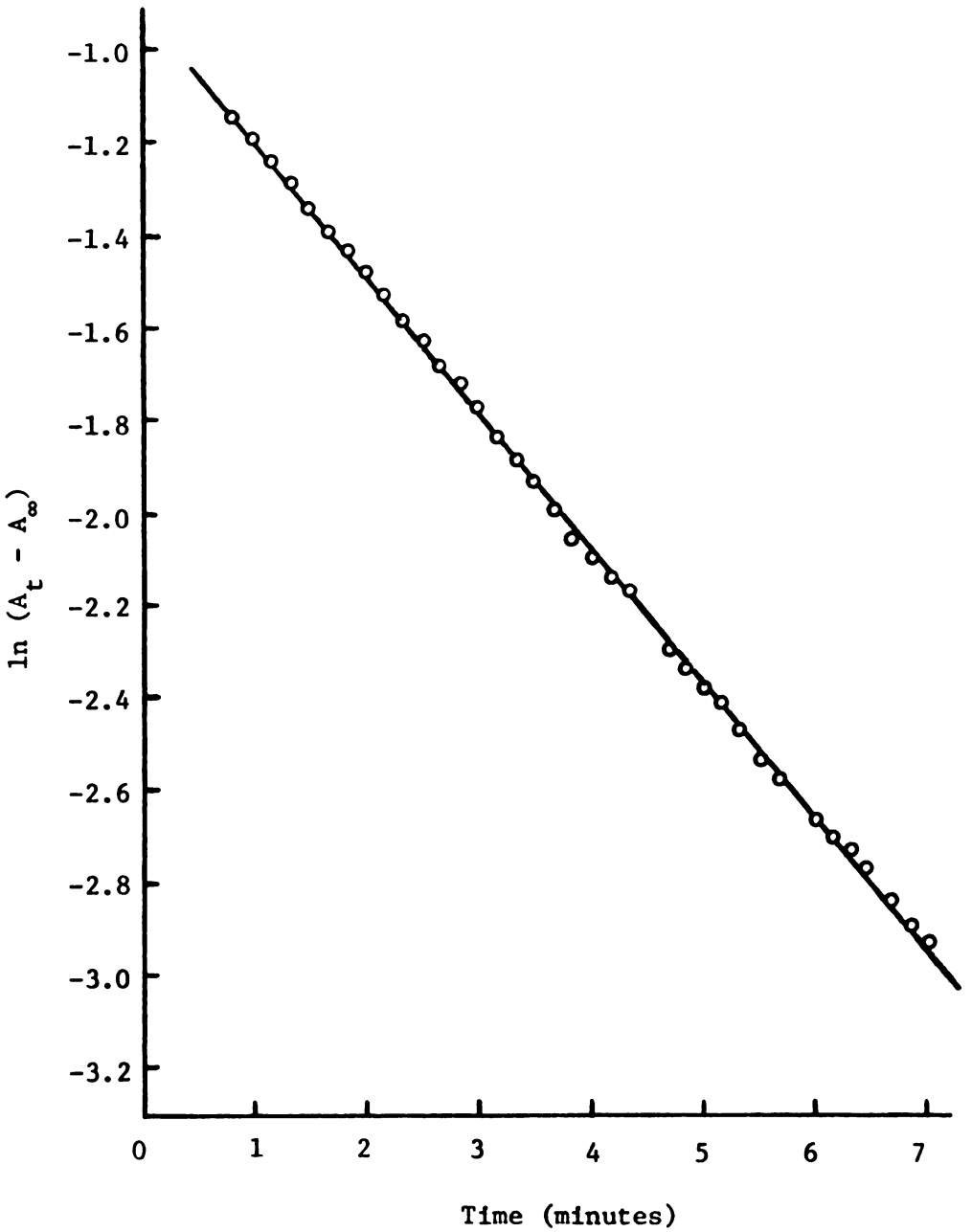


Figure 3: Run No. 204, Methyl 1-naphthoate, 54.1% Dioxane, .194M Sodium Hydroxide, 50.004°

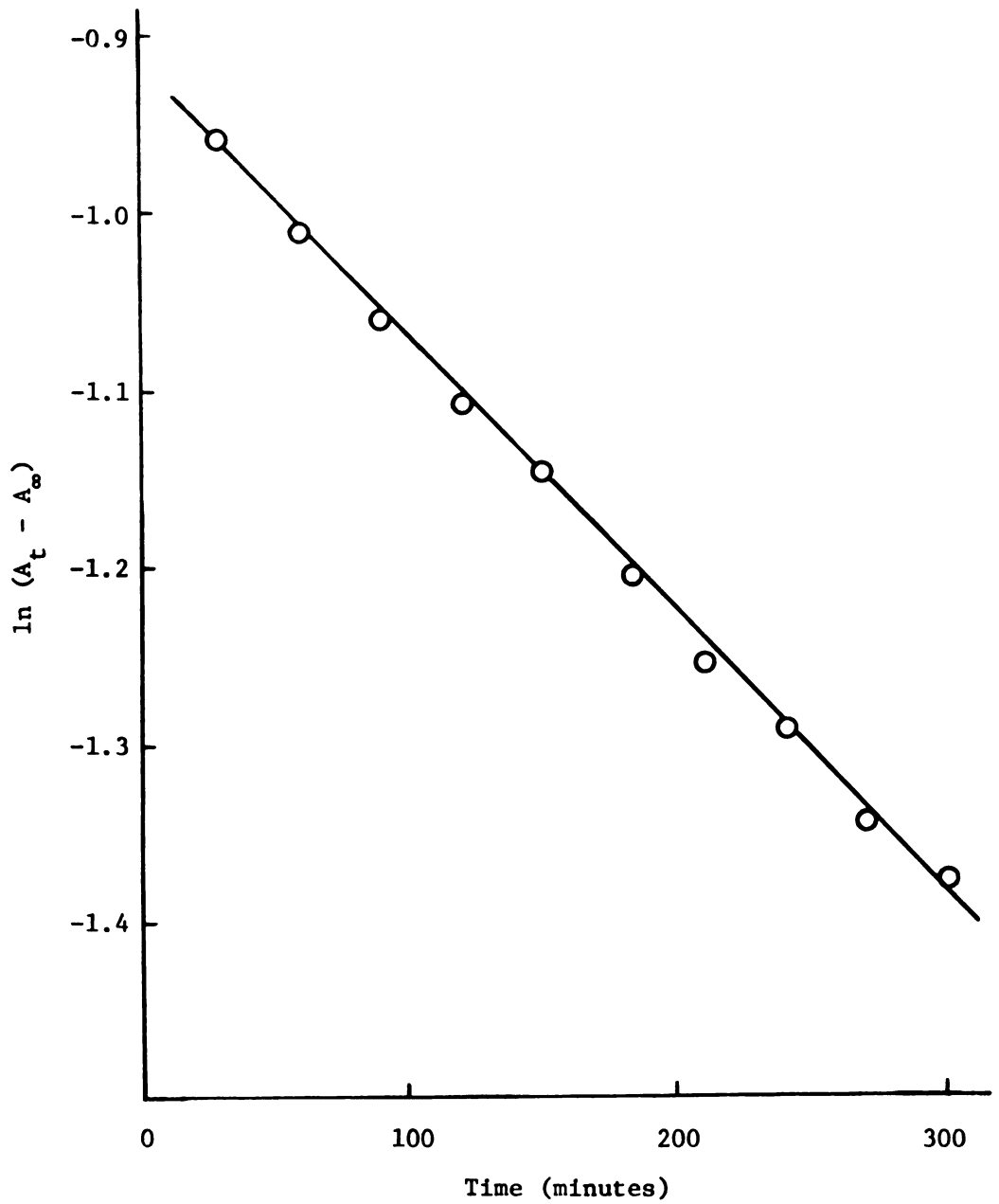


Figure 4: Run No. 312, Methyl 8-methyl-1-naphthoate, 48.1% Methanol, .198M Sodium Hydroxide, 100.384°

added to a two liter, three-necked round-bottomed flask (equipped with mechanical stirrer, addition funnel, and thermometer). While cooling in an ice bath, a solution of 64.0 g (.40 mole) bromine in 285 ml concentrated aqueous sodium bromide was added dropwise. The mixture was heated slowly to 90° and the resulting yellow solution poured onto 900 g ice/900 ml water. The aqueous mixture was extracted with three 600 ml portions ether. The combined ether solutions were extracted with three 480 ml portions 10% aqueous sodium hydroxide. The combined aqueous extracts were acidified with concentrated hydrochloric acid and filtered. The white precipitate was washed with six 500 ml portions cold water and recrystallized from 30% aqueous ethanol; yield = 61.5 g (70%), mp 175-6°.

