CONTRIBUTIONS OF NONBONDED INTERACTIONS TO SECONDARY KINETIC ISOTOPE EFFECTS

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G. J. Karabatsos
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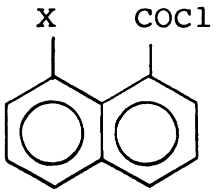
ABSTRACT

CONTRIBUTIONS OF NONBONDED INTERACTIONS TO SECONDARY KINETIC ISOTOPE EFFECTS

by Christos George Papaioannou

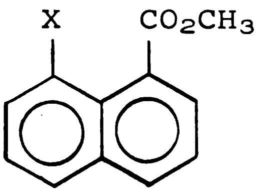
Secondary kinetic isotope effects have been studied extensively by many investigators and the information accumulated so far indicates that these effects are due mainly to differences in either inductive effects, hyperconjugation, nonbonded interactions, or a combination of the three (1).

In order to assess the contribution of nonbonded interactions to secondary isotope effects and test the applicability of Bartell's model (2), a series of compounds of the general formula I and II were synthesized and their solvolytic rates were measured.



I

Ia X = H
Ib X = D
Ic X = CH_3
Id X = CD_3
Ie X = Br



II

IIa X = H
IIb X = D
IIc X = CH_3
IId X = CD_3

It was found that methyl 1-naphthoate (IIa) hydrolyzes in alkaline solution about 10^3 times faster than methyl 8-methyl-1-naphthoate (IIc). The ratio of the measured rate constants for the hydrolysis of 1-naphthoyl chloride (Ia),

8-bromo-1-naphthoyl chloride (Ie) and 8-methyl-1-naphthoyl chloride (Ic) in 95% acetone-water (w/w) was found to be 1:2.80:8.62 respectively. From the above evidence and the isotope effects observed in the solvolysis of 1-naphthoyl chloride-8-d (Ib) and 8-methyl-d_3-1-naphthoyl chloride (Id), it is postulated that 8-methyl-1-naphthoyl chloride solvolyzes by a limiting S_N1 mechanism while 1-naphthoyl chloride solvolyzes most probably by a mixed (S_N1-S_N2) mechanism.

There is no significant isotope effect in the solvolysis of 1-naphthoyl chloride-8-d, most likely because the reaction takes place by a mixed mechanism. In the case of 8-methyl-d_3-1-naphthoyl chloride a normal isotope effect of 1.03 and 1.17 was observed in 95% acetone-water (w/w) at room temperatures and 75.23% acetone-water (w/w) at low temperatures (-20° to -34°) respectively.

The activation parameters found at low temperatures for the solvolysis of 8-methyl-1-naphthoyl chloride and its 8-d_3 analog show that the observed isotope effect is the result of a normal isotope effect due to an enthalpy of activation difference, which is about equal to that calculated from Bartell's model, and an inverse isotope effect due to an entropy of activation difference.

In the alkaline hydrolysis of methyl 1-naphthoate-8-d no significant isotope effect was found. Comparison of the observed values with those calculated (3) is rather difficult because of uncertainties associated with the potential functions used.

It is concluded that nonbonded interactions can be of primary importance with regard to the origin of secondary isotope effects. Bartell's model (2) gives reasonable estimates of these effects.

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CONTRIBUTIONS OF NONBONDED INTERACTIONS
TO SECONDARY KINETIC ISOTOPE EFFECTS

By

Christos George Papaioannou

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INTRODUCTION

Ever since secondary kinetic isotope effects were observed for the first time in S_N1 type solvolytic reactions (1) the subject has been intensively and systematically studied.

Secondary isotope effects on rate and equilibrium constants can be defined as those occurring although no bond to an isotopic atom is being broken or formed. As the term implies, these effects are quite small (2).

Bigeleisen (3) and Melander (4) have carried out extensive theoretical treatments of the effects of isotopic substitution on reaction rates and although the details in the two procedures are a little different the results are equivalent. Both workers have considered the effects of changing nuclear mass on the parameters of the equation derived from the "theory of absolute rates". According to the theory, a secondary deuterium isotope effect, if it is an activation energy effect and not a frequency factor effect (5), and neglecting tunnelling and anharmonicity factors, is due to changes of vibration frequencies involving the isotopic bond in going from the ground to the transition state. These changes of vibration frequencies in turn, result from changes in inductive interactions, hyperconjugative interactions and/or changes in nonbonded interactions (5,6,7).

Numerous examples of secondary isotope effects which have been observed in organic reactions have been discussed and variously interpreted in terms of the usual effects of organic chemistry, i.e., induction, conjugation and hyperconjugation, hybridization and steric interactions or in terms of solvent or temperature effects on the entropy of activation. Halevi (8) first emphasized the importance of the C-D versus C-H bond inductive effect as the possible origin of secondary isotope effects. He pointed out that secondary isotope effects which had been interpreted as arising from the difference in "zero-point" vibrational energy between the ground state and the transition state, leading to less effective hyperconjugative stabilization of the latter in the case of β-deuterated or para-deuteriomethyl compounds (1), could be explained by considering the difference in the ground-state inductive effects of the C-H and C-D bonds. The reported decrease of acidity of phenylacetic acid and increase of basicity of benzylamine (9) caused by α-deuteration, a thermodynamic secondary isotope effect, has been ascribed to ground-state differences that presumably derive from differential inductive electron release which is stronger from C-D than from C-H bonds. It has been argued (9) that the direction of this isotope effect indicates a greater effective inductive electron release from $-CD_3$ (or $-CD_2-$) than from $-CH_3$ (or $-CH_2-$). The same author (8) commenting on the slight inverse isotope effect observed in the decomposition of methyl-deuterated p-toluenediazonium ion (10), a reaction influenced by both inductive and hyperconjugative effects, points out that it may well result from a balance between two opposing isotope effects: the one, a normal effect arising from higher stabilization of the transition state through hyperconjugation for the p-CH_3 compound than for the p-CD_3 compound which however, as has been pointed out, is almost negligible because of the orthogonality of the vacant orbital and the aromatic π-orbital in the intermediate aryl cation; the other, a stronger, inverse effect arising from the greater "+ I Effect" (11) of the p-CD_3 versus the p-CH_3 group.

Streitwieser and Klein (12) have carried out similar studies of isotope effects on the acidity of deuterated organic acids and their results match those of Halevi and co-workers (9). Deuterated formic, acetic, pivalic and benzoic acids were studied by a highly precise conductometric method and the following results were obtained for $pK_D - pK_H$: DCOOH, 0.030 ± 0.004; CD_3 COOH, 0.014 ± 0.002; C_6D_5COOH, 0.010 ± 0.002; 2,6-$C_6H_3D_2COOH$, 0.003 ± 0.001; $(CD_3)_3C$-COOH, 0.018 ± 0.001. Using an empirical approach they have treated these effects as "normal" inductive substituent effects. The same workers (13) provide more evidence for the significance of the inductive factor as the origin of secondary isotope effects in a study of the solvolysis of various deuterated benzydryl chlorides in 80% and 70% aqueous acetone.

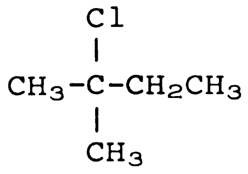
It was found that the isotope effect depends clearly on the position of the ring substitution in the order: ortho > meta > para. Moreover, the effect is approximately additive. Using the per cent acceleration per deuterium atom (ortho, 1.9; meta, 1.5; para, 1.0), the calculated and found accelerations in 80% and 70% acetone are respectively, 9.2, 9.4 and 9.5% for benzydryl-2,4,6-2',4',6'-d_6 chloride and 15.2, 16.0, 17.0% for benzydryl -2,3,4,5,6-2',3',4',5',6'-d_{10} chloride. The most significant feature of these results is that the effect of deuteration in different positions is of comparable magnitude. It was argued that because of the conjugation of the positive charge of the carbonium ion intermediate to the para position, a stronger effect for a para deuterium might have been anticipated, while the actual effect was found to be weaker than at the meta position. No definite explanation was given for this but a working hypothesis was offered that these isotope effects measure inductive and field effect polarization in the σ-bond system.

Even in systems in which hyperconjugation has been solely advocated as the main factor for secondary isotope effects (<u>vide infra</u>) the inductive effect cannot be neglected. E. S. Lewis and co-workers (14) in studying the solvolysis of methyl-p-tolylcarbinyl chloride and methyl-m-tolylcarbinyl chloride in acetic acid and aqueous acetone, have found a sizeable normal isotope effect for the isotopically substituted para compound and a small inverse isotope effect for the meta compound. The latter could be explained only by advocating a higher electron-donating effect by the $-CD_3$ group than by the $-CH_3$ group. For the completely deuterated meta isomer the observed acceleration was 1% in 70% acetone and 2.5% in 80% acetone, being in the right inductive direction but at the same time denoting that solvation is an important factor also. In some cases the importance of the inductive effect is even less obvious. An inverse isotope effect of the order of about 5% observed by Robertson et al. (15) in the hydrolysis of gamma-deuterated n-propyl sulfonates and chlorides has been ascribed by the authors to inhibition of vibrations involving the γ-CH_3 group in the S_N2 type transition state. This "steric" explanation has been seriously questioned by Halevi (16) who suggests a tentative hypothesis that in general, the γ-effects are due to the effectively greater electropositivity of the CD_3 versus the CH_3 group.

In recent years a novel spectroscopic method has been used in studying isotope effects in terms of normal substituent characteristics of inductive and resonance effects. The F^{19} chemical shifts of m- and p- fluorotoluene - α,α,α-d_3 and their nondeuterated analogs were determined (17) and while the chemical shift of the p-deuterated compound was 0.7 c.p.s. less than that of p-fluorotoluene, the meta isomer showed no appreciable isotope effect. These results, correlated to inductive and resonance σ-constants, σ_I and σ_R^o, by utilizing Taft's correlations (18) of the F^{19} shifts for the above compounds, imply negligible or zero inductive isotope effects of the methyl group, but a small resonance isotope effect in the same direction expected from kinetic studies.

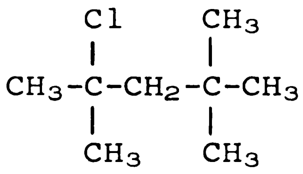
In the early works on secondary isotope effects hyperconjugation was almost exclusively invoked as the origin of these effects. One reason for this might have been that the systems which were studied were not selectively chosen for the purpose of discriminating among the various possible sources of origin of an isotope effect and by some strange coincidence most of them were by nature apt to the hyperconjugation explanation. As more and more information accumulated it was recognized more and more that hyperconjugation cannot be the only cause of secondary isotope effects, and finally by the late fifties the initial agreement on the significance of hyperconjugation for secondary isotope effects had changed to an open controversy (5,7) which has not been quite settled so far. Besides recognizing other factors such as steric interactions, inductive effects etc., as being equally important as hyperconjugation, workers have not been able to quantitatively correlate them with resulting isotope effects and assess the relative importance of these factors.

Shiner (1b,19) in a series of studies investigated the rate decrease caused by deuteration of the β-methyl and β-methylene groups in solvolysis of t-amyl chlorides (I) in 80% aqueous ethanol. The isotope effects found in the S_N1 reaction were respectively 1.34 and 1.40 and were attributed to a difference in zero-point energies between the ground and electron-deficient transition states. This difference occurs because the transition state is better stabilized in the hydrogen compound than in the deuterium compound due to a greater weakening of the C-H bond than of the C-D bond through hyperconjugation.



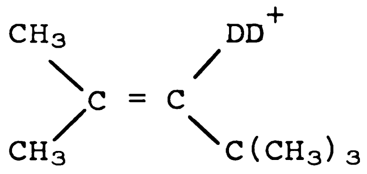
$$\mathrm{CH_3{-}\overset{\overset{Cl}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}CH_2CH_3}$$

I



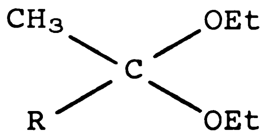
$$\mathrm{CH_3{-}\overset{\overset{Cl}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}CH_2{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}CH_3}$$

II



III

The same studies (19) showed that the effect is cumulative as the degree of β-deuteration increases and that it is dependent on the nature of the other groups on the carbon which is the site of isotopic substitution. Thus, the $\Delta\Delta G^{\ddagger}$ per α-deuterium atom increases in the series of groups methyl (56 cal/mole), ethyl (96 cal/mole), isopropyl (156 cal/mole). A striking similarity was established between this case and the acid-catalyzed hydrolysis of diethyl ketals of acetone, methyl ethyl ketone and methyl isopropyl ketone (20) of the general type IV.

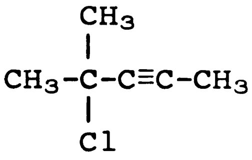


IV

In this series of compounds the change of $\Delta G^{\ddagger}$ per α-deuterium atom in R follows the pattern: CD_3-, 14 cal/mole; CH_3CD_2-, 30 cal/mole; $(CH_3)_2CD$-, 51 cal/mole. The difference in the size of the isotope effect between the two classes of compounds was attributed (20) to a smaller degree of electron deficiency in the ketal hydrolysis transition state, in which a carbonium-oxonium ion is formed, than in the alkyl chloride hydrolysis transition state, which forms a carbonium ion.

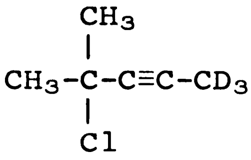
In order to further support the above argument he next studied the solvolysis of 2,4,4-trimethyl-2-chloropentane (II) (21) under the same conditions and found that the k_H/k_D ratio for β-methyl deuteration and β-methylene deuteration were respectively 1.40 and 1.08. He uses this big difference as a confirmation of his hyperconjugation explanation since the steric requirement for hyperconjugation in the carbonium ion intermediate arising from II would be hardly fulfilled and contributing form III would be sterically very unfavorable.

A piece of strong evidence supporting the hyperconjugation explanation was provided by the fact that a secondary isotope effect can be transmitted through a conjugated system of bonds. One of the first such systems to be studied was the solvolysis in various aqueous solvents of p-CD_3-, p-CH_3CD_2-, p-$(CH_3)_2CHCD_2$- and p-$(CH_3)_2CD$- benzhydryl chlorides and their protium analogs (22). The isotope effects observed are positive and of the order of 6% or less and become progressively smaller in the order listed above. Steric inhibition of hyperconjugation was invoked to explain the fact that the isotope effect in the case of the p-isobutyl-α,α-d_2 compound is smaller than that for the p-ethyl-α,α-d_2 compound. The same kind of evidence had been obtained earlier in a study of the acetolysis of methyl-p-tolylcarbinyl chloride (23), the effects of p-alkyl deuteration observed being similar to those of the previous case (22) and to the effect of β-deuteration in the solvolysis of alkyl chlorides (19,24). In their study of solvolysis of methyl-p-tolylcarbinyl chloride and methyl-m-tolylcarbinyl chloride in acetic acid (14) E. S. Lewis and co-workers observed a 10% retardation of the solvolysis for deuteration of the p-CH_3 group and about 1% acceleration for deuteration of the m-CH_3 group. The effect of β-deuteration is in the same direction and of comparable size as that of para deuteration. The authors conclude that hyperconjugation of the reaction site with the para position in the electron deficient intermediate is responsible for the para effect while the small inverse isotope effect observed with the meta compound is a manifestation of an inductive factor (<u>vide ante</u>). A case of transmission of an isotope effect across a C≡C bond was reported by Shiner and co-workers for the first time in a study of the S_N1-type solvolysis of 4-chloro-4-methyl-2-pentynes (Va - Vc) in several aqueous solvents (25).



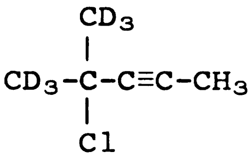
$$CH_3-\underset{Cl}{\overset{CH_3}{C}}-C\equiv C-CH_3$$

Va



$$CH_3-\underset{Cl}{\overset{CH_3}{C}}-C\equiv C-CD_3$$

Vb



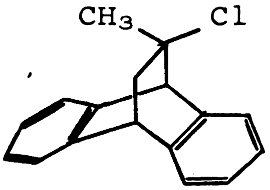
$$CD_3-\underset{Cl}{\overset{CD_3}{C}}-C\equiv C-CH_3$$

Vc

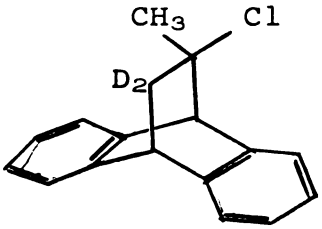
The selection of the system was appropriately made since, as it has been shown (26), the triple bond can be used to distinguish between steric and electronic effects on reactivity. The k_H/k_D ratio for compound Vb is about 1.09 while for compound Vc it is 1.66. Both the beta (Vc) and delta (Vb) isotope effects were attributed to electronic interaction by hyperconjugation with the reaction center, in the case of compound Vc being transmitted across the C≡C bond. The fact that the delta isotope effect per deuterium atom is about one-third as large as the beta isotope effect forced the authors to admit that part of the latter should be attributed to changes in nonbonded interactions.

Perhaps the most important piece of evidence about the significance of hyperconjugation as a possible source of secondary isotope effects was provided by work showing that when the steric requirements for hyperconjugation cannot be met, such effects do not occur at all or are negligibly small. A strong conformational dependence of isotope effects was previously observed, e.g., in the case of solvolysis of 2,4,4-trimethyl-2-chloropentane (II) (21), but there was always a lack of independent evidence about the assumed conformations of ground and transition states. Shiner and

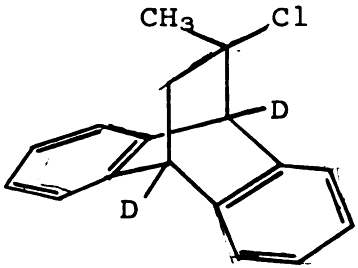
Humphrey (27) first presented a case of a β-deuterium isotope effect in the solvolysis of bicyclic chlorides VIa, VIb, VIc in which the C-D bond axis was fixed in a direction perpendicular to the axis of the developing vacant p-orbital.



VIa



VIb



VIc

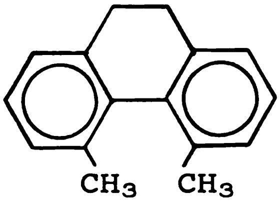
While compound VIb, in which the vacant p-orbital forming in the incipient carbonium intermediate is almost parallel to the beta C-D bond axis, exhibits a typical β-isotope effect, $k_H/k_D = 1.14$, the bridge-head deuterium analog VIc, in which the vacant p-orbital forming is perpendicular to the beta C-D bond axis, shows an effect very close to unity. Analogous results were obtained from the solvolysis of cis-4-t-butylcyclohexyl brosylate-trans-2-d (single axial beta deuterium) and cis-4-t-butylcyclohexyl brosylate-cis-2-d (single equatorial beta deuterium) (28), a system which has been shown to be conformationally homogeneous (29). So, k_H/k_D for the beta deuterium when trans or cis to the leaving group is 1.43 and 1.09 respectively.

Finally, various isotope effects have been observed in reactions of carbonyl compounds (30), mechanistically different from the S_N1 solvolysis of alkyl halides, and although hyperconjugation has been claimed as the cause of these effects

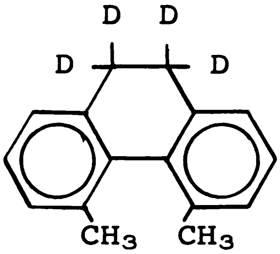
(30), the situation here is less clean-cut and the arguments even less obvious.

Bartell (31) was the first to emphasize the importance of nonbonded repulsions as a possible origin of secondary isotope effects. He proposed a model, predicting isotope effects to be expected in particular reactions involving carbonium ions (32). The principle of his model is that the amplitudes of vibration of C-H bonds are characteristically greater than those of C-D bonds and therefore the latter-type bonds should have a smaller van der Waal's radius (33). According to this theory, nonbonded repulsions, averaged over stretching and bending atomic vibrations, are greater for hydrogen atoms than for deuterium atoms and consequently, reactions proceeding from a crowded tetrahedral ground state to a less crowded trigonal transition state, should exhibit a direct isotope effect and *vice versa*. These theoretical predictions in general agree with experimental results although quantitatively they are very much dependent on assumptions made about molecular structures (32) and conformations (34). Also Bartell's formulation assumes the nonbonded interactions to be strictly repulsive, which has been seriously questioned (35), and it does not account for the interactions of solvent molecules and leaving group with the carbonium ion intermediate in calculations for solvolyses (32). Independent evidence for the existence of strong nonbonded repulsions between atoms bonded to a given atom had been obtained before in a study of bond angles in ethylene derivatives and an estimation of the magnitude of these repulsions presented (36). It was suggested that intramolecular van der Waals forces may be even more important than effects of hybridization and conjugation or hyperconjugation in affecting bond angles, bond lengths, energies of reactions, and bending vibrations of molecules. Bartell et al. (37), by an electron diffraction study of the structures of C_2H_6 and C_2D_6, established a primary deuterium isotope effect of 0.0050 ± 0.0006 A for the C-H bond and a possibly significant secondary one for the C-C bond of 0.0016 ± 0.0007 A. The authors, however, were only able to speculate that the secondary effect on the C-C bond length comes from nonbonded H•••H repulsions across the C-C bond. In a similar study (38) of the structures of gaseous NH_3 and ND_3 it was found that the N-H and N-D bond lengths were virtually the same but the amplitude of vibration of the N-H bond was significantly greater than that of the N-D bond and the H-N-H angle was larger than the D-N-D angle by 3 degrees. Theoretical calculations were carried out (31,32) on three cases for which experimental results had been reported. The effect of deuterium substitution on the activation energy of the solvolysis of t-butyl chloride was calculated to be 22 cal per deuterium atom which is well less than half the $\Delta\Delta G^{\ddagger}$ observed (39). In the solvolysis of tosylates the calculated isotope effect values ranged from rather less than the observed values to considerably more depending on the assumed molecular configurations. The gas phase equilibrium between trimethylborane and trimethylamine and their complex appeared to be an excellent case for testing Bartell's model because the reaction is free of solvent effects and the configurations of all molecules involved are known. The calculated ΔE_a for the dissociation turns out to be about 66 cal per deuterium atom of the borane, while the observed ΔE_a (40) was about 22 cal per deuterium atom. As can be seen, the quantitative agreement of the theory with the experimental results is rather poor which is most probably due to the "hard" (34) potential functions used in the calculations.

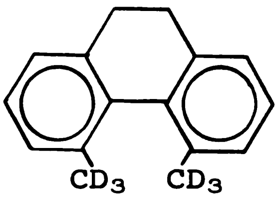
Aside from Bartell's model, there is ample experimental evidence pointing to the importance of nonbonded interactions in secondary isotope effects. An unambiguous demonstration of this importance was the inverse isotope effects observed in the rates of racemizations of optically active derivatives of 9,10-dihydro-4,5-dimethylphenanthrenes VIIa—VIId (41). Since these racemizations are purely conformational changes any isotope effects found must be purely steric in origin.



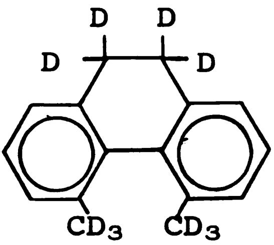
VIIa



VIIb



VIIc



VIId

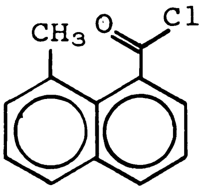
The ratio k_D/k_H found was 1.05 for VIIb, 1.13 for VIIc and 1.18 for VIId. These isotope effects are believed to arise from the replacement of the methyl groups in the 4,5-blocking positions by the less bulky trideuteriomethyl groups. The authors are reluctant to definitely assign the origin of the small VIIb/VIIa rate ratio but they feel that it could stem from the torsion barrier about the 9,10-bond, which is not necessarily associated with steric repulsions of adjacent hydrogen atoms (42). In an analogous study of the racemization of 2,2'-dibromo-4,4'-dicarboxybiphenyl and its 6,6'-d_2 derivative (43) a k_D/k_H ratio of 1.18 was obtained. A calculation of $\Delta\Delta E^{\ddagger}$ according to Bartell's theory gives a value in good agreement with the experimental results only if a particular (44) H···Br nonbonded repulsion potential is used, which gives the impression that the agreement is fortuitous and could be easily lost if another potential function was to be used. A characteristic example of the manifestation of a steric isotope effect is the partial kinetic resolution of α-phenylbutyric acid by alcoholysis of α-phenylbutyric anhydride with (+)-(S)-2-propanol-1-d_3 in pyridine (45). Here a "normal" steric substituent effect is operating, confirming the earlier conclusion that the $-CH_3$ group is effectively bulkier than the $-CD_3$ group (41).

Inverse isotope effects observed in two cases of the Menschutkin reaction have been explained differently. Leffek and MacLean (46) studied the reactions between CH_3I and CD_3I

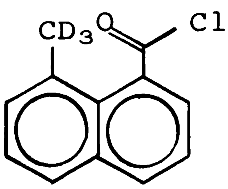
and a series of tertiary amines of varying structure and established an alpha-isotope effect k_H/k_D from 0.88 to 0.92 which showed no systematic variation with the structure of the amine. The activation parameters were determined for the reaction of 2-picoline and it was possible to separate $\Delta\Delta G^{\ddagger}$ into the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ components, which were respectively: $\Delta H^{\ddagger}_D - \Delta H^{\ddagger}_H = -2 \pm 36$ cal/mole and $\Delta S^{\ddagger}_D - \Delta S^{\ddagger}_H = 0.25 \pm 0.11$ e.u./mole. It was mainly this latter difference that led the authors to the conclusion that these isotope effects must most probably be due to internal rotation effects of the methyl group in the transition state as the N-C bond is partially formed. It should be noted though, that nonbonded interaction effects cannot be excluded, expecially in view of the rather small experimental significance of the above results. The second case, the reaction of methyl-d_3-pyridines with alkyl iodides, was presented by H. C. Brown and coworkers (47) and constitutes evidence for the steric origin of secondary isotope effects. It was found that methyl deuteration of 2-methylpyridine and 2,6-dimethylpyridine led to a 3% and 9.5% increase of the rate of the reaction with alkyl iodides respectively while methyl deuteration of either 3- or 4-methylpyridine had no significant effect on the reaction rate. Nonbonded interactions and the smaller steric requirements of the $-CD_3$ group compared to $-CH_3$ group were claimed as the reason for the observed inverse isotope effects. On the other hand, it was argued that the absence of any significant isotope effect in 4-methylpyridine-4-d_3

and 3-methylpyridine-3-d_3 denotes that hyperconjugation cannot be the reason for the observed isotope effect in the present system and that the $-CD_3$ group exerts no significant inductive effect on the reaction center (vide ante). Inverse isotope effects observed in the acid-catalyzed reactions of several ketones with 2,4-dinitrophenylhydrazine have also been explained on the basis of nonbonded interactions (48). The observed k_D/k_H ratios for $PhCOCD_3$, $PhCOC(CH_3)(CD_3)_2$ and $PhCOCD_2CH_3$ were respectively 1.119± 0.005, 1.046± 0.0015 and 1.124± 0.005. Considering the Jencks mechanism (49) for such reactions evidence was presented that the attack by base of the conjugate acid of the ketone is the rate-determining step. The increased rate owing to deuterium substitution is then explained as a result of increased steric crowding in the transition state for this step and the higher steric requirements of hydrogen compared to deuterium. In conclusion then it should be noted that both Bartell's theoretical calculations and compiled experimental evidence have rendered it impossible to ignore nonbonded interactions in considering the origin of secondary isotope effects, although it is generally recognized that much more should be learned, both theoretically and experimentally, before the relative contribution of these interactions could be assessed.

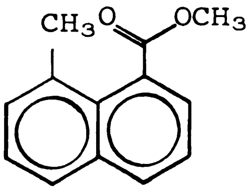
It was the aim of this work to present evidence about the relative importance of nonbonded interactions for secondary isotope effects by selecting a system which would provide a better test for Bartell's model. In order that the steric factor could be studied separately from the hyperconjugative and inductive factors, the system to be selected should fulfill the following three conditions: first, there should be considerable nonbonded interactions between the position of isotopic substitution and the reaction site; second, the crowding of the reaction site should change upon activation, and, third, there should be no possibility of electronic interaction, either by hyperconjugation or by induction, between any electric charge at the reaction site and the isotopically substituted group. It was thought that 8-methyl-1-naphthoyl chloride, methyl 8-methyl-1-naphthoate and their 8-d_3 derivatives (VIIIa-VIIId) would be ideal compounds to study and that their hydrolysis would meet all three of the above conditions.



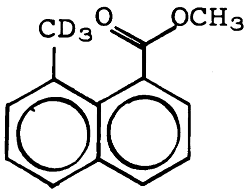
VIIIa



VIIIb



VIIIc



VIIId

There is a great deal of evidence to date about the peri-interaction in naphthalene derivatives (50). This evidence can be physical, originating from studies of crystal structure, molecular spectra, electric dipole moments etc., or chemical, steming from peri-effects on chemical reactivity of substituted naphthalene derivatives. A number of crystallographic studies have been made on 1-monosubstituted and 1,8-disubstituted naphthalene derivatives which throw considerable light on the nature of peri-interactions in these molecules and help to arrive at a quantitative picture of nonbonded repulsion energies in organic molecules (51). It has been found (52) that in order that the strain be partly relieved in 1-naphthoic acid, the carboxyl group is twisted out of the nuclear plane by 12°. In addition, there occurs a slight in-plane displacement of the C_{Ar}-COOH bond away from the peri-position. The strain in 1,8-dinitronaphthalene is even worse (50). The result is that the nitro groups are out of the nuclear plane by 45°, the C-N bonds are leaning apart from each other to increase the N···N distance and deviate from the aromatic plane by 0.37 A in opposite directions, while the aromatic system itself is slightly distorted. X-ray analysis of crystals of octamethylnaphthalene (53) revealed that the molecule is not planar, the methyl groups being displaced from the aromatic plane in an up-and-down pattern around the molecule.