3. Silver 8-bromo-1-naphthoate

To a one liter, round-bottomed flask (equipped with magnetic stirrer and addition funnel) was added a solution of 30.0 g (.12 mole) 8-bromo-1-naphthoic acid, 6.6 g (.062 mole) sodium carbonate, and 600 ml water. A solution of 20.8 g (.122 mole) silver nitrate in 180 ml water was added dropwise and the resulting mixture stirred at room temperature for one hour. The white silver salt was filtered and washed with two 150 ml portions water, 150 ml methanol, and 150 ml acetone. The solid was dried in a vacuum desiccator over phosphorous pentoxide; yield = 40.7 g (95%).

4. 8-Bromo-1-iodonaphthalene

A suspension of 38.0 g (.106 mole) silver 8-bromo-1-naphthoate in 800 ml dry carbon tetrachloride was added to a three

liter, three-necked round-bottomed flask (equipped with mechanical stirrer, reflux condenser, addition funnel, and calcium sulfate drying tube). A solution of 27.9 g (.11 mole) iodine in 1700 ml dry carbon tetrachloride was added dropwise and the resulting mixture refluxed for ten hours. The solution was filtered and the filtrate washed with two 500 ml portions water, 300 ml saturated aqueous sodium bicarbonate, 400 ml 20% aqueous sodium thiosulfate, and 300 ml water. After drying the carbon tetrachloride solution over anhydrous magnesium sulfate, the solvent was removed by distillation and the residue recrystallized from 90% aqueous ethanol; yield = 20.0 g (60%), mp 99-100°.

5. 8-Deuterio-1-bromonaphthalene (43)

To a 250 ml, three-necked round-bottomed flask (equipped with mechanical stirrer, reflux condenser, addition funnel, and calcium sulfate drying tube) was added a mixture of 1.25 g (.051 mole) powdered magnesium, 60 ml anhydrous ether, 16.5 g (.050 mole) 8-bromo-1-iodonaphthalene, and one crystal iodine. The mixture was heated gently until the reaction began, then stirred at room temperature until all of the magnesium was dissolved. The reaction was cooled in an ice bath and 6.5 ml D_2O was added dropwise. After stirring the mixture overnight at room temperature, the mixture was filtered and the magnesium salts washed with two 30 ml portions ether. The ether was removed from the combined ether solutions by distillation and the residue fractionally distilled under vacuum; yield = 6.4 g (62%), bp 90° (.05 mm).

6. 8-Deuterio-1-naphthoic acid (42)

The acid was synthesized according to the procedure outlined by C. G. Papaioannou. The crude product was recrystallized three times from 30% aqueous ethanol.

7. N,N-Nitrosomethyl urea (44)

N,N-Nitrosomethyl urea was synthesized according to the procedure outlined by F. Arndt in Organic Syntheses; yield = 68%.

8. Methyl 8-deuterio-1-naphthoate (45)

A mixture of 5.8 ml 40% aqueous potassium hydroxide and 20 ml ether was added to a 50 ml erlenmeyer flask. The flask was cooled in an ice bath to <5° and the temperature maintained while 2.0 g N,N-nitrosomethyl urea was added slowly. The ether layer was decanted and added to a solution of 1.66 g (.0096 mole) 8-deuterio-1-naphthoic acid in 60 ml ether. The mixture was stirred at <5° for one hour, then at room temperature for two hours. The excess diazomethane was destroyed by the dropwise addition of glacial acetic acid. The ether solution was washed with two 20 ml portions 8% aqueous potassium bicarbonate, 25 ml water, and dried over anhydrous magnesium sulfate. The ether was removed by distillation and the crude product fractionally distilled under vacuum; yield = 1.22 g (68%), bp 124° (1.3 mm). The ester was purified by vapor phase chromatography on an Aerograph A 90-P3 by using a six foot x 1/4 inch carbowax column. NMR showed the ester to be >98% $\underline{d}_1$.

B. Methyl-$\underline{d}_3$ 1-naphthoate

1. Silver 1-naphthoate

Silver 1-naphthoate was synthesized by the procedure outlined previously for silver 8-bromo-1-naphthoate; yield = 89%.

2. Methyl-$\underline{d}_3$ 1-naphthoate

A mixture of 2.44 g (.0087 mole) silver 1-naphthoate, 1.31 g (.0090 mole) methyl-$\underline{d}_3$ iodide and 30 ml ethyl acetate was added to a 50 ml round-bottomed flask (equipped with magnetic stirrer and reflux condenser). The mixture was refluxed for 24 hours and filtered. The yellow precipitate was washed with two 15 ml portions of ethyl acetate. The solvent was removed from the combined solutions by distillation. The crude yield was 1.32 g (80%). The ester was purified by vapor phase chromatography on an Aerograph A 90-P3 by using a six foot x 1/4 inch carbowax column. NMR showed the ester to be >98% $\underline{d}_3$.

C. Methyl 8-methyl-d_3-1-naphthoate (42)

The samples of methyl 8-methyl-1-naphthoate and methyl 8-methyl-$\underline{d}_3$-1-naphthoate used in this study were synthesized by C. G. Papaioannou. The esters were purified by vapor phase chromatography on a Hewlett Packard F & M Scientific 700 Laboratory Chromatograph by using a six foot x 1/4 inch carbowax column. NMR showed the deuterated ester to be >98% $\underline{d}_3$.

D. 2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate

1. Pinacol-$\underline{d}_{12}$ hydrate (46)

Pinacol-$\underline{d}_{12}$ hydrate was synthesized according to the procedure outlined by R. Adams in Organic Syntheses by using acetone-$\underline{d}_6$; yield = 41%.

2. Pinacolone-$\underline{d}_{12}$ (46)

Pinacolone-$\underline{d}_{12}$ was synthesized according to the procedure outlined by R. Adams in Organic Syntheses; yield = 70%.

3. Pivalic-$\underline{d}_9$ acid (46)

To a 50 ml, three-necked round-bottomed flask (equipped with magnetic stirrer, addition funnel, fractionating column, and thermometer) was added a solution of 3.1 g (.0775 mole) sodium hydroxide in 25 ml water. The solution was cooled to 0° in an ice-salt bath and 4.45 g (.0279 mole) bromine was added at such a rate that the temperature never exceeded 5°. After cooling again to 0°, 0.91 g (.0084 mole) pinacolone-$\underline{d}_{12}$ was added and the reaction mixture stirred at 0° until it was decolorized. Then, 3.7 ml concentrated sulfuric acid was added dropwise and the acidic solution extracted with four 10 ml portions ether. The combined ether solutions were washed with three 10 ml portions 10% aqueous sodium hydroxide. The combined aqueous extracts were then acidified with concentrated hydrochloric acid and extracted with four 10 ml portions ether. The combined ether extracts were washed with 10 ml 20% aqueous sodium thiosulfate and 10 ml water. After drying the ether solution over anhydrous magnesium sulfate, the ether was removed by

distillation; yield = 0.67 g (72%).

4. 2,2-Dimethylpropanol-$\underline{d}_{11}$

A slurry of 0.35 g (.0083 mole) lithium aluminum deuteride and 15 ml anhydrous ether was added to a 50 ml, three-necked round-bottomed flask (equipped with reflux condenser, addition funnel, magnetic stirrer, and calcium sulfate drying tube). A solution of 0.67 g (.0059 mole) pivalic-$\underline{d}_9$ acid in 10 ml anhydrous ether was added dropwise at such a rate so as to maintain a gentle reflux. After the addition was complete, the mixture was refluxed for four hours. While cooling the reaction in an ice bath, 1.45 ml water was added dropwise. The mixture was then stirred at room temperature until white crystalline salts formed. The lithium salts were filtered and washed with two 10 ml portions ether. The combined ether solutions were dried over anhydrous magnesium sulfate and the ether removed by distillation; yield = 0.48 g (82%).

5. 1-Naphthoyl chloride

1-Naphthoic acid was refluxed for 20 hours with a two-fold excess of thionyl chloride. The excess thionyl chloride was removed by distillation and the crude product was fractionally distilled under vacuum; yield = 91%, bp 203-5° (65 mm).

6. 2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate

To a 25 ml, three-necked round-bottomed flask (equipped with reflux condenser, addition funnel, and magnetic stirrer) was added a solution of 0.93 g (.0049 mole) 1-naphthoyl chloride in 10 ml dry pyridine. A solution of 0.49 g (.0050 mole)

2,2-dimethylpropanol-$\underline{d}_{11}$ in 10 ml dry pyridine was added dropwise. The mixture was heated slowly to reflux, then cooled to room temperature and the solution poured into 50 ml water. The aqueous mixture was extracted with three 25 ml portions ether. The combined ether extracts were washed with three 25 ml portions 10% hydrochloric acid, two 15 ml portions saturated aqueous sodium bicarbonate, and 15 ml water. The ether solution was dried over anhydrous magnesium sulfate and the ether removed by distillation. The crude yield was 1.13 g (90%). The crude product was recrystallized four times from 70% aqueous ethanol; mp 51-51.5°. The hydrogen compound melted at 52.5-53°. NMR showed the ester to be >96% $\underline{d}_{11}$.

E. 2,2-Dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate

The ester was synthesized by the same procedure outlined for the synthesis of 2,2-dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate; mp 52.5-53°. NMR showed the ester to be >98% $\underline{d}_2$.

F. 2,2-Dimethylpropyl 8-$\underline{d}$-1-naphthoate

The ester was synthesized by the same procedure outlined for the synthesis of 2,2-dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate by using 8-deuterio-1-naphthoyl chloride, mp 52.5-53°. NMR showed the ester to be >98% $\underline{d}_1$.

RESULTS AND DISCUSSION

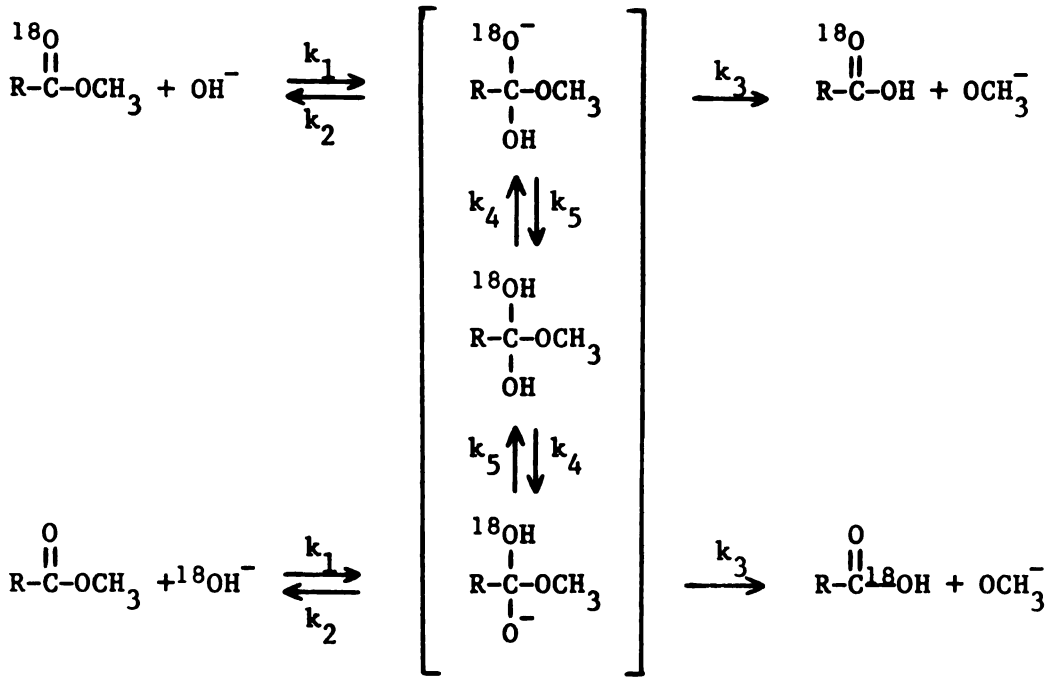
A serious problem is encountered when attempting to interpret secondary kinetic isotope effects in terms of reaction mechanisms. This problem is partially due to our lack of understanding concerning the effects of deuterium substitution on enthalpies and entropies of activation. It was shown previously that secondary kinetic isotope effects may vary considerably with temperature and solvent. The data reported by Evans (2) and Smith (38) where k_H/k_D increases with increasing temperature cogently illustrated this point. It is obvious, therefore, that mechanistic interpretations based on an isotope effect at a single temperature are meaningless and may often lead to the wrong conclusions. Furthermore, the possible solvent dependence of a secondary kinetic isotope effect must also be investigated if any realistic conclusions are to be drawn concerning the mechanism of the reaction under investigation.

Before secondary kinetic isotope effects may be classified as a useful mechanistic tool, their origin must be well understood. Due to the considerable controversy over the nature of secondary kinetic isotope effects, one is left with a serious doubt as to its usefulness in mechanistic interpretations. In order to probe further into the origin of secondary isotope effects, reactions must be studied in which the mechanism is fully established by other methods and does not rely on secondary kinetic isotope effects.

I. Mechanism for the Base Hydrolysis of Alkyl Esters

Unlike many reactions in organic chemistry, the mechanism for the alkaline hydrolysis of alkyl oxygen esters is well established. The reaction is believed to proceed via rate determining attack of hydroxide at the carbonyl carbon of the ester function. Thus, in the rate determining step, a neutral substrate is converted to a tetrahedral anion in which the steric interactions should increase. This reaction is, therefore, of considerable interest in terms of secondary kinetic isotope effects originating from non-bonded interactions.

Based on the second order kinetic behavior first reported by Warder (49) and the oxygen labeling experiments of Bender (47) and of Polanyi and Szabo (48), Moffat and Hunt (50) have proposed the following reaction scheme for the base hydrolysis of alkyl esters.



Since oxygen-18 exchange occurs for these reactions, the lifetime of the tetrahedral anion must be significantly longer than the time for a molecular vibration. The tetrahedral anion is, therefore, classified as a true intermediate. The kinetic importance of the tetrahedral intermediate is further supported by the observation of a change in the rate determining step with varying pH for the base hydrolysis of several amides (51).

Table 12: Effects of para-substituents on the rates of alkaline hydrolysis of ethyl benzoates at 25° (53).

p-Substituent	Relative Rate	E_A
NH_2	0.023	20.00
OCH_3	0.21	18.65
CH_3	0.45	18.20
H	1.00	17.70
Br	5.25	16.80
NO_2	100.3	14.50

Another consequence arises from the proposed mechanism for the base hydrolysis of alkyl esters. In forming the transition state leading to the tetrahedral intermediate, the electron density at the carbonyl carbon is increased considerably. As a result, the hydrolysis reaction should be facilitated by electron withdrawing substituents. The effects of para-substituents on the rates of

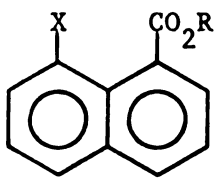
base hydrolysis of ethyl benzoate, Table 12, clearly illustrates the sensitivity of these reactions to electronic interactions, $\rho = +2.56$. This is also reflected in the relative rates of methyl acetate, methyl chloroacetate, and methyl dichloroacetate, Table 13.

Table 13: Substituent effects on the rates of alkaline hydrolysis of alkyl esters at 25° (52).

Compound	$k/k_{(MeOAc)}$	$k/k_{(EtOAc)}$
$CH_3CO_2CH_3$	1.0	1.67
$ClCH_2CO_2CH_3$	761	
$Cl_2CHCO_2CH_3$	16,000	
$CH_3O_2CCO_2CH_3$	170,000	
$CH_3CO_2CH_2CH_3$		1.00
$CH_3CO_2CH_2CH(CH_3)_2$		0.70
$CH_3CO_2CH_2C(CH_3)_3$		0.18
$CH_3CH_2CO_2CH_2CH_3$		0.47
$(CH_3)_2CHCO_2CH_2CH_3$		0.10
$(CH_3)_3CCO_2CH_2CH_3$		0.011

The rate retardations of alkyl substituents on the acid portion of the ester, Table 13, may be safely attributed to a combination of inductive and steric effects. The effects of alkyl substitution on the alcohol moiety, however, are generally ascribed to steric factors alone.