From the vast amount of chemical evidence for the peri steric interactions in substituted naphthalene derivatives, the base-catalyzed hydrolysis of substituted 1-naphthoates and 2-naphthoates (54) and the S_N1 solvolysis of naphthylcarbinyl halides (55) are both characteristic and quite similar to the reactions under study. Both ethyl and methyl esters of 1-naphthoic acid are found to undergo hydrolysis more slowly than their 2-isomers. In the base-catalyzed hydrolyses of ethyl 1-naphthoates, the 8-nitro compound reacts 13 times more slowly than the 2-nitro compound, which reacts 7.5 times more slowly than the parent ester. This order in reactivity has been explained as a consequence of steric effects. It is of interest to mention that even the intervention of a methylene group does not abate the peri hindrance, as is shown in the study of the saponification rates in the naphthyl acetate series (56) where the carboxylate group is separated from the ring by a methylene group. In the case of S_N1 solvolysis of aryl carbinyl halides, the rate of solvolysis is governed by the stability of the carbonium ion intermediate as well as by steric effects on the stretching of the carbon-halide bond during activation. The stability of the incipient carbonium ion is lowered by bulky substituents in the peri position (a decelerating effect) because of steric inhibition of resonance, while the same substituents exert an accelerating effect on breaking the carbon-halide bond. Therefore it is more difficult here to explain reactivity trends along the line of steric interactions. On the other hand, there is an additional advantage in selecting the hydrolysis of acid chlorides as opposed to carbinyl chlorides, because the acylium ion intermediate (see Results & Discussion) has a linear configuration, and consequently, the effect of steric inhibition of resonance is minimized in the present case.

As a measure of the size of the peri nonbonded interactions in naphthalene systems in terms of energy, work by Packer _et_ _al_. (57) has shown that strain in 1-methylnaphthalene and 1,8-dimethylnaphthalene is respectively 1.6 kcal and 7.6 kcal per mole. These strains are greater than those of comparable alkylbenzenes, the differences being attributed to the rigidity of the naphthalene system.

Concerning the second of the three conditions set above, it was hoped that the hydrolysis of acid chlorides VIIIa and VIIIb takes place by an S_N1-type mechanism, proceeding via an acylium ion-like intermediate. This intermediate must have a linear configuration as compared with the trigonal ground state. In the saponification of esters VIIIc and VIIId, assuming that it takes place by the well-known $B_{AC}2$ mechanism, it is easy to see that one goes from a trigonal ground state to a tetrahedral transition state.

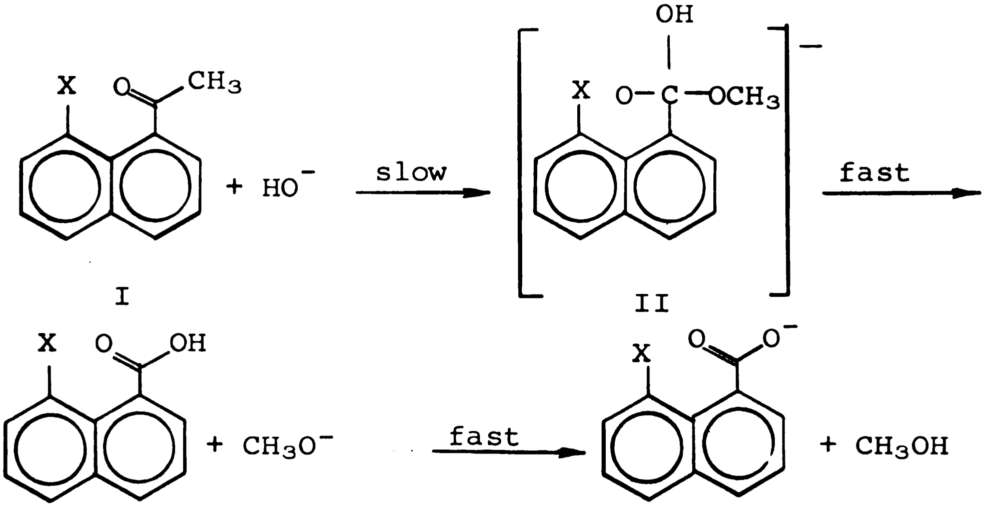
Finally, the third condition is met by the very nature of the system under study. Electronic interaction by hyperconjugation between the reaction site and the isotopically substituted 8-substituent must be ruled out here. Any positive charge on the carbonyl carbon of the esters cannot be depleted by hyperconjugation with the 8-substituent (ground state effect) because it could be placed on the 7-position or the 9-position but not on the 8-position. Similarly, the positive charge developed on the carbonyl carbon atom during activation in the hydrolysis of the acid chlorides cannot interact with the 8-position by hyperconjugation (transition state effect).

RESULTS AND DISCUSSION

A. Alkaline Hydrolysis of Methyl 1-Naphthoate and its 8-Deuterium Analog

I. The Kinetic Method

The molecularity and mechanism of the basic hydrolysis of esters is well established. In terms of Ingold's notation (58) this reaction usually takes place by the $B_{AC}2$ mechanism (59), as illustrated for methyl 1-naphthoate (Ia) and methyl 1-naphthoate-8-d (Ib):



Ia, X = H; Ib, X = D

The kinetics of the alkaline hydrolysis of these esters were studied first by using Tommila and Hinshelwood's method (60). The results are summarized in Table I. The runs of the

Table I. Rate Constants and Isotope Effect of the Alkaline Hydrolysis[a] of Methyl 1-Naphthoate (Ia) and Methyl 1-Naphthoate-8-d (Ib),[b] Measured by Titration of the Base

Run Number	Compound	k x 10^3 $M^{-1}sec^{-1}$	Aver. k x 10^3 $M^{-1}sec^{-1}$	k_D/k_H	Aver. k_D/k_H[c]	$\Delta\Delta G^\ddagger$[d] cal/mole
1	Ia	3.131±0.011	3.107±0.020			
2	Ib	3.120±0.007	3.112±0.008	0.996		
3	Ia	3.108±0.014				
4	Ib	3.101±0.008		0.998		
5	Ia	3.082±0.011				
6	Ib	3.115±0.009		1.011	1.001±0.007	-0.6±4.1

[a] Initial concentration of sodium hydroxide and ester, 5 x 10^{-2} M; solvent, 56% acetone-water (w/w); temperature, 24.450°C.

[b] Isotopic purity for $\underline{d}_1$ compound: 98% $\underline{d}_1$, 2% $\underline{d}_0$.

[c] Ratio corrected for isotopic purity.

[d] $\Delta\Delta G^\ddagger = \Delta G_D^\ddagger - \Delta G_H^\ddagger$.

labeled and unlabeled compound were staggered and the second-order kinetic expression (1) was applied, with the initial concentrations of the reactants being the same.

$$[\mathrm{NaOH}]^{-1} = kt + [\mathrm{NaOH}]_0^{-1} \qquad (1)$$

Plots of $[\mathrm{NaOH}]^{-1}$ vs. t gave perfect straight lines. The data of a typical run are given in Table II and the corresponding plot in Figure 1. The percent standard deviation of individual runs in this series of experiments was from 0.26 to 0.45. The reported value (61) of the rate constant of the alkaline hydrolysis of methyl 1-naphthoate in the same solvent, but at 25°, is $3.465 \times 10^{-3}\ M^{-1}\ \mathrm{sec}^{-1}$.

The conductometric method used by Fischer and coworkers (54b) to measure the kinetics of the alkaline hydrolysis of various substituted naphthoic acid esters seemed, at first, to offer great convenience. In order to test this method for possible use in determining the rate constant of the alkaline hydrolysis of methyl 8-methyl-1-naphthoate and its 8-d_3 derivative (see next section) it was applied to redetermine the rate constants of hydrolysis of the esters in this section. The method is based on the assumption that the concentration of the carboxylate anion, x, is at any moment proportional to the conductance L of the solution, i.e.,

$$x = a + b\,L$$

$$\text{or} \quad [\mathrm{NaOH}] = [\mathrm{NaOH}]_0 - a - bL \qquad (2)$$

Table II. Rate Data for the Alkaline Hydrolysis[a] of Methyl 1-Naphthoate-8-d, by Titration of the Base. Run No. 2.[a]

Reading Number	Time min.	0.09807 N HCl ml	$[NaOH]^{-1} \times 10^{-2}$ M^{-1}
1	20	4.220	0.2404
2	35	3.786	0.2680
3	50	3.417	0.2970
4	65	3.125	0.3247
5	80	2.886	0.3516
6	95	2.665	0.3808
7	110	2.479	0.4093
8	125	2.334	0.4348
9	140	2.177	0.4661
10	155	2.063	0.4919
11	170	1.947	0.5212
12	185	1.852	0.5480
13	200	1.757	0.5776
14	220	1.649	0.6154

[a] $k = (3.120 \pm 0.007) \times 10^{-3}\ M^{-1}sec^{-1}$; temperature, 24.450° ; initial concentration of each reactant, 5×10^{-2} M; initial volume, 200 ml; solvent, 56% acetone-water (w/w).

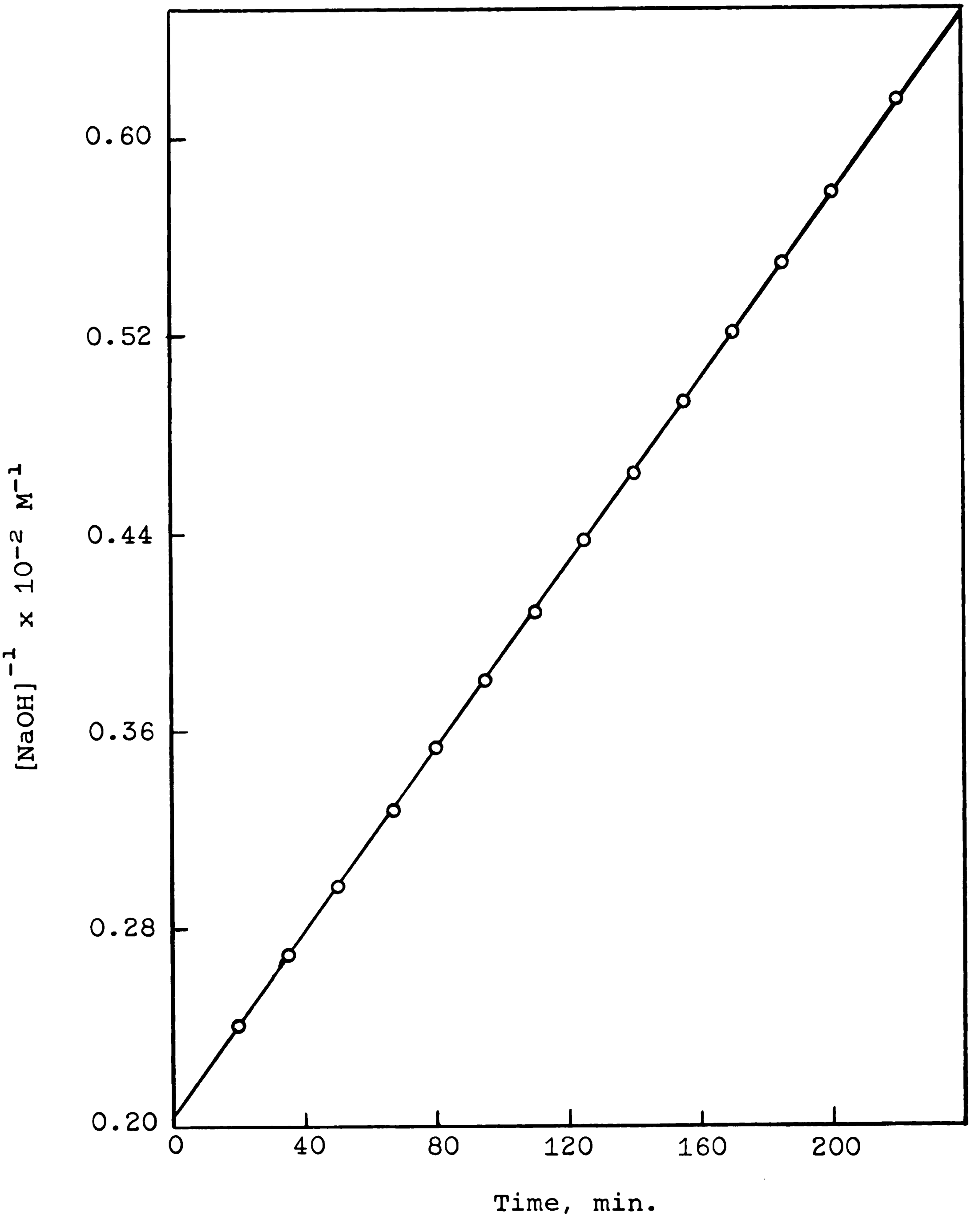


Figure 1. A second-order plot for the hydrolysis of methyl 1-naphthoate-8-d in 56% aqueous acetone (w/w), at 24.450° ; run No. 2, $[\mathrm{ESTER}]_o = [\mathrm{NaOH}]_o =$ 5×10^{-2} M, k = (3.120 ± 0.007) $\times 10^{-3}$ M^{-1} sec^{-1}.

where a, b are constants. From equations (1), (2) and three pairs of conductance-time values, (L_a, t_a), (L_m, t_m), (L_x, t_x) relationship (3) is easily derived:

$$[\mathrm{NaOH}]_o\, k = \frac{(L_m - L_x)(t_m - t_a) - (L_a - L_m)(t_x - t_m)}{t_a(L_a - L_m)(t_x - t_m) - t_x(L_m - L_x)(t_m - t_a)} \qquad (3)$$

Thirty pairs of L-t values were taken and ten values of k were computed. This was done by taking each time three pairs of L-t values as far from each other as possible. The results from this series of conductance measurements are summarized in Table III.

Table III. Rate Constants of Alkaline Hydrolysis[a] of Methyl 1-Naphthoate (Ia) and Methyl 1-Naphthoate-8-d (Ib), Measured by Conductance in 56% Aqueous Acetone (w/w), at 24.450°

Run Number	Compound	k x 10^3 $M^{-1}sec^{-1}$	Aver. k x 10^3 $M^{-1}sec^{-1}$
1	Ia	3.565 ± 0.120	
2	Ib	3.299 ± 0.107	
3	Ia	3.387 ± 0.085	3.417 ± 0.110

[a] Initial concentrations of the reactants, 5×10^{-2} M; Volume 200 ml.

Data of a typical run by this method are given in Table IV. The percent standard deviation of individual runs ranged from 3.37 (Run No. 1) to 2.51 (Run No. 3). Comparison of the data in Tables I and III shows that the reproducibility of the

Table IV. Conductance Rate Data of Alkaline Hydrolysis of Methyl 1-Naphthoate. Run No. 1.[a]

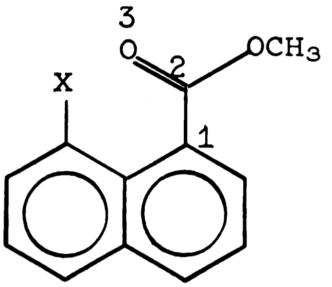
Reading Number	Time min.	L x 10^3 Mho	k x 10^3 $M^{-1}sec^{-1}$	Aver. k x 10^3 $M^{-1}sec^{-1}$
1	11.95	6.3040	3.759	
2	15.04	6.2514	3.729	
3	18.81	6.1899	3.682	
4	22.33	6.1353	3.593	
5	26.15	6.0827	3.577	
6	29.90	6.0324	3.508	
7	33.83	5.9845	3.474	
8	38.14	5.9363	3.475	
9	42.93	5.8857	3.471	
10	47.71	5.8378	3.379	3.565 ± 0.120
11	52.92	5.7892		
12	58.18	5.7447		
13	64.98	5.6903		
14	71.22	5.6459		
15	79.10	5.5933		
16	87.55	5.5427		
17	96.04	5.4958		
18	104.33	5.4540		
19	114.77	5.4055		
20	127.09	5.3555		
21	140.45	5.3062		
22	154.23	5.2611		
23	174.37	5.2017		
24	191.38	5.1587		
25	207.75	5.1218		
26	233.83	5.0707		
27	295.23	5.0274		
28	290.94	4.9828		
29	325.37	4.9413		
30	363.82	4.9003		

[a] Temperature, 24.450°C; initial concentration of each reactant, 5 x 10^{-2} M; volume, 200 ml; solvent, 56% acetone-water (w/w); measurements were taken at about equal decrements of the conductance.

titration method is much better than that of the conductance method, the percent standard deviations for the second method being ten times those of the first method. For this reason only the results from the titration method (Table I) were considered. The rather poor reproducibility of the conductance method must be due to the assumption that the conductance of the reacting solution is linearly proportional to the concentration of the carboxylate ion.

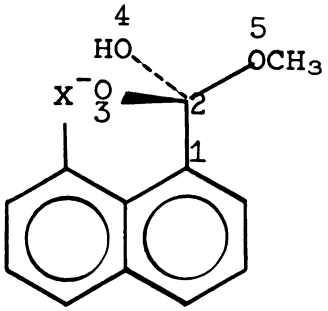
II. Comparison of the Observed and Calculated Effects

Experiments by Bender (62) involving labeled oxygen have shown that II is an intermediate. According to Hammond's Postulate (63) the transition state for the formation of the tetrahedral intermediate II resembles that intermediate closely (64). The increase or decrease of the steric interaction between the 8-substituent and the reaction site in going from the planar ground state to the tetrahedral-like transition state depends on the conformation of both the first and the second with respect to the aromatic ring. Calculations have shown (65) that the conformation of the transition state with the minimum energy would be as in IV, where the aromatic plane is bisecting the O_3-C_2-O_4 angle.



III

IIIa, X=H; IIIb, X=D



IV

IVa, X=H; IVb, X=D

Also it has been shown (65) that both the direction and magnitude of the isotope effect to be expected in this reaction strongly depend on the dihedral angle between the carbonyl group and the aromatic plane in III. These calculations have been carried out following Bartell's procedure (32), using two different forms of potential functions for the H···O steric interactions and varying the dihedral angle between the carbonyl group and the aromatic ring. The results are recorded in Table V. The first thing to be noted in Table V is the rather large deviation in magnitude between isotope effects calculated by using different potential functions, a fact which points to the great importance of chosing the right form of potential function. According to the experimental results (Table I) and assuming that the predictions of Table V are correct, the dihedral angle θ in the ground state III should be more than 50 degrees. This seems unreasonable in view of the crystallographic studies on the structure of 1-naphthoic acid. Trotter (52) has shown that

Table V. Calculated[a] Isotope Effects for the Alkaline Hydrolysis of Methyl 1-Naphthoate and Its 8-Deuterium Analog at 25°

Function Used	θ[b] Degrees	$\Delta\Delta E$(Calc.)[f] cal/mole	k_H/k_D(Calc.)[c]
Bartell's[e]	0	-270	1.57
Bartell's	15	-206	1.42
Bartell's	30	-111	1.21
Bartell's	45	-10.4	1.02
Bartell's	90	50	0.92
Scheraga's[d]	0	-160	1.31
Scheraga's	15	-124	1.23
Scheraga's	30	-53	1.09
Scheraga's	45	-5.7	1.01
Scheraga's	90	14	0.98

[a] Ref. 65.

[b] Dihedral angle of the carbonyl and aromatic planes.

[c] Calculated from $\Delta\Delta E$.

[d] Ref. 66.

[e] Ref. 32.

[f] $\Delta\Delta E = \Delta E_H - \Delta E_D$.

the carbonyl group in 1-naphthoic acid is twisted out of the plane of the ring by only 11 degrees. The discrepancy may arise from the assumptions involved in the above calculations (65). First, the potential functions used for the H···O interactions in the ground state and the transition state were the same although the carbonyl oxygen atom has acquired much more negative charge in the transition state by attack of the carbonyl group by hydroxide ion. The use of the same potential functions underestimates the calculated value of the H···O steric interaction in the transition state, and, therefore, increases the k_H/k_D ratio. Second, the transition state leading to intermediate IV must be actually different than IV, with the dihedral angle between the O_3-C_2-C_1 plane and the aromatic plane being less than the assumed 60 degrees. In this case the X···O_3 distance would be smaller and the associated X···O interaction greater. The calculated k_H/k_D ratio is thus larger than it should be. As a result of these uncertainties definite conclusions about the applicability of Bartell's theory in the present case are impossible.

B. Alkaline Hydrolysis of Methyl 8-Methyl-1-naphthoate

Difficulties were encountered in attempting to determine the rate constant of the alkaline hydrolysis of methyl 8-methyl-1-naphthoate by the titrimetric method. Steric effects being important in $B_{AC}2$ reactions, it was expected that methyl 8-methyl-1-naphthoate would hydrolyze at a much slower rate than methyl 1-naphthoate. From the data of Fischer and co-workers (54b) it is found by extrapolation that the rate constant of the alkaline hydrolysis of methyl 8-nitro-1-naphthoate in 85% ethanol-water (w/w) is $1.80 \times 10^{-6} M^{-1} sec^{-1}$ at 25^{o}. This value is 158 times lower than that for the parent compound. Indeed, the reaction rate at room temperature in 56% aqueous acetone (w/w) was far too slow for measurement.

The conductometric method used by Fischer and co-workers (54b), which is much more sensitive in measuring small changes in the base concentration, was tried next. The main problem encountered was the reaction of the alkali with the Pyrex glass of the conductance cell at a rate comparable to that of the hydrolysis. In a series of blank runs, the conductance of a 5×10^{-2} M solution of sodium hydroxide in 56% acetone-water (w/w) solution kept decreasing for a period of about 8 hours. This change of conductance with time was irregular and attempts to fit it into some form of a simple linear or exponential equation proved unsuccessful. Increase of the temperature to 50^{o} increased the rate of hydrolysis as well as the rate of the alkali-Pyrex glass reaction. In spite of these shortcomings Fischer's conductometric method provided a better alternative to the titration method. The results of the run with the smallest standard deviation are recorded in Table VI. As can be seen the reproducibility of the method

Table VI. Rate Data from the Conductometric Determination[a] of the Rate Constant of the Alkaline Hydrolysis of Methyl 8-Methyl-1-naphthoate at 50°

Reading Number	Time min.	$L^b \times 10^3$ Mho	$R^c \times 10^{-2}$ Ohm	$k \times 10^6$ $M^{-1}sec^{-1}$	Aver.$k \times 10^6$ $M^{-1}sec^{-1}$
11	91.94[d]				
12	122.40	8.7692	1.1403		
13	139.80	8.7797	1.1389		
14	153.43	8.7898	1.1376	7.471	
15	168.24	8.7889	1.1377	7.172	
16	185.36	8.7874	1.1379	7.162	
17	224.05	8.7824	1.1386	7.951	
18	255.37	8.7783	1.1391	8.163	
19	298.45	8.7714	1.1400	8.916	
20	365.39	8.7643	1.1409	8.863	
21	408.37	8.7555	1.1421	9.869	
22	435.03	8.7550	1.1422	9.405	8.33 ± 0.92

[a] See Experimental section.

[b] Conductance of the solution.

[c] Resistance of the solution.

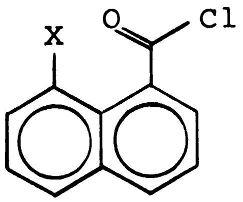
[d] Time of addition of the ester.

is rather poor and unsatisfactory for the present study. The percent standard deviation of the recorded run is 11%. The slight increase of the conductance of the solution, shortly after the addition of the ester, is unexpected and should be noted. The k-value must, therefore, be considered as tentative and only indicative of the order of magnitude of the real value.

C. Solvolysis of 8-X-1-Naphthoyl Chlorides and Their 8-Deuterated Derivatives

I. General

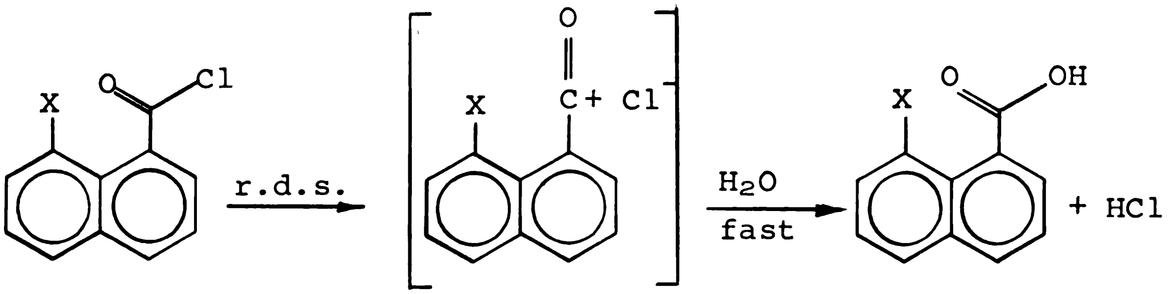
As mentioned in the Introduction, the study of the hydrolyses of acid chlorides of the general type V would offer a good opportunity for an estimation of the contribution of the steric factor to secondary kinetic isotope effects.



V

Va, X = H
Vb, X = D
Vc, X = CH_3
Vd, X = CD_3
Ve, X = Br

Provided that this solvolysis proceeds by the S_N1 mechanism via an acylium ion-like transition state as depicted below, all three conditions set forth in the Introduction as necessary for such a study are met in the present system.



V VI

For compounds Va-Vd, calculations of the steric isotope effect have been carried out (65) by using both Bartell's (32) and Scheraga's (66) potential functions. The magnitude of the steric interactions between the 8-substituent and the carbonyl group depends on the dihedral angle between the carbonyl and aromatic planes. For the least crowded compound, 1-naphthoyl chloride (Va), when the dihedral angle is zero degrees, the interaction between the peri-hydrogen and the carbonyl group, calculated by using the less "hard" Scheraga's potential function, amounts to about 4 kcal/mole. The peri-interaction is more severe in the more crowded 8-methyl-1-naphthoyl chloride.

II. Previous Mechanistic Studies

Among others, Brown and Hudson (67) have studied the mechanism of the hydrolysis of aromatic acid chlorides extensively. For substituted benzoyl chlorides they found that whereas the parent compound hydrolyzes by a mixed mechanism, mesitoyl chloride hydrolyzes by a purely limiting S_N1

mechanism, due partly to the steric effect of the two ortho-methyl groups and partly to the hyperconjugation effect of all three methyl groups. For the hydrolysis of the same chloride in 99% acetonitrile-water the Hammett ρ-constant is -3.85 (68). It was imperative for the study of isotope effects in this system to establish the mechanism of the reaction, therefore a study of this mechanism was undertaken first.

III. The Kinetic Method

The rate of the hydrolysis was followed conductometrically by measuring the changes of the hydrogen chloride concentration x with time t. For the concentration ranges and the mixed solvents used in the present study the relationship between the concentration x of hydrogen chloride, which is the only strong electrolyte in the solution, and the conductance L of the solution is linear and has the form (21b, 20)

$$x = a' + b'L \tag{6}$$

where a', b' are constants. This form has given excellent results in cases of solvolyses of alkyl chlorides (13,27). For first order kinetics,

$$\ln \frac{A_o}{A} = kt \tag{7}$$

where A_o and A are the concentrations of the acid chloride at times 0 and t. At times t and ∞,

$$A_o = x_\infty = a' + b'L_\infty \qquad (8)$$

and

$$A = A_o - x = x_\infty - x = b'(L_\infty - L). \qquad (9)$$

From equations (6), (7), (8), and (9) equation (10) is derived.

$$\ln(L_\infty - L) = -kt + \ln(\frac{a'}{b'} + L_\infty). \qquad (10)$$

Equation (10) implies that if the assumption made about the relationship of the hydrogen chloride concentration x and the conductance L of the solution (equation 6) is correct and the reaction follows first-order or pseudo-first-order kinetics, ln $(L_\infty - L)$ has to be a linear function of the time. This was fully justified by the results in this study (vide infra).

This kinetic method offers several advantages. Calibration of the conductance cell and accurate determination of its constant are unnecessary. In addition, the initial concentration of the reactant does not need to be accurately known. In general, the reproducibility of the method is satisfactory.

IV. Hydrolysis of 1-Naphthoyl Chloride and Its 8-Deuterium Analog

The rate constants and isotope effects of the hydrolysis of 1-naphthoyl chloride and its 8-deuterium analog were determined in 90 and 95% acetone-water (w/w) solutions at three temperatures in the 15-35° range. The results are given in Table VII. The standard deviation for individual runs being usually well below 1%, the isotope effects found are statistically significant. The runs for the protium and deuterium compounds were usually staggered. In accord with and supporting equation (6) plots of $\ln(L_\infty - L)$ vs. t gave perfect straight lines. Data of a typical run are given in Table VIII and the corresponding plot in Figure 2.

From the appropriate data in Table VII the thermodynamic activation parameters were calculated and are recorded in Table IX.

V. Hydrolysis of 8-Bromo-1-naphthoyl Chloride

In order to obtain evidence about the steric effect of the 8-substituent on the rate of solvolysis of 8-X-1-naphthoyl chlorides (V), and therefrom elucidate the mechanism of the reaction (*vide infra*), the solvolysis of 8-bromo-1-naphthoyl chloride (Ve) in aqueous acetone was studied and the rate constant determined. The results are given in Table X.
It should be mentioned that this reaction also followed first-order kinetics and as in the previous case plots of $\ln(L_\infty - L)$ vs. t gave perfect straight lines.

VI. Hydrolysis of 8-Methyl-1-naphthoyl Chloride and Its 8-d_3 Analog

The rate constants and isotope effects of the hydrolysis of 8-methyl-1-naphthoyl chloride (Vc) and 8-methyl-d_3-1-naphthoyl

Table VII. Rate Constants and Isotope Effects of the Hydrolyses of 8-X-1-Naphthoyl Chlorides Va and Vb[a] in 90% Acetone-Water (w/w)

Run Number	X Group	Temp. °K	k x 10^4 sec^{-1}	Aver. k x 10^4 sec^{-1}	k_H/k_D[b]
1	H	288.274	0.849 ± 0.004		
2	H	288.274	0.846 ± 0,004	0.847 ± 0.003	0.999 ± 0.009
3	H	297.607	1.806 ± 0.009		
4	H	297.607	1.796 ± 0.012		
5	H	297.607	1.822 ± 0.002		
6	H	297.607	1.771 ± 0.005	1.799 ± 0.018	0.994 ± 0.013
7	H	307.388	3.914 ± 0.010		
8	H	307.388	3.925 ± 0.012		
9	H	307.388	3.920 ± 0.014	3.920 ± 0.005	0.998 ± 0.002
10	D	288.274	0.847 ± 0.003		
11	D	288.274	0.849 ± 0.003	0.848 ± 0.002	
12	D	297.607	1.788 ± 0.008		
13	D	297.607	1.912 ± 0.009		
14	D	297.607	1.818 ± 0.005		
15	D	297.607	1.786 ± 0.008		
16	D	297.607	1.845 ± 0.006	1.809 ± 0.024	
17	D	307.388	3.942 ± 0.010		
18	D	307.388	3.929 ± 0.012		
19	D	307.388	3.911 ± 0.009	3.927 ± 0.013	
20[c]	H	297.607	0.542 ± 0.011		
21[c]	H	297.607	0.546 ± 0.008	0.544 ± 0.008	

[a] Isotopic purity for $\underline{d}_1$ compound: 98% $\underline{d}_1$, 2% $\underline{d}_0$.