The absence of hyperconjugative structures involving the 8-substituents for alkyl 1-naphthoates makes these compounds ideal



for studying the magnitude of secondary kinetic isotope effects arising from non-bonded interactions. The rates of hydrolysis of methyl 1-naphthoate, methyl 8-methyl-1-naphthoate, 2,2-dimethylpropyl 1-naphthoate, and their deuterated analogs are reported in Tables 14-17. The variations of k_H/k_D with solvent and temperature are summarized in Tables 18 and 19. The thermodynamic parameters calculated by the least-squares programs AKTIV, HANDS, and KINFIT are reported in Tables 20-22. The errors reported for the thermodynamic parameters are two standard deviations yielding 95% confidence limits.

II. Correlation of Thermodynamic Parameters

Following the analysis of Gore and coworkers (54), we will discuss separately each effect of substitution on the enthalpies and entropies of activation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The following factors operate in the base hydrolysis of alkyl esters of aromatic acids.

(a) Inductive effects (+I) that donate electrons to the carbonyl carbon thus stabilizing the ground state and increasing $\Delta H^{\ddagger}$.

(b) Polar effects that increase the solvation of the transition state, thus decreasing $\Delta H^{\ddagger}$. These effects are usually small when

Table 14: Rates of base hydrolysis of methyl 1-naphthoate and methyl 8-d-1-naphthoate in aqueous methanol.

10.0% Methanol/Water (w/w)			
Temp.(°C)	$k_H \times 10^3$ sec^{-1}	$k_D \times 10^3$ sec^{-1}	k_H/k_D
15.571 ± .006	2.9548 ± .0385	2.9897 ± .0285	.988 ± .016
35.728 ± .008	12.113 ± .084	12.257 ± .148	.988 ± .014
50.021 ± .009	28.691 ± .289	28.815 ± .376	.996 ± .016
30.0% Methanol/Water (w/w)			
Temp.(°C)	$k_H \times 10^4$ sec^{-1}	$k_D \times 10^4$ sec^{-1}	k_H/k_D
15.565 ± .006	6.1733 ± .0515	6.3842 ± .0361	.967 ± .010
35.722 ± .008	32.108 ± .421	32.471 ± .244	.989 ± .015
50.011 ± .010	85.663 ± .947	85.576 ± .402	1.001 ± .012

Table 14: (cont'd.)

48.1% Methanol/Water (w/w)			
Temp.(°C)	$k_H \times 10^4$ sec^{-1}	$k_D \times 10^4$ sec^{-1}	k_H/k_D
15.565 ± .006	1.4176 ± .0136	1.4654 ± .0030	.965 ± .009
26.361 ± .008	4.3323 ± .0194	4.4232 ± .0201	.979 ± .006
35.729 ± .008	9.7586 ± .0375	9.9154 ± .0946	.984 ± .010
41.141 ± .010	14.447 ± .060	14.622 ± .036	.988 ± .006
50.007 ± .012	28.875 ± .112	28.941 ± .522	.998 ± .018
57.963 ± .010	58.216 ± .194	57.914 ± .700	1.005 ± .013
66.629 ± .012	100.85 ± .89	100.66 ± 1.92	1.002 ± .021

80.0% Methanol/Water (w/w)			
Temp.(°C)	$k_H \times 10^5$ sec^{-1}	$k_D \times 10^5$ sec^{-1}	k_H/k_D
15.577 ± .006	1.5212 ± .0156	1.5293 ± .0147	.995 ± .014
35.722 ± .008	11.726 ± .110	11.745 ± .051	.998 ± .010
50.014 ± .012	47.108 ± .473	47.180 ± .804	.998 ± .020

Table 15: Rates of base hydrolysis of methyl 1-naphthoate, methyl 8-d-1-naphthoate, and methyl-d_3 1-naphthoate in 54.1% dioxane/water (w/w).

Temp.(°C)	$k_H \times 10^4$ sec^{-1}	$k_{8\text{-}D} \times 10^4$ sec^{-1}	$k_{OCD_3} \times 10^4$ sec^{-1}	$k_H/k_{8\text{-}D}$	k_H/k_{OCD_3}
24.722 ± .008	8.5849 ± .0488	8.7365 ± .0503	8.3319 ± .0485	.983 ± .008	1.030 ± .008
35.413 ± .010	18.588 ± .122	18.729 ± .108	18.276 ± .123	.991 ± .008	1.015 ± .010
50.004 ± .010	49.028 ± .221	49.768 ± .240	47.910 ± .310	.985 ± .006	1.023 ± .008

Table 16: Rates of base hydrolysis of 2,2-dimethylpropyl 1-naphthoate, 2,2-dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate, 2,2-dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate, and 2,2-dimethylpropyl 8-$\underline{d}$-1-naphthoate.

54.1% Dioxane/Water (w/w); T = 24.721 ± .010°

Compound	k x 10^5 sec^{-1}	k_H/k_D
2,2-Dimethylpropyl 1-naphthoate	6.2152 ± .0312	
2,2-Dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate	5.6563 ± .0414	1.099 ± .010
2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate	5.3868 ± .0284	1.154 ± .008
2,2-Dimethylpropyl 8-$\underline{d}$-1-naphthoate	6.2646 ± .0332	.992 ± .007

54.1% Dioxane/Water (w/w); T = 35.404 ± .008°

Compound	k x 10^4 sec^{-1}	k_H/k_D
2,2-Dimethylpropyl 1-naphthoate	1.3128 ± .0057	
2,2-Dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate	1.2091 ± .0057	1.086 ± .007
2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate	1.1224 ± .0048	1.170 ± .007
2,2-Dimethylpropyl 8-$\underline{d}$-1-naphthoate	1.3238 ± .0053	.992 ± .006

Table 16: (cont'd.)

54.1% Dioxane/Water (w/w); T = 50.016 ± .010°		
Compound	k x 10^4 sec^{-1}	k_H/k_D
2,2-Dimethylpropyl 1-naphthoate	3.2965 ± .0120	
2,2-Dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate	2.9851 ± .0214	1.104 ± .009
2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate	2.8846 ± .0126	1.143 ± .006
2,2-Dimethylpropyl 8-$\underline{d}$-1-naphthoate	3.3178 ± .0146	.994 ± .006

30.0% Methanol/Water (w/w); T = 50.006 ± .010		
Compound	k x 10^4 sec^{-1}	k_H/k_D
2,2-Dimethylpropyl 1-naphthoate	6.8492 ± .0356	
2,2-Dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate	6.2258 ± .0753	1.100 ± .014
2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate	5.8134 ± .0458	1.178 ± .011

Table 16: (cont'd.)

48.1% Methanol/Water (w/w); T = 50.016 ± .010°		
Compound	$k \times 10^4$ sec^{-1}	k_H/k_D
2,2-Dimethylpropyl 1-naphthoate	3.2241 ± .0182	
2,2-Dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate	2.8396 ± .0126	1.135 ± .008
2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate	2.6961 ± .0155	1.196 ± .010

Table 17: Rates of base hydrolysis of methyl 8-methyl-1-naphthoate and methyl 8-methyl-$\underline{d}_3$-1-naphthoate in 48.1% Methanol/Water (w/w).

Temp.(°C)	$k_H \times 10^6$ sec^{-1}	$k_D \times 10^6$ sec^{-1}	k_H/k_D
70.201 ± .042	2.1663 ± .0115	2.2035 ± .0302	.983 ± .014
84.985 ± .030	7.8550 ± .0598	8.0862 ± .0463	.971 ± .009
100.384 ± .020	25.864 ± .204	26.752 ± .186	.967 ± .010

Table 18: Variation of k_H/k_D with temperature and solvent composition for methyl 8-d-1-naphthoate.

Temp.(°C)	10.0% MeOH[a]	30.0% MeOH	48.1% MeOH	80.0% MeOH	54.1% Dioxane
15.57	.988 ± .016	.967 ± .010	.965 ± .009	.995 ± .014	
26.36			.979 ± .006		.983 ± .007
35.73	.988 ± .014	.989 ± .015	.984 ± .010	.998 ± .010	.991 ± .008
41.11			.988 ± .006		
50.01	.996 ± .016	1.001 ± .012	.998 ± .018	.998 ± .020	.985 ± .006
57.96			1.005 ± .013		
66.63			1.002 ± .021		

[a]The solvents are weight ratios of the named solvent and water.