[b] Ratio corrected for isotopic purity.

[c] Solvent, 95% acetone-water (w/w).

Table VIII. Conductance Rate Data from the Solvolysis of 1-Naphthoyl Chloride-8-d(Vb) in 90% Acetone-Water (w/w), at 25°. Run No. 13.

Reading Number	Time min.	$L^a \times 10^3$ Mho	6+log $(L_\infty - L)^b$	$k \times 10^4$ sec^{-1}
1	37.28	0.0800	2.09132	
2	44.17	0.0900	2.05461	
3	50.97	0.0990	2.01870	
4	58.58	0.1080	1.97955	
5	66.05	0.1160	1.94151	
6	76.71	0.1262	1.88762	
7	86.51	0.1344	1.83885	
8	97.46	0.1424	1.78533	
9	107.46	0.1490	1.73560	
10	117.98	0.1550	1.68485	
11	127.98	0.1600	1.63749	
12	132.26	0.1620	1.61700	1.912±0.009

[a] Conductance of the solution.

[b] The infinity value of the conductance, L_∞, was taken after 800 min and was 0.2034 x 10^{-3} Mho.

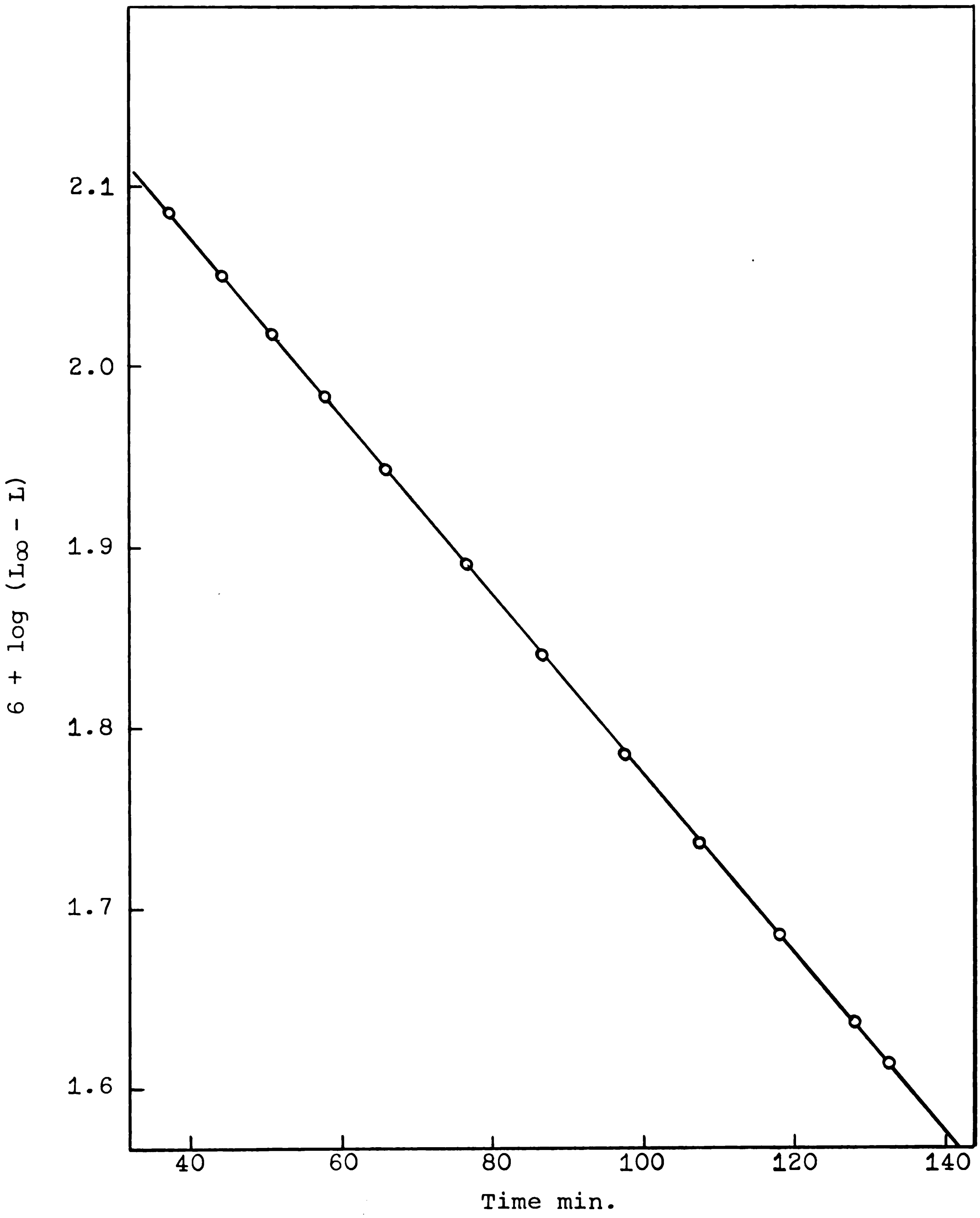


Figure 2. Plot of rate data from Table VIII.

Table IX. Thermodynamic Activation Parameters[a] for the Hydrolyses of 8-X-1-Naphthoyl Chlorides Va and Vb in 90% Acetone-Water (w/w)

X Group	Ea^{b} cal/mole	$\Delta H^{\ddagger b}$ cal/mole	$\Delta G^{\ddagger b}$ cal/mole	$\Delta S^{\ddagger b}$ e.u./mole
H	14,113±114	13,540±114	22,229±2	-30.15±0.39
D	14,125±80	13,552±80	22,228±4	-30.10±0.28

[a] Slope $d\underline{\ln}k/d(1/T)$ found by the least-squares method in the 15-35° range.

[b] Calculated according to Reference 11, p. 178, at 15°.

Table X. Rate Constants of Hydrolysis of 8-Bromo-1-naphthoyl Chloride (Ve) in 95% Acetone-Water (w/w), at 24.447°

Run Number	$k \times 10^{4}$ sec^{-1}	Aver. $k \times 10^{4}$ sec^{-1}
1	1.519 ± 0.008	
2	1.517 ± 0.005	
3	1.514 ± 0.009	1.517 ± 0.002

chloride (Vd) were determined at two different temperature ranges and in two different acetone-water mixtures. The first study was carried out at room temperatures (15-35^{o}) and in 95% acetone-water (w/w) solution. Then, in order to examine the change of the isotope effect with temperature and also the change in the entropy of activation with the percentage of acetone in the mixed solvent (vide infra), the same reaction was studied at low temperatures (-34^{o} to -20^{o}) and in 75% acetone-water (w/w) mixtures. The results are summarized in Tables XI and XII. As in the case of the previous acid chlorides, the reaction followed first-order kinetics with the fitting of the data to the first-order kinetic expression showing very low deviations. The runs for the protium and deuterium compounds were usually staggered. From the data in Tables XI and XII the thermodynamic activation parameters for the hydrolysis of 8-methyl-1-naphthoyl chloride and 8-methyl-d_3-1-naphthoyl chloride in 95% and 75.23% acetone water (w/w) were calculated. They are recorded in Tables XIII and XIV respectively.

VII. The Mechanism of Hydrolysis of the Acid Chlorides

Steric hindrance decreases the rate of S_N2 reactions and increases that of S_N1 reactions. The relative rates of hydrolysis of 8-X-1-naphthoyl chlorides (V) are summarized in Table XV.

Table XI. Rate Constants and Isotope Effects in the Hydrolysis of 8-X-1-Naphthoyl Chlorides Vc and Vd[a] in 95%-Acetone-Water (w/w), in the Room Temperature Range

Run Number	X Group	Temp °K	k x 10^4 sec^{-1}	Aver. k x 10^4 sec^{-1}	k_{CH_3}/k_{CD_3} [b]
1	CH_3	288.274	2.048±0.003		
2	CH_3	288.274	2.076±0.003		
3	CH_3	288.274	2.026±0.006	2.050±0.020	1.016±0.011
4	CD_3	288.274	2.031±0.002		
5	CD_3	288.274	2.023±0.002		
6	CD_3	288.274	2.004±0.006	2.019±0.011	
7	CH_3	297.607	4.706±0.048		
8	CH_3	297.607	4.734±0.028		
9	CH_3	297.607	4.616±0.065		
10	CH_3	297.607	4.752±0.013		
11	CH_3	297.607	4.637±0.011		
12	CH_3	297.607	4.700±0.017		
13	CH_3	297.607	4.580±0.012	4.675±0.059	1.030±0.015
14	CD_3	297.607	4.568±0.038		
15	CD_3	297.607	4.541±0.019		
16	CD_3	297.607	4.580±0.031		
17	CD_3	297.607	4.498±0.045		

18	CD_3	297.607	4.485±0.011		
19	CD_3	297.607	4.537±0.015		
20	CD_3	297.607	4.589±0.019		
21	CD_3	297.607	4.575±0.032		
22	CD_3	297.607	4.522±0.015	4.544±0.034	
23	CH_3	307.388	9.791±0.020		
24	CH_3	307.388	9.876±0.013		
25	CH_3	307.388	9.935±0.015		
26	CH_3	307.388	10.283±0.037	9.971±0.189	1.013±0.026
27	CD_3	307.388	9.743±0.022		
28	CD_3	307.388	9.722±0.017		
29	CD_3	307.388	9.920±0.033		
30	CD_3	307.388	9.666±0.019		
31	CD_3	307.388	9.934±0.017		
32	CD_3	307.388	9.759±0.031		
33	CD_3	307.388	10.233±0.048	9.854±0.181	
34[c]	CH_3	288.274	1.821±0.004		
35[c]	CH_3	288.274	1.802±0.005		
36[c]	CH_3	288.274	1.724±0.006	1.782±0.042	0.992±0.025
37[c]	CD_3	288.274	1.792±0.002		
38[c]	CD_3	288.274	1.781±0.003		
39[c]	CD_3	288.274	1.819±0.002	1.797±0.016	

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[a] Isotopic purity for $\underline{d}_3$ compounds: 97.3% $\underline{d}_3$, 2.7% $\underline{d}_2$. We thank Mr. S. Meyerson of American Oil Company, Whiting, Indiana, for the mass spectral analyses.

[b] Ratio corrected for isotopic purity.

[c] Solvent, 95.24% acetone-water (w/w).

Table XII. Rate Constants and Isotope Effects in the Hydrolysis of 8-X-1-Naphthoyl Chlorides Vc and Vd[a] in 75.23% Acetone-Water (w/w) at Low Temperatures

Run Number	X Group	Temp. °K	k x 10^4 sec^{-1}	Aver. k x 10^4 sec^{-1}	k_{CH_3}/k_{CD_3}[b]
1	CH_3	239.157	1.009±0.004		
2	CH_3	239.157	1.004±0.002		
3	CH_3	239.157	1.006±0.004	1.006±0.002	1.168±0.009
4	CD_3	239.157	0.870±0.009		
5	CD_3	239.157	0.858±0.004		
6	CD_3	239.157	0.858±0.003	0.862±0.006	
7	CH_3	246.547	2.930±0.011		
8	CH_3	246.547	3.034±0.004		
9	CH_3	246.547	2.976±0.005	2.980±0.042	1.127±0.018
10	CD_3	246.547	2.715±0.014		
11	CD_3	246.547	2.583±0.010		
12	CD_3	246.547	2.637±0.020	2.645±0.053	
13	CH_3	252.707	7.422±0.015		
14	CH_3	252.707	7.211±0.024		
15	CH_3	252.707	7.009±0.194	7.214±0.168	1.129±0.026
16	CD_3	252.707	6.370±0.054		
17	CD_3	252.707	6.398±0.030		
18	CD_3	252.707	6.389±0.070	6.386±0.012	
19[c]	CH_3	246.547	6.758±0.005		
20[d]	CH_3	241.274	0.645±0.001		

[a] Isotopic purity for $\underline{d}_3$ compounds: 97.3% $\underline{d}_3$, 2.7% $\underline{d}_2$.

[b] Ratio corrected for isotopic purity.

[c] Solvent, 70% acetone-water (w/w).

[d] Solvent, 80% acetone-water (w/w).

Table XIII. Thermodynamic Activation Parameters[a] for the Hydrolysis of 8-X-1-Naphthoyl Chlorides Vc and Vd in 95% Acetone-Water (w/w)

X Group	Ea^b cal/mole	$\Delta H^{\ddagger b}$ cal/mole	$\Delta G^{\ddagger b}$ cal/mole	$\Delta S^{\ddagger b}$ e.u./mole
CH_3	14,577±238	14,005±238	21,722±3	-26.77±0.83
CD_3	14,607±49	14,034±47	21,731±3	-26.69±0.08

[a] Slope d*ln*k/d(1/T) calculated by the least-squares method in the 15-35° range.

[b] Calculated according to Reference 11, p. 178, at 15°.

Table XIV. Thermodynamic Activation Parameters[a] for the Hydrolysis of 8-X-1-Naphthoyl Chlorides Vc and Vd in 75.23% Acetone-Water (w/w)

X Group	Ea^b cal/mole	$\Delta H^{\ddagger b}$ cal/mole	$\Delta G^{\ddagger b}$ cal/mole	$\Delta S^{\ddagger b}$ cal/mole
CH_3	17,448±94	16,946±94	18,344±11	-5.32±0.37
CD_3	17,755±138	17,253±138	18,405±1	-4.56±0.54

[a] Slope d*ln*k/d(1/T) calculated by the least-squares method in the temperature range -34° to -20°.

[b] Calculated according to Reference 11, p. 178, at -20°.

Table XV. Rate Constants of the Hydrolysis of 8-X-1-Naphthoyl Chlorides (V) in 95% Acetone-Water (w/w), at 24.447°

X Group	$k \times 10^4$ sec^{-1}	Relative Rate
H	0.542±0.011	1.00
Br	1.517±0.002	2.80
CD_3	4.544±0.034	8.38
CH_3	4.675±0.059	8.62

It is clear that increase of the effective volume of the 8-substituent enhances the rate of the reaction. If 1-naphthoyl chloride and 8-methyl-1-naphthoyl chloride hydrolyzed by an S_N2 and a mixed S_N1-S_N2 mechanism respectively, from the 10^3 ratio of the rate constants of the alkaline hydrolysis of methyl 1-naphthoate (Table I) and methyl 8-methyl-1-naphthoate (Table VI), one would expect 8-methyl-1-naphthoyl chloride to solvolyze more slowly than 1-naphthoyl chloride by several orders of magnitude. 8-Methyl-1-naphthoyl chloride, therefore, solvolyzes by an S_N1 mechanism.

One possible objection to postulating an S_N1 mechanism for the hydrolysis of 8-methyl-1-naphthoyl chloride is the sign and magnitude of the entropy of activation, -26.77 e.u./mole, observed in 95% acetone-water (Table XIII). However, there are numerous examples of S_N1 solvolyses in solvents similar to those used here in which the entropy of activation has large negative values. Some of these are tabulated in Table XVI.

Table XVI. Entropy of Activation Values for S_N1 Solvolyses in Various Solvents

Number	Compound	Solvent[a]	Temp. °C	$\Delta S^{\ddagger}$ e.u./mole	Reference
	Ar- in $ArCHClC_6H_5$				
1	Phenyl	90% Acetone	25	-18.5	55f
2	1-Naphthyl	90% Acetone	25	-16.7	55f
3	2-Naphthyl	90% Acetone	25	-17.8	55f
4	1-Pyrenyl	90% Acetone	25	-23.2	55f
	Ar- in $ArCHClCH_3$				
5	2-Fluorenyl	90% Acetone	25	-13.7	55c
6	2-Fluorenyl	80% Acetone	25	-6.5	55c
7	9-Anthryl	90% Acetone	25	-16.7	55c
8	3-Pyrenyl	90% Acetone	25	-14.0	55c
9	t-BuCl	90% Acetone	25	-16.8	69
10	t-BuCl	80% Acetone	25	-11.0	69
11	t-BuCl	70% Acetone	25	-10.0	69
12	p-FC_6H_4-	90% Acetone	25	-11.7	70
13	p-ClC_6H_4	90% Acetone	25	-13.6	70
14	p-BrC_6H_4	90% Acetone	25	-15.2	70
15	p-IC_6H_4	90% Acetone	25	-16.0	70
16	p-$CH_3OC_6H_4$-	94.8% Acetone	25	-21.1	71
17	1-Adamantyl-CH_2OTs	HOAc	100	-13.2	72
18	1-Adamantyl-CH_2ONs	HOAc	119	-16.2	72
19	t-BuCl	50% Ethanol	20	-2.9	39
20	t-BuCl	H_2O	20	14.4	39

[a] Volume percent.

In general, these negative entropies of activation result from the changes in solvent orientation (69). The usual increase of the entropy of activation with increase of percent polar component in the mixed solvent (Nos. 5, 6 and 9, 10, 11 in Table XVI) was also observed in the present study of the hydrolysis of 8-methyl-1-naphthoyl chloride (Tables XIII and XIV).

In summary, therefore, 8-methyl-1-naphthoyl chloride and its 8-d_3 analog solvolyze by a limiting S_N1 mechanism. Under the circumstances it is rather difficult to postulate a mechanism for the hydrolysis of 1-naphthoyl chloride. Most likely it is a mixed S_N1-S_N2 type mechanism.

VIII. Isotope Effects of Steric Origin

A summary of the most significant results obtained in the present study is given in Table XVII. In order to correlate the hydrolyses of 8-methyl-1-naphthoyl chloride and its 8-d_3-analog in the two different solvents and at the two different temperature ranges, the results in Tables XI and XII were extrapolated to the low temperature range (-34° to -20°) and to the room temperature range (15-35°) respectively. The computed values are also included in Table XVII. The isotope effects calculated by using Bartell's model (65) for the hydrolysis of 1-naphthoyl chloride-8-d and 8-methyl-d_3-1 naphthoyl chloride are recorded in Tables XVIII and XIX respectively.

Table XVII. Combined Kinetic Data for the Hydrolysis of 8-X-1-Naphthoyl Chlorides (V)

X Group	Solvent percent acetone[a]	Temp. °K	$k \times 10^4$ sec^{-1}	k_H/k_D	$\Delta\Delta G^{\ddagger b}$ cal/mole	$\Delta\Delta H^{\ddagger c}$ cal/mole	$\Delta\Delta S^{\ddagger d}$ e.u./mole
<u>Observed</u>[e]							
H	90	288.274	0.847	0.999±0.009	0±4	12±139	0.06±0.48
D	90	288.274	0.848				
H	90	297.607	1.799	0.994±0.013			
D	90	297.607	1.809				
H	90	307.388	3.920	0.998±0.002			
D	90	307.388	3.927				
CH_3	95	288.274	2.050	1.016±0.011	9±4	29±243	0.07±0.83
CD_3	95	288.274	2.019				
CH_3	95	297.607	4.675	1.030±0.015			
CD_3	95	297.607	4.544				
CH_3	95	307.388	9.971	1.013±0.026			
CD_3	95	307.388	9.854				
CH_3	75.23	239.157	1.006	1.168±0.009			
CD_3	75.23	239.157	0.862				
CH_3	75.23	246.547	2.980	1.127±0.018			
CD_3	75.23	246.547	2.645				
CH_3	75.23	252.707	7.214	1.129±0.026	61±11	307±167	0.97±0.66
CD_3	75.23	252.707	6.386				
<u>Computed</u>[f]							
CH_3	95	239.157	1.132[g]	1.042±0.015			
CD_3	95	239.157	1.087[g]				
CH_3	95	246.547	2.838[g]	1.039±0.015			
CD_3	95	246.547	2.730[g]				
CH_3	95	252.707	5.862[g]	1.038±0.015	19±4	30±243	0.05±0.08
CD_3	95	252.707	5.650[g]				

CH_3	75.23	288.274	0.516[h]	1.029±0.025			
CD_3	75.23	288.274	0.502[h]				
CH_3	75.23	297.607	1.342[h]	1.012±0.025	7±10	307±167	1.01±0.09
CD_3	75.23	297.607	1.326[h]				
CH_3	75.23	307.388	3.434[h]	0.996±0.027			
CD_3	75.23	307.388	3.446[h]				

[a] Weight by weight percentage.

[b] $\Delta\Delta G^{\ddagger} = \Delta G_D^{\ddagger} - \Delta G_H^{\ddagger}$.

[c] $\Delta\Delta H^{\ddagger} = \Delta H_D^{\ddagger} - \Delta H_H^{\ddagger}$.

[d] $\Delta\Delta S^{\ddagger} = \Delta S_D^{\ddagger} - \Delta S_H^{\ddagger}$.

[e] Data from Tables VII, IX, XI, XII, XIII and XIV.

[f] From extrapolation of the observed data.

[g] $k \times 10^{-6}$ in sec^{-1}.

[h] k in sec^{-1}.

From the information obtained in this work nothing can be said with certainty about the transition state of the hydrolysis of 1-naphthoyl chloride. Consequently, one could not correlate the observed absence of isotope effects (Table XVII) with those predicted by Bartell's theory (Table XVIII), since the latter have been calculated on the assumption that the transition state is represented by an acylium ion. However, the very absence of any isotope effect is good evidence that the reaction takes place mostly by an S_N2 mechanism.

The hydrolysis of 8-methyl-1-naphthoyl chloride and its 8-d_3 analog, as mentioned, proceeds via an acylium ion-like transition state. Considering the greater effective volume of the CH_3 group vs. the CD_3 group (41), the decrease of the steric interaction between 8-substituent and reaction site in the transition state should lead to $k_H/k_D > 1$. The magnitude of this k_H/k_D depends on such factors as the conformation of the ground state (dihedral angle of the carbonyl and the aromatic planes, conformation of the 8-methyl group), the form of the transition state (extent of breaking of the C-Cl bond, configuration of the 8-methyl group), and the interaction of the solvent with the ground and transition states. In calculating the results of Tables XVIII and XIX some of these factors, like the conformation of the ground and transition states, have been taken into account. Others, like the solvent effect, are very difficult to estimate quantitatively. The dependence of the calculated values on the

Table XVIII. Calculated[a] Isotope Effects for the Hydrolysis of 1-Naphthoyl Chloride-8-d at 25°

Function Used	θ[b] Degrees	$\Delta\Delta E$(Calc.)[c] cal/mole	k_H/k_D(Calc.)[d]
Bartell's[e]	0	317	1.70
Bartell's	15	253	1.53
Bartell's	30	158	1.31
Bartell's	45	57	1.10
Bartell's	90	-3	1.00
Scheraga's[f]	0	183	1.36
Scheraga's	15	147	1.28
Scheraga's	30	76	1.14
Scheraga's	45	29	1.05
Scheraga's	90	-8	0.99

[a] Reference 65.

[b] Dihedral angle of the carbonyl and aromatic planes.

[c] $\Delta\Delta E = \Delta E_D - \Delta E_H$.

[d] Calculated from $\Delta\Delta E$.

[e] Reference 32.

[f] Reference 66.

Table XIX. Calculated[a] Isotope Effects for the Hydrolysis of 8-Methyl-d_3-1-naphthoyl Chloride at 25°

Function Used	θ[b] Degrees	$\Delta\Delta E$(Calc.)[c] cal/mole	k_H/k_D(Calc.)[d]
Bartell's[e]	0	1380	10.20
Bartell's	15	1150	6.94
Bartell's	30	576	2.64
Bartell's	45	288	1.63
Bartell's	90	89	1.16
Scheraga's[f]	0	662	3.03
Scheraga's	15	554	2.53
Scheraga's	30	302	1.66
Scheraga's	45	125	1.23
Scheraga's	90	14	1.02

[a] Reference 65.

[b] Dihedral angle of the carbonyl and aromatic planes.

[c] $\Delta\Delta E = \Delta E_D - \Delta E_H$.

[d] Calculated from $\Delta\Delta E$.

[e] Reference 32.

[f] Reference 66.

form of the potential function used must be stressed once more.

From Table XVII it is clear that the size of the isotope effect increases in the more aqueous solvent. This may be due to the C-Cl bond in the transition state being broken to a greater extent in the more aqueous solvent, or to some entropy effect. One of the purposes of the temperature studies was to separate the observed $\Delta\Delta G^{\ddagger}$ into its $\Delta\Delta H^{\ddagger}$ and $T\Delta\Delta S^{\ddagger}$ components since Bartell's theory (32) accounts for that part of the isotope effect which is due exclusively to $\Delta\Delta H^{\ddagger}$. From the values in the 15-35° range this separation failed, because of the relatively high standard error; it became possible in the low temperature range. Thus, as can be seen in Table XVII, the observed isotope effect must be the result of two opposite isotope effects: a normal isotope effect due to $\Delta\Delta H^{\ddagger}$ and a reverse isotope effect due to $\Delta\Delta S^{\ddagger}$. Cases of isotope effects attributed to the $T\Delta\Delta S^{\ddagger}$ component of $\Delta\Delta G^{\ddagger}$ are not unusual in the literature. The secondary isotope effects observed in the hydrolysis of isopropyl-d_6 methanesulfonate, toluenesulfonate and bromide were found to be due exclusively to $T\Delta\Delta S^{\ddagger}$ (73). Halevi and Margolin (74) showed that the isotope effect observed by Bender and Feng (30a) in the alkaline hydrolysis of ethyl trideuteroacetate is also due to $T\Delta\Delta S^{\ddagger}$. One could conclude, therefore, that non-bonded interactions do cause isotope effects of the magnitude predicted by Bartell's theory. For example, for a value of the dihedral angle of about 45°, which is a reasonable angle to assume (34), the observed $\Delta\Delta H^{\ddagger}$ of about 300 cal/mole (Table XVII) is in good agreement with that predicted by Bartell's theory (Table XIX).

In conclusion, from the accumulated experimental data and preceding discussion it therefore appears that reasonable estimates of isotope effects due to nonbonded interactions can be obtained by using Bartell's model and procedure. The choice of the potential function, however, is rather crucial for accurate estimates of these effects.

D. Synthesis

The compounds used in the kinetic studies were prepared according to the scheme visualized in Figure 3.

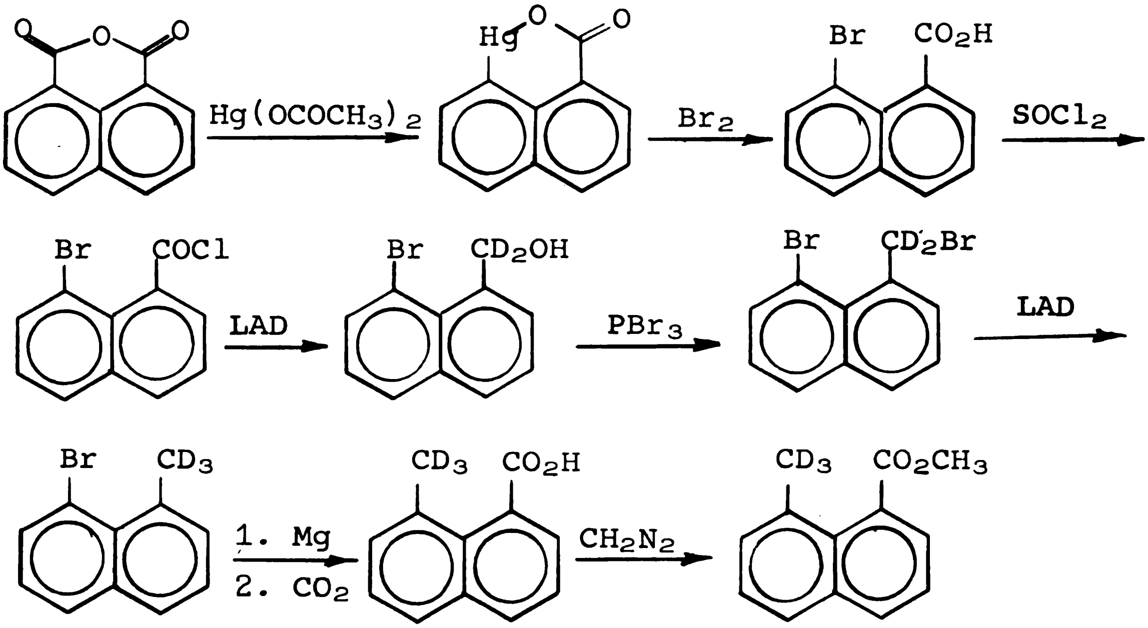

Figure 3. Synthetic scheme.

A quantity of 1-naphthoic acid-8-d was provided by R. L. Shone (79).

EXPERIMENTAL

A. Preparative Part

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

The general procedure given in Organic Syntheses (75) was applied. In a 2-liter, round-bottomed flask, 19.8 g (0.1 mole) of 1,8-naphthalic anhydride (Aldrich Chemical Co., Inc., m.p. 272-4°C) was suspended in a solution of 14 g (0.35 mole) sodium hydroxide in 600 ml of water. The suspension was refluxed until complete solution was attained. To this, while hot, a solution of 35 g (0.11 mole) of mercuric acetate in about 15 ml of glacial acetic acid and 75 ml of water was added and the new solution was made acidic by adding about 25 ml of glacial acetic acid. The flask was fitted again with the condenser which was equipped this time with a rubber tubing attached at the top, its other end submerged in a beaker of water. The refluxing was continued until evolution of carbon dioxide ceased (about 24 hours). The mixture was allowed to settle and the hot supernatant liquid was poured through a preheated suction filter. The product was washed in the flask by shaking with water several times and then transferred to the filter. After the product was dried, the suction was turned off, and 50 ml of ethanol was added.

Suction was reapplied. Finally the product was washed once with ether and dried. Yield, 92%.

II. Preparation of 8-Bromo-1-naphthoic Acid

The procedure of Rule *et al*. (76) was used. In 150 ml of glacial acetic acid and 25 ml of water in a round-bottomed, 3-necked liter flask, equipped with a mechanical stirrer, was suspended 36.56 g (0.098 mole) of anhydro-8-hydroxymercuri-1-naphthoic acid. The solution was cooled in an ice-water bath and 16 g (0.1 mole) of bromine in 75 ml of concentrated aqueous sodium bromide solution was added dropwise and with vigorous stirring over a period of one and a half hour. The slurry formed was heated slowly to 90° and poured into a mixture of 250 ml of water and 250 g of ice. The mixture was extracted with two 250-ml portions of ether and then the combined ether layers were extracted with two 200-ml portions of 10% sodium hydroxide solution. The combined aqueous layers were acidified with a 20% solution of hydrochloric acid and the precipitate formed was filtered by suction, washed several times with water and dried. The product was recrystallized from 30% ethanol-water (v/v). M.p. $171\text{-}2^{\circ}$, yield 77.2%.