Table 19: Variation of k_H/k_D with temperature and solvent composition for methyl 1-naphthoates and 2,2-dimethylpropyl 1-naphthoates.

Compound	Solvent[a]	k_H/k_D (50.0°)	k_H/k_D (35.4°)	k_H/k_D (24.7°)
Methyl 8-d-1-naphthoate	30.0% MeOH	1.001 ± .012	.989 ± .015	
	48.1% MeOH	.998 ± .018	.984 ± .010	.979 ± .006[b]
	54.1% Dioxane	.985 ± .006	.991 ± .008	.983 ± .008
Methyl-d_3 1-naphthoate	54.1% Dioxane	1.023 ± .008	1.015 ± .010	1.030 ± .008
2,2-Dimethylpropyl-1,1-d_2 1-naphthoate	30.0% MeOH	1.100 ± .014		
	48.1% MeOH	1.135 ± .008		
	54.1% Dioxane	1.104 ± .009	1.086 ± .007	1.099 ± .010
2,2-Dimethylpropyl-d_{11} 1-naphthoate	30.0% MeOH	1.178 ± .011		
	48.1% MeOH	1.196 ± .010		
	54.1% Dioxane	1.143 ± .006	1.170 ± .007	1.154 ± .008
2,2-Dimethylpropyl 8-d-1-naphthoate	54.1% Dioxane	.994 ± .006	.992 ± .006	.992 ± .007

[a]The solvents are weight ratios of the named solvent and water.

[b]Temperature = 26.4°.

Table 20: Thermodynamic parameters for methyl 1-naphthoate and methyl 8-d-1-naphthoate.[a]

Solvent[b]	$\Delta H_H^{\ddagger}$	$\Delta S_H^{\ddagger}$	$\Delta H_D^{\ddagger}$	$\Delta S_D^{\ddagger}$
10.0% MeOH	11.68 ± .16	-29.57 ± .54	11.63 ± .18	-29.73 ± .62
30.0% MeOH	13.58 ± .28	-26.09 ± .92	13.39 ± .28	-26.67 ± .90
48.1% MeOH	15.59 ± .38	-21.98 ± 1.20	15.45 ± .36	-22.42 ± 1.16
80.0% MeOH	17.83 ± .40	-18.78 ± 1.32	17.81 ± .42	-18.85 ± 1.36
54.1% Dioxane	12.57 ± .01	-30.37 ± .01	12.55 ± .08	-30.39 ± .24

[a]Reported errors are two standard deviations yielding 95% confidence limits.

[b]The solvents are weight ratios of the named solvent and water.

Table 20: (cont'd.)[a]

Solvent[b]	$\Delta\Delta H^{\ddagger c}$	$\Delta\Delta S^{\ddagger c}$	$\Delta\Delta H^{\ddagger d}$	$\Delta\Delta S^{\ddagger d}$
10.0% MeOH	39 ± 34	0.11 ± .12	39 ± 62	0.11 ± .20
30.0% MeOH	187 ± 10	0.58 ± .04	187 ± 14	0.58 ± .04
48.1% MeOH	154 ± 26	0.47 ± .08	157 ± 28	0.48 ± .10
80.0% MeOH	17 ± 8	0.05 ± .02	18 ± 16	0.05 ± .06
54.1% Dioxane	11 ± 72	0.01 ± .24	9 ± 116	0.00 ± .38

[a]Reported errors are two standard deviations yielding 95% confidence limits.

[b]The solvents are weight ratios of the named solvent and water.

[c]Program HANDS.

[d]Program KINFIT.

Table 21: Thermodynamic parameters for methyl 1-naphthoates and 2,2-dimethylpropyl 1-naphthoates in 54.1% dioxane/water (w/w).[a]

Compound	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Methyl 1-naphthoate	12.57 ± .01	-30.37 ± .01
Methyl 8-d-1-naphthoate	12.55 ± .08	-30.39 ± .24
Methyl-d_3 1-naphthoate	12.61 ± .12	-30.27 ± .38
2,2-Dimethylpropyl 1-naphthoate	11.99 ± .10	-37.50 ± .34
2,2-Dimethylpropyl-1,1-d_2 1-naphthoate	11.95 ± .24	-37.83 ± .80
2,2-Dimethylpropyl-d_{11} 1-naphthoate	12.08 ± .08	-37.52 ± .24
2,2-Dimethylpropyl 8-d-1-naphthoate	11.98 ± .12	-37.52 ± .38

[a]Reported errors are two standard deviations yielding 95% confidence limits.

Table 21: (cont'd.)[a]

Compound	$\Delta\Delta H^{\ddagger b}$	$\Delta\Delta S^{\ddagger b}$	$\Delta\Delta H^{\ddagger c}$	$\Delta\Delta S^{\ddagger c}$
Methyl 8-d-1-naphthoate	11 ± 72	0.01 ± .24	9 ± 116	0.00 ± .38
Methyl-d_3 1-naphthoate	-45 ± 116	-0.10 ± .38	-46 ± 186	-0.10 ± .30
2,2-Dimethylpropyl-1,1-d_2 1-naphthoate	42 ± 140	0.32 ± .46	46 ± 286	0.33 ± .92
2,2-Dimethylpropyl-d_{11} 1-naphthoate	-83 ± 180	0.02 ± .58	-91 ± 304	-0.01 ± .98
2,2-Dimethylpropyl 8-d-1-naphthoate	16 ± 8	0.04 ± .02	17 ± 18	0.04 ± .06

[a]Reported errors are two standard deviations yielding 95% confidence limits.

[b]Program HANDS.

[c]Program KINFIT.

Table 22: Thermodynamic parameters for methyl 8-methyl-1-naphthoate and methyl 8-methyl-$\underline{d}_3$-1-naphthoate in 48.1% MeOH/water (w/w).[a]

Compound	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Methyl 8-methyl-1-naphthoate	20.23 ± .24	-25.80 ± .70
Methyl 8-methyl-$\underline{d}_3$-1-naphthoate	20.37 ± .28	-25.35 ± .80

Program	$\Delta\Delta H^{\ddagger}$	$\Delta\Delta S^{\ddagger}$
HANDS	-139 ± 44	-0.44 ± .12
KINFIT	-135 ± 82	-0.43 ± .24

[a]Reported errors are two standard deviations yielding 95% confidence limits.

the substituent is alkyl. (c) Primary steric effects that result from an increase in non-bonded interactions in forming the tetrahedral intermediate, thus increasing $\Delta H^{\ddagger}$. These effects should make $\Delta S^{\ddagger}$ more negative by decreasing the number of available energy levels of rotation in the transition state, i.e., by hindering internal rotation. (d) Secondary steric effects that force the carbonyl group out of coplanarity with a ring or center of unsaturation, thus decreasing the electron density at the carbonyl carbon and raising the energy of the ground state. This effect will operate primarily in the ground state and results in a smaller $\Delta H^{\ddagger}$ and a more negative $\Delta S^{\ddagger}$. The importance of this effect is reflected in the observed thermodynamic parameters in Table 23. When the ester function is in a position where it must interact with a peri-hydrogen, the rate is significantly retarded. However, the decrease in rate results from a more negative entropy and not from an increase in enthalpy. This is partially attributed to the opposing effects (c) and (d). Bulky substituents may also reduce the stability of the transition state by inhibiting formation of the solvent shell around the transition state, thus leading to (e) effects that sterically hinder solvation. Since the solvent is less efficient in stabilizing the developing charge in the transition state, $\Delta H^{\ddagger}$ will increase while $\Delta S^{\ddagger}$ will become more positive.

These factors are also expected to influence the secondary isotope effects observed for the base hydrolysis of alkyl esters. Due to the complexity of the interaction mechanisms, it is evident that only a qualitative interpretation can be offered at this point.

Table 23: Steric effects in the base hydrolysis of some alkyl esters.

Ester	Relative Rates	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Ethyl 2-naphthoate[a]	1.0	16.4	-17.1
Ethyl 1-naphthoate[a]	0.32	16.3	-19.8
Ethyl 2-phenanthroate[a]	1.0	17.2	-14.5
Ethyl 9-phenanthroate[a]	0.54	15.6	-21.2
Ethyl benzoate[b]	1.0	17.1	-15.9
Ethyl 2-methylbenzoate[b]	0.12	17.3	-19.2
Ethyl 3-methylbenzoate[b]	0.70	17.4	-15.5
Methyl 2-anthroquinone carboxylate[c]	1.0	12.7	-22
Methyl 1-anthroquinone carboxylate[c]	0.0011	9.8	-45

[a]Reference 55. [b]Reference 56. [c]Reference 57.