III. Preparation of 8-Bromo-1-naphthoyl Chloride

The thionyl chloride used in this preparation was treated, just before using, according to L. F. Fieser (77). A mixture of 26 g (0.1 mole) of 8-bromo-1-naphthoic acid and 12 ml

(0.15 mole) of thionyl chloride was refluxed on a steam bath until evolution of hydrogen chloride and sulfur dioxide stopped. The refluxing condenser was fitted at the top with a drying tube filled with Drierite. The dark solution was kept overnight and then twice distilled successively under vacuum through a short path distillation head. The b.p. of the second distillation was 137-140°/0.06 mm. The product was a white crystalline solid, m.p. 67-8°. Yield, 88%. The infra-red spectrum in carbon tetrachloride showed major absorptions at 912, 1024, 1075, 1170, 1490, 1690, 1780 and 3060 cm^{-1}.

IV. Preparation of 8-Bromo-1-naphthylcarbinol-α,α-d_2

The apparatus was composed of a 500 ml, three-necked round bottomed flask fitted with a mechanical stirrer, a 250-ml dropping funnel and a refluxing condenser. The whole set-up, while being swept out with dry nitrogen, was carefully dried by heating externally with a small burner. After it was cooled to room temperature, about 80 ml of dry ether (distilled from lithium aluminum hydride, LAH) was placed into the reaction flask. Lithium aluminum deuteride (LAD) (3.04 g or 0.072 mole) was added while stirring and then a solution of 8-bromo-1-naphthoyl chloride in about 200 ml of dry ether was added dropwise through the funnel to the deuteride slurry at such a rate as to maintain a slight refluxing. After the addition of the chloride solution, the refluxing was continued another 2 hours on a steam bath. The mixture was then cooled by immersion in an ice-water bath and quenched by the addition (dropwise through the funnel and under stirring) of first, 5.50 ml of water and then 5.50 ml of a 5% solution of sodium hydroxide in water. Stirring of the mixture was maintained overnight at room temperature. The solid was filtered by suction and washed twice with ether. The combined ether layers were washed twice with water and dried over anhydrous magnesium sulfate. After the ether was evaporated under suction, the white residue was recrystallized from cyclohexane and the colorless platelets obtained had a melting point of 84-5°. The yield was 92%. The infra-red spectrum of the alcohol in carbon disulfide showed absorptions at 732, 762, 795, 827, 878, 960, 982, 995, 1085, 1112, 1170, 1190, 1282, 1337, 1362, 2225, 3070, 3470 and 3590 cm^{-1}. The N.M.R. spectrum in dry acetone showed an aromatic multiplet at 2.27-3.17 τ and a hydroxyl singlet at 5.97 τ.

V. Preparation of 8-Bromo-1-bromomethylnaphthalene-α,α-d_2

A 1-liter, three-necked round-bottomed flask, fitted with a mechanical stirrer, was dried out as described in the previous preparation. A solution of 20 g (0.084 mole) of 8-bromo-1-naphthylcarbinol-α,α-d_2 in about 770 ml of dry benzene was placed into the flask and 25 drops of dry pyridine was added. Phosphorus tribromide (Reagent Grade), 16.8 ml (0.177 mole) was added next and the mixture was heated under stirring for three hours on a steam bath to about 50°. The solution was cooled at room temperature and washed twice with water, once with saturated sodium bicarbonate solution, again with water, and finally overnight dried over anhydrous magnesium sulfate. The benzene was distilled off carefully and the residue was recrystallized from a mixture of 112 ml of hexane and 17 ml of dry benzene. The white crystalline product was filtered by suction, washed with a small quantity of hexane and dried overnight under vacuum. M.p. 78-9°. Yield 83%. The N.M.R. spectrum in acetone showed only an aromatic multiplet at 2.20-3.03 τ.

VI. Preparation of 1-Methyl-d_3-8-bromonaphthalene

The setup used here was the same as for the preparation of 8-bromo-1-naphthylcarbinol-α,α-d_2. The same drying procedure was followed. A suspension of 1.46 g (0.035 mole) of lithium aluminum deuteride in about 110 ml of ether distilled from LAH was placed in the flask. A solution of 21.07 g (0.0698 mole) of 1-bromomethyl-8-bromonaphthalene-α,α-d_2 in 230 ml of dry ether was added dropwise through the funnel under slight reflux. The refluxing was continued for four hours after which the mixture was quenched with 2.7 ml of water and 2.7 ml of 5% sodium hydroxide solution. The mixture was filtered, washed with ether and the ether solution was dried over anhydrous magnesium sulfate for several hours. Then the ether was stripped off in the rotatory evaporator and the crude product was distilled under vacuum, b.p. 128-130°/0.7 mm. The distillate was recrystallized from pure methanol, from which it crystallized in nice, white plates, m.p. 76-7°. Yield, 60%. The N.M.R. spectrum in dry acetone showed only an aromatic multiplet at 2.39-3.22 τ.

VII. Preparation of 8-Methyl-d_3-1-naphthoic Acid

A 300-ml, three-necked round-bottomed flask was fitted with a machanical stirrer, a 125-ml dropping funnel and a reflux condenser. The setup was carefully dried as described previously. High purity magnesium (Domal), 2.54 g (0.104 mole), and 25 ml of dry ether (distilled from LAH) were placed in the flask and then a solution of 7.15 g (0.0319 mole) of 1-methyl-d_3-8-bromonaphthalene and 4.63 ml (0.0609 mole) of recently distilled ethyl bromide in 40 ml of dry ether was added dropwise through the funnel at a brisk rate so that the stirred slurry was slightly refluxing. After the addition was completed the refluxing was maintained for four more hours. During the addition of the bromide, dry nitrogen was passing through the whole setup at a very slow rate. A thick, milky-white precipitate was formed. After cooling to room temperature, the mixture was poured over 30 g. of crushed dry ice and 47 ml of ether was added immediately. A 20% hydrochloric acid solution, 28 ml, was added next with stirring and enough ice to keep the mixture cool. The ether layer was washed with three 35-ml portions of water and finally extracted with 21 ml of 10% sodium hydroxide solution. The alkaline aqueous layer was acidified with 9.5 ml of 20% hydrochloric acid solution and left overnight. The product was filtered, washed with water and dried. It was recrystallized from 30% ethanol-water (v/v) and obtained in fine needles, m.p. 152-3°. The yield was 77%. The N.M.R. spectrum in acetone showed an aromatic multiplet at 2.25-2.92 τ and a singlet at 0.55 τ.

VIII. Preparation of N,N-Methylnitrosourea

The general procedure used was that found in Organic Syntheses (78).

IX. Preparation of Methyl 8-Methyl-d_3-1-naphthoate

The general procedure followed was that of Shone (79). Thirty ml of 40% aqueous potassium hydroxide and 100 ml of ether was placed in a 300-ml Erlenmeyer flask. To the mixture, which was cooled below 5°, 10.3 g (0.1 mole) of N,N-nitrosomethylurea was added in small portions with shaking. The ether layer was pipetted into a cooled (< 5°) solution of 9.30 g (0.05 mole) of 8-methyl-d_3-1-naphthoic acid in 300 ml of ether. This was kept for one hour at about 5° and then for 2 hours at room temperature. The excess of diazomethane was destroyed by dropwise addition of glacial acetic acid. The ether solution was washed twice with 8% aqueous potassium bicarbonate, once with water, and finally left overnight over anhydrous magnesium sulfate. After distillation of the ether under light vacuum the residue was distilled twice successively under vacuum; b.p. 139-140°/0.25 mm; yield, 85%. The infrared spectrum showed absorptions at 723, 745, 802, 862, 1020, 1048, 1062, 1108, 1145, 1200, 1250, 1280, 1332, 1430, 1458, 1510, and 1725 cm^{-1}. The ultraviolet spectrum in 95% ethanol solution showed peaks at 224 mμ (ϵ = 47400) and 288 mμ (ϵ = 5860). The N.M.R. spectrum showed an aromatic multiplet at 2.02-2.92 τ and a methyl singlet at 6.2 τ. The integrated area ratio was 56:26 or approximately 6:3. The purity of the final product was further established by vapor phase chromatography by using a "20%, GE,SF-96 (βilicone Fluid)," 5' x 1/4" column.

X. Preparation of Methyl-1-naphthoate-8-d

The method of esterification described in the previous section was applied. The product, a colorless liquid, had a b.p. 101-2°/0.1 mm. and was obtained in a 91% yield. Infrared spectrum: 785, 845, 855, 905, 1032, 1061, 1088, 1147, 1200, 1275, 1343, 1367, 1435, 1458, 1500, 1567, 1575, and 1700 cm^{-1}. The ultraviolet spectrum in 95% ethanol solution showed peaks at 213 mμ (ϵ = 15500), 218 mμ (ϵ = 16500) and 298 mμ (ϵ = 2700). N.M.R. spectrum: aromatic multiplet, 1.92-3.00 τ; methoxide singlet, 6.22 τ; integrated area ratio, 58:27 or approximately 6:3. The purity of the final product was verified by vapor phase chromatography. The column used was "20%, GE,SF-16 (Silicone Fluid)," 5' x 1/4".

XI. Preparation of 8-Methyl-1-naphthoyl Chloride-8-d_3

A mixture of 1.71 g (9.88 mmoles) of 8-methyl-d_3-1-naphthoic acid and 1.78 g (15 mmoles) of freshly distilled thionyl chloride (77) was refluxed for three hours on a steam bath. The reflux condenser was fitted with a drying tube filled with Drierite. After refluxing, the excess thionyl chloride was removed under vacuum and the residue was distilled three times successively under vacuum using a short path distillation head. The product, a crystalline white solid, was obtained in 66% yield, p.b. 105°/0.07 mm, m.p. 53-4°. The infra-red spectrum showed absorptions at 695, 745, 768, 800, 830, 862, 973, 1030, 1048, 1070, 1122, 1162, 1172, 1225, 1368, 1500, 1588, 1775, 1802 (shoulder), 2225, and 3050 cm^{-1}. Only an aromatic multiplet appeared at 1.88-2.63 τ in the N.M.R. spectrum of the compound.

XII. Preparation of 1-Naphthoyl Chloride-8-d

The preceding method was applied. The product was twice distilled, b.p. 100°/0.15 mm, and was obtained as a colorless liquid at a 93% yield. The infra-red spectrum showed absorptions at 650, 732, 770, 832, 850, 918, 1035, 1052 (shoulder), 1063 (shoulder), 1078, 1090, 1173, 1203, 1232, 1368, 1450, 1498, 1565, 1583, 1750, 1768 (shoulder), and 3050 cm^{-1}. The ultraviolet spectrum in 95% ethanol showed peaks at 211 $m\mu$ (ϵ = 41800), 218 $m\mu$ (ϵ = 42980) and 295 $m\mu$ (ϵ = 6590). The

N.M.R. spectrum showed only an aromatic multiplet at 1.50 - 3.10 τ.

XIII. Preparation of Methyl 8-Methyl-1-naphthoate

This ester was prepared from 8-methyl-1-naphthoic acid by the same procedure used in preparing its 8-methyl-d_3 analog. The product, a colorless oily liquid, distilled at $140^\circ/0.25$ mm. The infra-red spectrum showed absorptions at 732, 777, 820, 826, 974, 1018, 1043, 1090, 1148, 1173, 1200, 1248, 1282, 1335, 1355, 1380, 1435, 1448, 1463, 1512, 1798, 1828, 2845, 2880, 2910 (shoulder), 2960, and 3050 cm^{-1}. The ultraviolet spectrum of the compound in 95% ethanol solution was the same as that of the 8-methyl-d_3 analog. The N.M.R. spectrum showed an aromatic multiplet at 2.15-2.89 τ, a methoxide singlet at 6.15 τ and a methyl singlet at 7.39 τ in an integrated area ratio of 57:27:27 or approximately 6:3:3. The purity of the final product was checked by vapor phase chromatography using a "20%, GE,SF-96 (Silicone Fluid)," 5' x 1/4" column.

XIV. Preparation of Methyl 1-Naphthoate

The method described by Vogel (80) was followed. A solution of 30.15 g (0.175 mole) of 1-naphthoic acid and 1.2 ml of concentrated sulfuric acid in 72 ml (1.782 mole) of absolute methanol was refluxed for nine hours. After removal of the excess methanol, the residue was extracted with two 50-ml portions of ether. The ethereal solution was washed with concentrated sodium bicarbonate solution until evolution of carbon dioxide ceased, then with water and finally dried over anhydrous magnesium sulfate. The ether was removed in the rotatory evaporator and the ester was twice distilled under vacuum. B.p. $101^{\circ}/0.1$ mm, yield 70%. The infra-red spectrum showed peaks at 790, 823, 857, 952, 1032, 1078, 1135, 1162, 1200, 1245, 1278, 1290 (shoulder), 1345, 1368, 1435, 1458, 1508, 1567, 1582, 1700, 2905, and 3005 cm^{-1}. The ultraviolet spectrum of the compound in 95% ethanol solution was the same as that of the 8-d analog. The N.M.R. spectrum showed an aromatic multiplet at 2.02-3.00 τ and a methoxide singlet at 6.20 τ in an integrated area ratio of 61:26, or approximately 7:3. The purity of the final product was checked by vapor phase chromatography using a "20%, GE,SF-16 (Silicone Fluid)," 5'x 1/4" column.

XV. Preparation of 8-Methyl-1-naphthoyl Chloride

The usual procedure (see above) was followed. The product, after several distillations (b.p. $96\text{-}97^{\circ}/0.04\text{-}0.03$ mm) was obtained as a white, crystalline solid (m.p. 54°) in 81% yield. The infra-red spectrum in carbon tetrachloride showed absorptions at 700, 848, 960, 1023, 1112, 1157, 1172, 1224, 1368, 1382, 1445, 1458, 1500, 1777, and 1790 (shoulder) cm^{-1}. The N.M.R. spectrum of a dry acetone solution of the compound showed an aromatic multiplet at 1.90-2.65 τ and a methyl singlet at 7.25 τ in an integrated area ratio of 60:28, or approximately 6:3.

XVI. Preparation of 1-Naphthoyl Chloride

The usual method (see above) was applied. The product, after several successive distillations under vacuum, b.p. 95°/0.1 mm, was obtained as a colorless liquid in 90% yield. The infra-red spectrum showed absorptions at 655, 745, 772, 788, 805, 882, 1024, 1051, 1087, 1172, 1212, 1220, 1342, 1362, 1430, 1458, 1504, 1570, 1588, 1750, 1768 (shoulder), 1780 (shoulder), 3050 and 3080 (shoulder) cm^{-1}. The ultraviolet spectrum of the compound in 95% ethanol solution was identical to that of 1-naphthoyl chloride-8-d. The N.M.R. spectrum showed only an aromatic multiplet at 1.50-3.17 τ.

XVII. Analytical Instruments

Infra-red spectra were taken using either a UNICAM SP. 200 (Unicam Instruments, Ltd., Cambridge, England) Infra-red Spectrophotometer or a PERKIN-ELMER 237 B Model, Grading Infra-red Spectrophotometer.

Ultra-violet spectra were taken by means of a Cary 14 Recording Spectrophotometer (Applied Physics Corp.).

For the N.M.R. spectra an A-60 Spectrometer (Varian Associates) was used.

Melting points were determined in a Hershberg apparatus using a calibrated thermometer.