III. Temperature Dependence

Examination of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for methyl 1-naphthoate and methyl 8-methyl-1-naphthoate in 48.1% aqueous methanol indicates that the difference in rates ($\sim$5000) is due to both an increase in $\Delta H^{\ddagger}$ and a decrease in $\Delta S^{\ddagger}$. This is consistent with the primary steric effect discussed previously, which is taken here as the major reason for the rate difference, as well as the secondary steric effect and the effect of steric hindrance to solvation. The importance of solvation in these hydrolyses is illustrated by examining the solvent

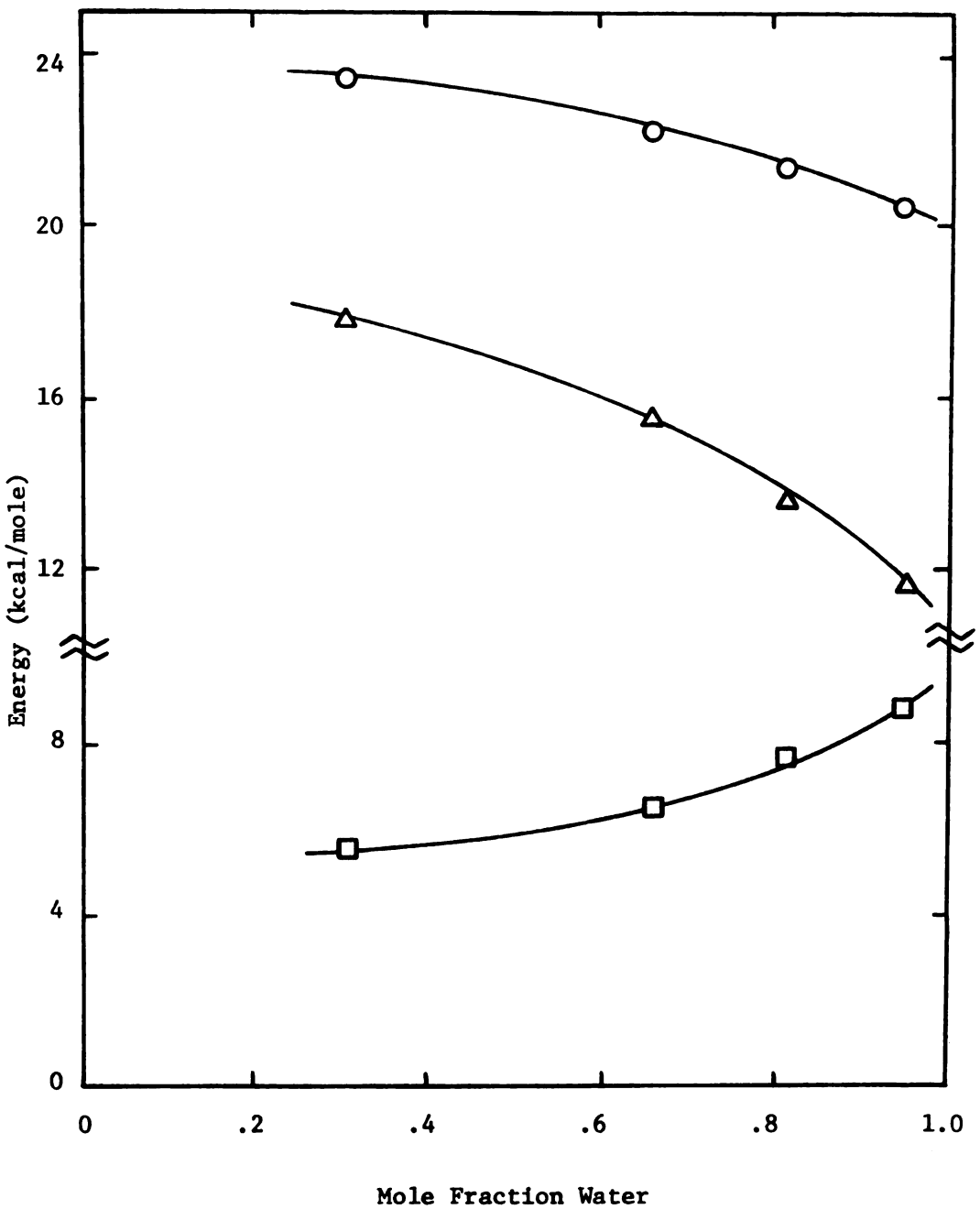


Figure 5: Solvent effects on the thermodynamic parameters for the base hydrolysis of methyl 1-naphthoate in aqueous methanol solutions at 25°. ○ = $\Delta G^{\ddagger}$, △ = $\Delta H^{\ddagger}$, □ = $-T\Delta S^{\ddagger}$

	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Methyl 1-naphthoate	15.59	-21.98
Methyl 8-methyl-1-naphthoate	20.23	-25.80

dependence of the thermodynamic parameters for methyl 1-naphthoate, Figure 5. $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ change dramatically with increasing solvent polarity. However, since they change in opposite directions, they result in a much smaller change in $\Delta G^{\ddagger}$.

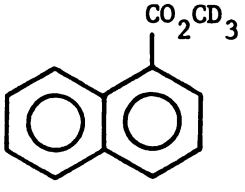
The difference in rates of hydrolysis of methyl 1-naphthoate and 2,2-dimethylpropyl 1-naphthoate in 54.1% aqueous dioxane ($\sim$14) is not due to an increase in the enthalpy of activation. $\Delta H^{\ddagger}$ actually decreases for the bulkier ester. The rate difference is entirely due to a difference of 7 e.u. in $\Delta S^{\ddagger}$. This observation is not unprecedented and has been observed in similar systems, Table 24.

Table 24: Effects of chain branching on the rates of base hydrolysis of some alkyl esters in 70% aqueous dioxane at 40° (54).

Ester	Relative Rates	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Methyl 1-naphthoate	1.0	14.5	-21.2
Ethyl 1-naphthoate	0.36	12.5	-29.7
Isopropyl 1-naphthoate	0.059	12.5	-33.3
Methyl benzoate	1.0	12.5	-25.9
Ethyl benzoate	0.37	13.0	-26.2
Isopropyl benzoate	0.064	13.8	-27.1
t-Butyl benzoate	0.0029	15.7	-27.3

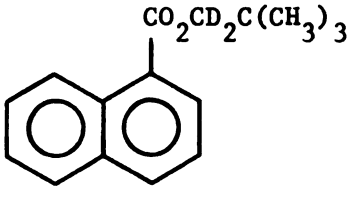
In the 1-naphthyl system where the ester function must interact with a peri-hydrogen, the effect of chain branching on the alcohol moiety is to greatly decrease $\Delta S^{\ddagger}$, while slightly decreasing $\Delta H^{\ddagger}$. Although these effects may be explained in terms of the opposing steric effects, i.e., primary and secondary, such an explanation is inconsistent with the parameters observed for methyl 8-methyl-1-naphthoate. It seems reasonable that the secondary steric effect should operate to a greater extent in the latter compound, since the 8-methyl substituent is in a better position to inhibit conjugation of the carbonyl entity with the naphthalene ring system. Yet, $\Delta H^{\ddagger}$ increases for the 8-methyl ester and $\Delta S^{\ddagger}$ decreases moderately. It appears that some other factor may be influencing the thermodynamic parameters for 2,2-dimethylpropyl 1-naphthoate.

The large difference in the isotope effects for methyl-$\underline{d}_3$ 1-naphthoate, XIII, and 2,2-dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate, XIV, is inconsistent with the mechanistic assumptions for this reaction. Based upon the mechanism outlined by Moffat and Hunt (50), it was



XIII

k_H/k_D = 1.030; 24.7°



XIV

k_H/k_D = 1.099; 24.7°

expected that k_H/k_D should be greater for XIII, due to the greater number of deuterium atoms. This was not observed experimentally.

This anomaly can be easily rationalized if there is a change in the rate determining step for the hydrolysis of XIV. Then, the greater inductive effect of deuterium will operate so as to create a difference in the stabilities of the developing anions, resulting in a significant normal isotope effect. The origin of the isotope effect will be discussed in more detail below.

The proposal of a change in the rate determining step for the hydrolysis of the neopentyl ester is not unrealistic in view of the predicted difference in stabilities of the two corresponding anions, CH_3O^- and $(CH_3)_3CCH_2O^-$. Although the pK_a for neopentyl alcohol has not been determined, it seems realistic that it should be significantly greater than that of ethanol, $pK_a = 17$, which is ten times less acidic than methanol, $pK_a = 16$ (58). Furthermore, changes in the rate determining step have been observed previously for the base hydrolysis of several amides (51) and for the aminolysis of substituted phenyl benzoates (59). All of these reactions are known to proceed through a tetrahedral intermediate.

IV. Interpretation of Isotope Effects

A. Methyl 8-d-1-naphthoate

A previous study of the secondary isotope effect for the base hydrolysis of methyl 8-d-1-naphthoate in 56% aqueous acetone reported $k_H/k_D = 1.00 \pm .01$ at 25° (32). The present investigation is consistent with that result. From Table 18, we see that k_H/k_D depends on the solvent composition. Unfortunately, because of the magnitude of the isotope effects and their errors, any speculation as to the

nature of this dependence is meaningless.

From the variation of k_H/k_D with temperature in 48.1% aqueous methanol, we find that the isotope effect decreases with increasing temperature. This trend is what is normally observed, however, the change in k_H/k_D is more pronounced than the exponential drift predicted if $\Delta\Delta G^{\ddagger} \simeq \Delta\Delta H^{\ddagger}$. Indeed, an examination of the thermodynamic parameters reveals that $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ oppose each other, 157 cal/mole and 0.48 e.u., respectively, to result in a relatively small value of $\Delta\Delta G^{\ddagger}$. The isotope effect predicted on the basis of $\Delta\Delta H^{\ddagger}$ alone is $k_H/k_D = .77$ at 25°. The factors determining this isotope effect, therefore, affect both the enthalpy and entropy of activation.

An inverse isotope effect would be predicted based on the primary steric effect, that is, the difference in steric hindrance to formation of the transition state. However, if this were the origin of the effect, then we would expect $\Delta\Delta H^{\ddagger} > 0$ and $\Delta\Delta S^{\ddagger} < 0$. Although $\Delta\Delta H^{\ddagger}$ is in the predicted direction, $\Delta\Delta S^{\ddagger}$ is not. Following the analysis discussed previously, one may expect that there may be a difference in the dihedral angle between the carbonyl function and the plane of the naphthalene ring system for the deuterated and the undeuterated compounds in the ground state, a secondary steric effect. This would tend to decrease $\Delta\Delta H^{\ddagger}$ and make $\Delta\Delta S^{\ddagger}$ even more negative. Therefore, an explanation of the isotope effect, which is consistent with the observed thermodynamic parameters, must entail some other factor.

Based on substituent effects on the aromatic proton chemical shifts of naphthalene, W. B. Smith and coworkers (60) have recently

reported that there is an attractive interaction between the carbonyl oxygen and the 8-hydrogen in 1-formyl naphthalene. Assuming that this type of interaction is also operating in methyl 1-naphthoate, there should be a greater attraction for the 8-hydrogen than for the 8-deuterium due to the lower polarizability of deuterium. Since the attractive interaction should be diminished in the transition state, the enthalpy of activation ought to be greater for the hydrogen compound, as observed. Similarly, the freedom of rotation of the ester function in the ground state should be greater for the deuterium compound, resulting in a more negative $\Delta S^{\ddagger}$. Although this explanation is consistent with the calculated thermodynamic parameters, the author wishes to point out that this is only a possible explanation and is subject to controversy.

B. Methyl 8-methyl-$\underline{d}_3$-1-naphthoate

The results obtained for methyl 8-methyl-$\underline{d}_3$-1-naphthoate are inconsistent with those reported by Karabatsos and Papaioannou, Table 25 (61). This may be partially due to the different methods and solvent used for the measurement of k_H/k_D.

Table 25: Isotope effects for the base hydrolysis of methyl 8-methyl-$\underline{d}_3$-1-naphthoate in ethanol (61).

Temp.(°C)	k_H/k_D
61.5 ± 0.5	.84 ± .02
79.5 ± 0.5	.89 ± .02

Like methyl 8-d-1-naphthoate, the small inverse isotope effect for methyl 8-methyl-d_3-1-naphthoate is the result of opposing enthalpy and entropy effects. However, the values of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ are opposite in sign, -135 cal/mole and -0.44 e.u., respectively, from those observed with methyl 8-d-1-naphthoate. The small experimental effect arises from the dominance of the entropy term in $\Delta\Delta G^{\ddagger}$. This inverse effect may be attributed to a combination of the various steric factors discussed in part II of this section. The primary steric effect, steric hindrance to formation of the transition state, is counterbalanced by the secondary steric effect and the difference in steric hindrance to solvation. The latter two effects would tend to make $\Delta\Delta H^{\ddagger} < 0$ while having little effect on $\Delta\Delta S^{\ddagger}$.

The significance of the isotope effect for this ester is the fact that it is small because of the opposing contributions of enthalpy and entropy to $\Delta\Delta G^{\ddagger}$. A similar observation was reported by Smith (38) for the solvolysis of the endo-norbornyl p-nitrobenzoate XII, $\Delta\Delta H^{\ddagger} = 157$ cal/mole and $\Delta\Delta S^{\ddagger} = 0.44$ e.u. A large effect was predicted originating from non-bonded interactions. However, steric factors apparently affected both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, resulting in a rather small isotope effect.

As previously reported, Mislow and coworkers (31) found that $\Delta\Delta S^{\ddagger}$ made a considerable contribution to $\Delta\Delta G^{\ddagger}$, opposing the effect of $\Delta\Delta H^{\ddagger}$ ($\Delta\Delta H^{\ddagger} = 240$ cal/mole; $\Delta\Delta S^{\ddagger} = 0.53$ e.u.), for the racemization of 4,5-dimethyl-d_6-9,10-dihydrophenanthrene, X, in benzene. Similar results were reported by Carter and Dahlgren (30) for the racemization of 2,2'-binaphthyl-d_2, IX, in dimethylformamide ($\Delta\Delta H^{\ddagger} = 270$ cal/mole; $\Delta\Delta S^{\ddagger} = 0.54$ e.u.). Non-bonded interactions,

therefore, appear to have a significant effect upon the zero-point energy differences for secondary kinetic isotope effects. However, these interactions also affect the entropy of activation so as to nearly cancel the zero-point energy differences.

These results indicate that secondary kinetic isotope effects originating from non-bonded interactions will be insignificant when other electronic factors operate. Only when severe crowding is occurring in the transition state, as in the racemization reactions mentioned, will non-bonded interactions be important.

C. Methyl-$\underline{d}_3$ 1-naphthoate

Due to the magnitude of the errors in the thermodynamic parameters for methyl-$\underline{d}_3$ 1-naphthoate, no definite conclusions can be drawn regarding the origin of the small normal isotope effect. It is reasonable to assume, however, that the major factor involved would be the greater inductive effect of deuterium. Thus, the electron density on the carbonyl carbon atom in the ground state would be greater for the deuterated compound and a normal isotope effect would be predicted.

D. 2,2-Dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate

From the difference in k_H/k_D for 2,2-dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate, XIV, and methyl-$\underline{d}_3$ 1-naphthoate, XIII, we conclude that there is a change in the rate determining step in going from the methyl to the neopentyl ester. We attribute the isotope effect for the neopentyl compound to the difference in the inductive effects of deuterium and hydrogen. Since deuterium is more

electropositive than hydrogen, it will donate electrons more effectively, thus, destabilizing the developing anion in the transition state. This rationalization is supported by the significant isotope effect on the acidity of formic acid, $K_H/K_D = 1.070$, which is attributed to the greater inductive effect of deuterium, Table 1. The thermodynamic parameters determined for this reaction are useless in supporting any further conclusions as to the origin of the effect.

E. 2,2-Dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate

The isotope effect for 2,2-dimethylpropyl-$\underline{d}_{11}$ 1-naphthoate may be ascribed primarily to the greater inductive effect of deuterium and its effect on the stability of the developing anion in the transition state, as was the case with 2,2-dimethylpropyl-1,1-$\underline{d}_2$ 1-naphthoate. The additional effect of 4-6% may be attributed to a combination of the difference in the inductive effects of the deuterated and undeuterated $\underline{t}$-butyl groups and on the relief of non-bonded interactions in the transition state. Again, the large errors in $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ make any conclusion based on them meaningless.