B. Kinetics

I. Calibration of Volumetric Glassware

All glassware used in the kinetic measurements of the saponification of methyl 1-naphthoate and its 8-deuterium analog was calibrated by established methods (81) to less than ± 0.4% standard deviation. Micro-burets were also calibrated and found to meet specifications.

II. Preparation of Solvents and Standard Solutions

Conductivity Water. The conductivity water was prepared by passing distilled water through a column filled with alternate beds of "Baker Analyzed" Reagent DOWEX 3, anion exchange resin (20-50 mesh) and "Baker Analyzed" Reagent DOWEX 50W-X8, cation exchange resin (50-100 mesh). The column, 40 cm long and 3.5 cm in diameter, contained 5 alternate layers of each resin. Water obtained from this column had a specific conductance of less than 3×10^{-6} mho cm^{-1} at 25°. It was regularly checked by measuring the conductance before every kinetic run.

Water Free of Carbon Dioxide. In preparing the solutions for the kinetics of saponification of esters carbon dioxide-free water was used. This was conductivity water, which had been boiled and cooled to room temperature shortly before preparation of the solutions.

Dry Acetone. The Conant-Kirner procedure (82) was followed for the preparation of dry acetone. Acetone U.S.P. was refluxed with potassium permanganate and a small quantity of sodium hydroxide (about 1.5 l of acetone with 60 g of potassium permanganate and five pellets of sodium hydroxide) for one hour and then distilled through a 40-cm column fitted with a glass helix. Both head and tail fractions were discarded and the 56.5-57° fraction was collected. Such acetone did not color anhydrous cupric sulfate, when in contact for more than an hour, and retained for days the faint pink color caused by a trace of potassium permanganate. The specific conductivity was less than 1×10^{-8} mho cm^{-1}.

Mixed Solvents. In order to obtain high accuracy, the mixed solvents of acetone-water used in the kinetic runs were prepared by one of the following two methods, depending on the size of the batch. For small batches, the volumes of dry acetone and water to be mixed were measured by using a calibrated 50-ml buret. Volume contraction upon mixing was taken into account by applying the following equation:

$$d = dw + AP_s + BP_s^2 + CP_s^3$$

where d is the density of a mixed solvent of P_s percent acetone-water (w/w) at 25° and dw the density of water at the same temperature. The constants used are as follows:
$A = -1.171 \times 10^{-3}$, $B = -9.04 \times 10^{-6}$ and $C = -5.6 \times 10^{-9}$ (83). For large batches, the dry acetone and water quantities to be

mixed were weighed to the nearest 0.5 g on a large, free swinging, 2 kg capacity balance. The conductance of the solvent was always 100-1000 times lower than that of the reacting mixture.

Standard Solutions. The standard sodium hydroxide solutions for use in the kinetics of saponification of the esters were prepared from decarbonated conductivity water and "Baker Analyzed" REAGENT sodium hydroxide pellets (assay 98.5%, sodium carbonate 0.63%). The standardization was carried out by titrating solutions of accurately weighed quantities of potassium hydrogen phthalate (Fisher Scientific Co., Analytical Reagent) in carbon dioxide-free conductivity water and using phenolphthalein as indicator (1-2 drops of a 0.1% solution in 95% ethanol). Each batch was standardized by carrying out 10 such titrations. The titer was always determined to within ± 0.05% and rechecked from time to time.

The standard hydrochloric acid solutions were prepared from Reagent concentrated hydrochloric acid and conductivity water. They were standardized to within ± 0.05% by titration with standard sodium hydroxide solution and using phenolphthalein as indicator.

III. Conductance Apparatus

Bridge. The conductance of a solution was measured by means of a WAYNE KERR Universal Bridge, Model B 221 (The Wayne Kerr Laboratories, Ltd., Surrey, England), equipped with an internal source operating at a frequency of 1592 c.p.s. ± 1%. The accuracy was ± 0.1%.

Conductance Cell. For the kinetic studies of the hydrolysis of the acid chlorides the conductance cell used was similar to that described by Murr (84). Basically it was made of a 250-ml Erlenmeyer flask to which the electrode compartment had been attached at the side and near the bottom. This compartment was a bulb of about 35 mm in diameter and was joined to the flask by means of two 20-mm connecting tubes. The electrodes, made of two platinum discs and supported by platinum wire, were sealed by means of platinum tubing and uranium glass to the electrode chamber at right angles to the axis of the conical flask. The cell was fitted at the neck of the flask with a 2-mm stopcock gas inlet and a ground joint cup at the top. The cell constant was found to be 1.1911 cm^{-1}.

After the electrodes of the cell were slightly platinized as recommended by Jones and Bollinger (85), the cell was cleaned following Murr's procedure (84).

IV. Constant Temperature Baths

The constant temperature bath used for the kinetic studies at about room temperature was a 41x26x27 cm glass aquarium insulated with polystyrene foam plastic and lined with plywood. On one of the 26-cm sides of the bath a rectangular window was cut open and a PENETRAY, 200 W infra-red heating lamp was mounted. This lamp was used as the heating element for the temperature control and was attached to an electronic relay (Precision Scientific Co.) which in turn was operated by a Micro-set Thermoregulator (Precision Scientific Co.). Water was used as the conditioning medium in the bath. Efficient circulation was provided by a small electric centrifugal pump (Gorman-Rupp Industries, Inc.) whose outlet and inlet were mounted in one of the corners of the bath near the window. A copper coil (ten 5.5-cm turns of 6-mm copper tubing) served as the cooling element. Water from the tap was used as the coolant (the lowest temperature at which this bath was used was 15^{o}). In order to maintain the rate of cooling constant, the tap water was fed through a 6-mm bottom inlet into a vertical 6x100 cm glass column. This column was fitted with a 9-mm glass tube, 72 cm long from the bottom of the column along its axis, and also with a 6-mm bottom outlet. The lower end of the 72 cm glass tubing was connected to the inlet of the cooling coil by means of a rubber tubing. The feeding of tap water into the column was regulated so that the water, although running out through the outlet, was filling the column up to the top of the co-axial tubing and overflowing into the cooling coil. In this manner the pressure of the water at the inlet of the cooling coil was kept constant and approximately equal to 72 x 1 g/cm.

The arrangement of the various elements in the bath was as follows: in one of the two corners near the heating lamp window were placed the thermoregulator and the cooling coil, as near to each other as possible. The water from the outlet of the stirring pump, which was mounted on the other corner, was directed so as to hit the cooling element first and the thermoregulator mercury bulb next. With this arrangement the temperature control in the bath was better than ± 0.005°.

The bath used in the low temperature (-20 to -34°) kinetic studies was a 50x34x34 cm tank made of galvanized metal sheet and insulated with polystyrene foam plastic. The cooling medium was a 52% ethylene glycol-water mixture (v/v) whose freezing point was -40°. Efficient circulation was attained by means of an electric stirrer fitted with a six-wing propeller and placed in the center of the bath. The heating element (a 500 W-heating knife, Central Scientific Co.) and the thermoregulator (Micro-Set, Precision Scientific Co.) were placed at a distance of 8 cm from each other and the axis of the stirrer and connected to an electronic relay (MANOSTAT, Model 4). The stirrer, the heating element and the thermoregulator were supported by a piece of plywood covering 2/3 of the open upper side of the bath. The cooling was provided by a 3/4 H.P. refrigerating unit (Tecumseh Products Co., Model C7T16LT) through eight rectangular loops of 8-mm copper tubing placed along the walls of the bath and close to the bottom. The temperature control in this bath was better than ± 0.003°.

V. Calibration of Beckmann Differential Thermometers

The Beckman differential thermometers (Arthur H. Thomas Co.) used for reading the temperature of the thermostatic baths were calibrated at the particular temperature range against a platinum resistance thermometer (THERMOHM, Leeds & Northrup Co.) which had been calibrated by the National Bureau of Standards. The procedure followed was as follows: the Beckmann thermometer and the platinum resistance thermometer was immersed in the constant temperature bath so that the platinum resistance was about 0.5 cm apart from the mercury bulb of the Beckmann thermometer. Care was taken to have the Beckmann thermometers always immersed in the bath to the same extent during calibrations as well as during kinetic runs. The value of the platinum resistance was found by balancing against a known resistance by means of a calibrated variable resistance box (Leeds and Northrup Co. No. 113758) and a galvanometer (SCALAMP, Ealing Corp.). Ten different values were taken at the range of temperature to be used. The platinum resistance was converted to degrees centigrade by using the Callendar-Van Dusen Equation (86), the values of the constants of this equation for the particular platinum resistance thermometer used being provided by the National Bureau of Standards. The precision of the calibrations was within $\pm$ 0.002°.

VI. Measurement of the Time

Time was measured by means of a synchronous motor timer with a five-digit reset counter (PRECISION TIME-IT, Precision Scientific Co.).

VII. Kinetics of Saponification of Methyl 1-Naphthoate and its 8-Deuterium Analog

Kinetics by Titration of the Remaining Base. The solution of the base was prepared in a dry 500 ml Erlenmeyer flask, containing a teflon-covered magnetic stirring bar, by mixing standardized 0.2 N aqueous solution of sodium hydroxide, dry acetone and decarbonated conductivity water. Volumes were measured with a calibrated 50-ml buret. After the mixing of the base and the ester solutions, the resulting final solution of 56% acetone-water (w/w) had a total volume of 200 ml. The initial concentrations of the base and the ester was each 5×10^{-2} M. The calculated quantity of ester was weighed in a 50-ml volumetric flask using a precision balance (Mettler) and dissolved in the appropriate quantity of dry acetone. The two solutions in the stoppered flasks were placed in the constant temperature bath for half an hour. After they had acquired the bath temperature, the ester solution was added to the base solution under stirring. The timer was started when the addition was half complete. The average time of complete mixing was less than two minutes. The stirring was maintained throughout the run. At 15 min intervals, aliquots of 10 ml were withdrawn with a calibrated pipet, were placed in a 50-ml Erlenmeyer flask containing a tiny teflon-covered magnetic stirring bar and titrated, using phenophthalein as indicator (1-2 drops of a 0.1% solution in 95% ethanol per sample), under stirring with standardized 0.1 N hydrochloric acid solution. Each reaction was followed for at least two half-lives.

Kinetics by Conductance Measurements. The method of Fischer and co-workers (54b) was used. Two hundred ml of a 5×10^{-2} M solution of sodium hydroxide in 56% acetone-water (w/w) was prepared in the dry, 250-ml conductance cell. Forty-five minutes after placing the cell in the constant temperature bath, the appropriate quantity of the ester, weighed accurately in a 2 ml glass cup, was dropped with the cup into the cell while the solution was under stirring. The timer was started at the same time. After an initial 30 min interval, thirty conductance-time measurements were made at approximately equal conductance decrements. This time period covered three half-lives.

From the simplified form (1) of the second-order equation, from

$$1/B = kt + 1/B_0 \tag{1}$$

the relation (2) between the conductance of the solution and the concentration of the base (54b)

$$B = a + bL \tag{2}$$

and from three pairs of conductance-time values, (L_1, t_1), (L_{11}, t_{11}), $L_{21}, t_{21})$ at corresponding times t_1, t_{11}, t_{21}, equation (3) is derived,

$$B_0k = \frac{(L_{11}-L_{21})\ (t_{11}-t_1)\ -\ (L_1-L_{11})\ (t_{21}-t_{11})}{t_1(L_1-L_{11})\ (t_{21}-t_{11})\ -\ t_{21}(L_{11}-L_{21})\ (t_{11}-t_1)} \tag{3}$$

where k is the rate constant, B_o is the initial concentration of base and ester, t is the time, L is the conductance of the solution at time t, B is the concentration of the base at time t, and a and b are constants. Using equation (3), ten values of k were calculated. The average of these values was used.

VIII. Kinetics of Saponification of Methyl 8-Methyl-1-naphthoate

By measuring the appropriate quantities of acetone and water 200 ml of 56% acetone-water (w/w) solution were prepared in the conductance cell. Recrystallized sodium 8-methyl-1-naphthoate, 2.08 g, was dissolved in the solution, which was thermostated at 50°. The conductance of this solution was 4.7382×10^{-3} mho. The reciprocal value, $R_\infty = 2.1105 \times 10^2$ ohm, was used in the subsequent determination of the rate constant of the saponification of methyl 8-methyl-1-naphthoate.

For this determination a slight modification of the method used by Fischer and co-workers (54b), was used. The initial concentration of base and ester was 5×10^{-2} M. The conductance cell containing 100 ml of base in 56% acetone-water (w/w), was placed in the bath. After temperature equilibrium with the bath had been attained, ten measurements of the conductance were made in the span of 90 minutes (blank run). After that, the calculated quantity of ester was weighed in a tiny cup as before and added under stirring. The conductance of the cell was then measured at frequent intervals over a period of about 5 hours.

From Fischer and co-workers (54b),

$$R = \frac{R_o A_o}{R_\infty} k (R_\infty - R) t + R_o \qquad (4)$$

R_o, R, R_∞ are the resistance of the solution, or the reciprocal of the measured conductance, at times zero, t and infinity, respectively. A_o is the initial concentration of the base or the ester and k is the rate constant of the reaction. When k is small, as in the present case, the difference (R_∞ - R) is approximately constant and thus R is a linear function of t. The values of R were plotted against t and the slope of the line was calculated. The "hydrolysis" plot was extrapolated back to the time of ester addition (t = 0) to find R_o. Then, from equation (4) and nine pairs of R-t values, nine values of k were calculated. The average of these values was used.

IX. Kinetics of Hydrolysis of Acid Chlorides

The general procedure for measurements at room temperature was as follows: about 150 ml of the mixed solvent was placed in the dry conductance cell and the latter was closed and placed in the constant temperature bath. After thermal equilibrium had been attained, the conductance of the solvent was measured and then the cell was quickly withdrawn from the bath. A quantity of the chloride was added and dissolved by swirling, the timer was started, and the cell was replaced in the bath. The whole process, from the moment of withdrawing the cell from the bath to the moment of replacing it in the bath, usually took 50-70 seconds. After an initial time interval fifteen to twenty conductance-time values were taken over a period of 2-5 half-lives. The infinity value of the conductance was taken after more than 12 half-lives. Its constancy over a period of time was checked. For the liquid 1-naphthoyl chloride and its 8-d derivative, the quantity added to 150 ml of solvent was one drop. In the case of the solid 8-methyl-1-naphthoyl chloride and its 8-methyl-d_3 analog as well as in the case of 8-bromo-1-naphthoyl chloride care was taken so that the initial concentration for the various compounds would be always about the same. The initial concentrations used were in the range of 5-9×10^{-4} M.

In the low temperature studies (-20 to -34°) the main difficulty was the slow dissolution of the solid chlorides. To overcome this problem a 5-ml solution of the chloride in dry acetone was prepared just before a series of experiments and 1 ml of this solution was added to 100 ml of the mixed solvent. The acetone for this solution was the dry acetone used for preparing the mixed solvent (see above).

X. Treatment of the Kinetic Data

For both the second-order alkaline hydrolysis of the esters and the first-order solvolysis of the acid chlorides, the series of conductances and corresponding times obtained in a kinetic run were fitted to the corresponding integrated rate expression by the method of least-squares. This was done by feeding the conductance-time values taken into a computer program which directly printed out the rate constant and the standard deviation of the straight line fitting. The program was processed in a CONTROL DATA CORP. 3600 digital computer.

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