F. 2,2-Dimethylpropyl 8-$\underline{d}$-1-naphthoate

The isotope effect reported for 2,2-dimethylpropyl 8-$\underline{d}$-1-naphthoate are on the edge of experimental error and for all practical purposes may be considered nonexistent.

V. Conclusion

In conclusion, the small inverse isotope effects observed for the base hydrolysis of methyl 8-d-1-naphthoate and methyl 8-methyl-d_3-1-naphthoate were found to result from opposing values of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. The origin of these effects was attributed to a combination of steric interactions that affect both the enthalpies and entropies of activation. From the relative magnitude of these isotope effects in comparison with other systems, it was concluded that secondary isotope effects arising from non-bonded interactions will be insignificant when other electronic factors operate, e.g., hyperconjugation and induction. Only under conditions of severe crowding in the transition state will non-bonded interactions be important.

Furthermore, the difference in the isotope effects for methyl-d_3 1-naphthoate and 2,2-dimethylpropyl-1,1-d_2 1-naphthoate was attributed to a change in the rate determining step for the latter compound. The origin of the normal isotope effect for 2,2-dimethylpropyl-1,1-d_2 1-naphthoate was attributed to an inductive effect on the stability of the developing alkoxide ion.

BIBLIOGRAPHY

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(1) E. A. Halevi, "Secondary Isotope Effects," Progress in Phys. Org. Chem., Vol. 1, S. G. Cohen, A. Streitweiser, and R. W. Taft, ed., John Wiley and Sons, New York (1963), p. 109.

(2) T. A. Evans, Ph.D. Thesis, Michigan State University, 1968.

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

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

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

(6) J. A. Dixon and R. W. Schiessler, J. Am. Chem. Soc., 76, 2197 (1954).

(7) A. Streitweiser, Jr., J. R. Wolfe, and W. D. Schaeffer, Tet., 6, 338 (1959).

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

(9) H. S. Klein and A. Streitweiser, Jr., Chem. and Ind. (London), 180 (1961).

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

(11) E. A. Halevi and B. Ravid, Pure and App. Chem., 8, 339 (1964).

(12) G. V. Calder and T. J. Barton, J. Chem. Ed., 48, 338 (1971).

(13) R. P. Bell and W. B. T. Miller, Trans. Far. Soc., 59, 1147 (1963).

(14) V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, J. Am. Chem. Soc., 85, 2413 (1963).

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

(16) a. V. J. Shiner, Jr., J. Am. Chem. Soc., 83, 240 (1961).
b. V. J. Shiner, Jr., J. Am. Chem. Soc., 78, 2653 (1956).
c. A. Streitweiser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, J. Am. Chem. Soc., 80, 2326 (1958).

(17) E. M. Arnett, T. Cohen, A. A. Bothner-By, R. D. Bushick, and G. Sowinski, Chem. and Ind. (London), 473 (1961).

(18) E. S. Lewis and G. M. Coppinger, J. Am. Chem. Soc., 76, 4495 (1954).

(19) V. J. Shiner, Jr. and G. S. Kriz, Jr., J. Am. Chem. Soc., 86, 2643 (1964).

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

(21) V. J. Shiner, Jr. and C. J. Verbanic, J. Am. Chem. Soc., 79, 373 (1957).

(22) a. W. A. Sweeney and W. M. Schubert, J. Am. Chem. Soc., 76, 4625 (1954).
b. W. M. Schubert, J. M. Craven, R. G. Minton, and R. B. Murphy, Tet., 5, 194 (1959).

(23) J. P. Schaefer, M. J. Dagani, and D. S. Weinberg, J. Am. Chem. Soc., 89, 6938 (1967).

(24) J. P. Schaefer, M. J. Dagani, and D. S. Weinberg, J. Am. Chem. Soc., 90, 6938 (1968).

(25) E. M. Arnett, P. M. Duggleby, and J. J. Burke, J. Am. Chem. Soc., 85, 1350 (1963).

(26) H. C. Brown and G. J. McDonald, J. Am. Chem. Soc., 88, 2514 (1966).

(27) H. C. Brown, M. E. Azzaro, J. C. Koelling, and G. J. McDonald, J. Am. Chem. Soc., 88, 2520 (1966).

(28) a. L. S. Bartell, J. Am. Chem. Soc., 83, 3567 (1961).
b. L. S. Bartell, Iowa State J. Sci., 36, 137 (1961).

(29) a. L. Melander and R. E. Carter, J. Am. Chem. Soc., 86, 295 (1964).
b. L. Melander and R. E. Carter, Acta Chem. Scand., 18, 1138 (1964).

(30) R. E. Carter and L. Dahlgren, Acta Chem. Scand., 23, 504 (1969).

(31) K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., J. Am. Chem. Soc., 86, 1733 (1964).

(32) G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaioannou, S. E. Schepple, and R. L. Shone, J. Am. Chem. Soc., 89, 463 (1967).

(33) R. A. Scott and H. A. Scheraga, J. Chem. Phys., 42, 2209 (1965).

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

(35) G. J. Frisone and E. R. Thornton, J. Am. Chem. Soc., 90, 1211 (1968).

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

(37) M. Wolfsberg and M. J. Stern, Pure and App. Chem., 8, 325 (1964).

(38) V. F. Smith, Ph.D. Thesis, Michigan State University, 1972.

(39) L. F. Fieser, "Experiments in Organic Chemistry," 3rd edition, D. C. Heath and Co., Boston (1957), p. 285.

(40) J. L. Dye and V. A. Nicely, J. Chem. Ed., 48, 443 (1971).

(41) F. Daniels, J. W. Williams, P. Bender, R. A. Alberty, and C. D. Cornwell, "Experimental Physical Chemistry," 6th edition, McGraw-Hill Book Co., Inc., New York (1962), p. 402.

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

(43) S. E. Scheppele, Ph.D. Thesis, Michigan State University, 1964.

(44) F. Arndt, "Organic Syntheses," Coll. Vol. 2, A. H. Blatt, ed., John Wiley and Sons, Inc., New York (1946), p. 461.

(45) R. Shone, Ph.D. Thesis, Michigan State University, 1965.

(46) R. Adams and E. W. Adams, "Organic Syntheses," Coll. Vol. 1, A. H. Blatt, ed., John Wiley and Sons, Inc., New York (1946), pp. 459, 462.

(47) M. L. Bender, J. Am. Chem. Soc., 73, 1626 (1951).

(48) M. Polanyi and A. L. Szabo, Tran. Far. Soc., 30, 508 (1934).

(49) R. Warder, Chem. Ber., 14, 1361 (1881).

(50) A. Moffat and H. Hunt, J. Am. Chem. Soc., 81, 2082 (1959).

(51) S. L. Johnson, "Advances in Physical Organic Chemistry," V. Gold, ed., Academic Press, Inc., London (1967), p. 237.

(52) a. E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York (1959), pp. 317-318.
b. S. Sarel, L. Tsai, and M. S. Newman, J. Am. Chem. Soc., 78, 5420 (1956).

(53) a. R. W. Taft, Jr., J. Am. Chem. Soc., 74, 3120 (1952).
b. C. K. Ingold and W. S. Nathan, J. Chem. Soc., 222 (1936).

(54) J. F. Corbett, A. Feinstein, P. H. Gore, G. L. Reed, and E. C. Vignes, J. Chem. Soc. (B), 974 (1969).

(55) M. Adam-Briers. P. J. C. Fierens, and R. H. Martin, Helvitica Chimica Acta, 38, 2021 (1955).

(56) D. P. Evans, J. J. Gordon, and H. B. Watson, J. Chem. Soc., 1430 (1937).

(57) P. H. Gore, A. Rahim, and D. N. Waters, J. Chem. Soc. (B), 202 (1971).

(58) J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry," 3rd edition, McGraw-Hill Book Co., New York (1970), p. 304.

(59) F. M. Menger and J. H. Smith, J. Am. Chem. Soc., 94, 3824 (1972).

(60) W. B. Smith, D. L. Deavenport, and A. M. Ihrig, J. Am. Chem. Soc., 94, 1959 (1972).

(61) G. J. Karabatsos and C. G. Papaioannou, Tet. Let., 2629 (1968).


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