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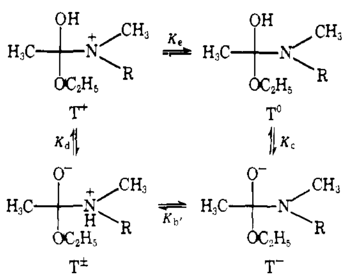

(30) R = CH_3: pK_e based on pK_a for $(CH_3)_3N$ = 9.69 (30°);[31] σ_I for OH = OC_2H_5 = 0.25;[25] pK_d and pK_c based on pK_a for C_2H_5OH = 15.9,[32] σ_I for $N^+H(CH_3)_2$ = 0.7,[25] σ_I for $N(CH_3)_2$ = 0.10.[33] R = C_6H_5: pK_e based on pK_a for $C_6H_5N(CH_3)_2$ = 5.0 (30°);[31] pK_c based on assumed σ_I for $C_6H_5NCH_3$ = 0.18, intermediate between values for amine and amides;[29] pK_c − pK_d = p$K_{b'}$ − pK_e assumed to be 5.0 units, intermediate between values of 5.1 calculated for R = CH_3 and 4.8 previously estimated.[29]

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$A_{Al}2$ Hydrolysis of 2,6-Dimethylbenzimidate Esters in Sulfuric Acid Solutions

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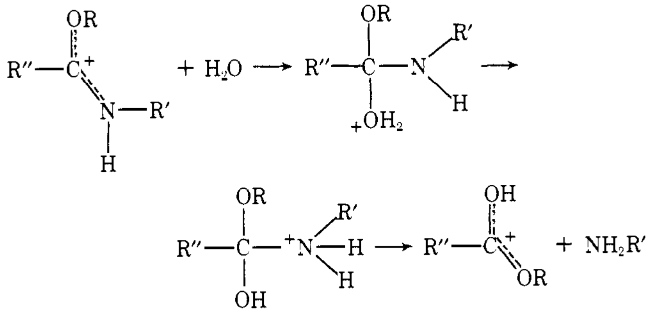
Abstract: Methyl and ethyl 2,6-dimethylbenzimidate hydrolyze at all acidities via a reaction analogous to $A_{Al}2$ carboxylate ester hydrolysis. The product of hydrolysis is principally (>99%) 2,6-dimethylbenzamide, and this arises with cleavage of the alkyl carbon-oxygen bond. Other factors consistent with this mechanism are discussed. The $A_{Al}2$ reaction is compared with the more commonly observed hydrolysis involving a tetrahedral intermediate, particularly with respect to the solvation of the transition states for the two processes. In more general terms, it is shown that entropies of activation for acid-catalyzed reactions of an S_N2 displacement type are less negative than entropies of activation for acid-catalyzed reactions involving a tetrahedral intermediate.

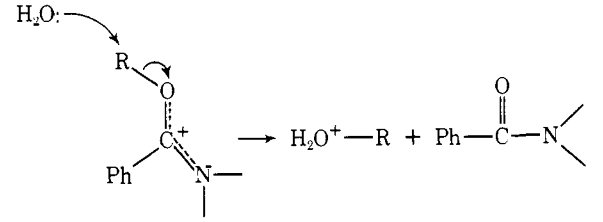
The hydrolysis of imidate esters generally proceeds through a tetrahedral addition intermediate[1] and has therefore seen considerable investigation because of the information that can be obtained regarding this important species. These compounds can in principle hydrolyze in two directions, giving either ester and amine products or amide and alcohol. In acidic media, the reaction proceeds with attack of water on the protonated imidate and generally gives ester and amine.[1] The formation of these products has been attributed to the fact that the tetrahedral intermediate exists in its N-protonated form under these conditions so that the amine is the superior leaving group (Scheme I).

Scheme I



In more concentrated acids (i.e., 65% H_2SO_4), benzimidates have been found to give (at least partly) the amide and alcohol.[2] Using labeled imidates we have recently shown[3] that the amide retains the oxygen of the starting material. This rules out a tetrahedral intermediate precursor and suggests that the reaction responsible for the amide is an S_N2 displacement analogous to the as yet unobserved $A_{Al}2$ hydrolysis of carboxylate esters[4] (Scheme II).

Scheme II



Thus, two competing pathways for imidate hydrolysis in acid solutions appear to be possible. Both involve attack of water on the protonated imidate but differ in the site of that attack, as well as in the nature of the products. Although there have been substantial investigations of the acyl[5] addition reaction, little is known of alkyl[5] substitution in these systems, other than the demonstration of its presence in relatively concentrated acids. A number of questions can be asked. Chiefly, is the mechanism of Scheme II correct in the first place and, if so, why should it take over from the other in more concentrated acids?

We report here a study of a pair of 2,6-dimethylbenzimidate esters (I, II) which answers these questions and, in addition, offers new insights into the general area of bimolecular acid-catalyzed reactions. This system was chosen in

Table I. Products of Hydrolysis of Imidates I and II

		% products[a]	
Substrate	% H_2SO_4	Amide[b]	Ester[c]
I	1.9	97	1.0
I	12.3	99	0.7
I	24.9	106	0.4
I	38.7	97	0.04[d]
II	1.9	98	0.7

[a] After 10 half-lives of hydrolysis. Temp, 86.1°. [b] ±5%. [c] ±25%. [d] Partially hydrolyzed under reaction conditions.

Table II. ^{18}O Content of 2,6-Dimethylbenzamide from Hydrolysis in Enriched Solvents

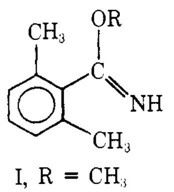
Imidate	% ^{18}O
I	0.16 ± 0.05
II	0.18 ± 0.07

Table III. Rate Constants for Hydrolysis of Imidates I and II

		$k_{obsd} \times 10^5$ sec^{-1}	
% H_2SO_4	T, °C	I	II
0.50	86.1	13.88	7.42
1.88	86.1	13.60	7.55
1.88	97.8	45.2	25.33
1.88	107.5	96.7	60.23
4.88	86.1	13.00	7.00
12.30	86.1	11.12	6.18
18.11	86.1	9.75	5.48
18.11	97.8	31.3	
18.11	107.5	70.3	
24.50	86.1	7.58	4.62
30.41	86.1	6.13	3.97
30.41	97.8	20.2	
30.41	107.5	47.7	
38.67	86.1	4.05	2.97
38.67	97.8	13.71	
38.67	107.5	32.5	
45.04	86.1	3.04	2.02
50.85	86.1	1.79	1.367
50.85	97.8	6.04	
50.85	107.5	15.03	
54.50	86.1	1.257	1.050
60.03	86.1	0.653	

Table IV. Activation Parameters for Acid Hydrolysis of 2,6-Dimethylbenzimidates

Substrate	% H_2SO_4	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
I	1.88	24.3	-9.0
I	18.11	24.4	-9.3
I	30.41	25.4	-7.6
I	38.67	25.8	-7.2
I	50.85	26.3	-7.3
II	1.88	25.7	-6.3



I, R = CH_3
II, R = CH_2CH_3

light of the well-known effect of ortho substituents on retarding acyl addition in carboxylate esters.[6] The alkyl position, on the other hand, remains relatively unhindered, and these compounds could therefore be forced to hydrolyze $A_{Al}2$ at all acidities.

Experimental Section

Materials. Sulfuric acid solutions were prepared and standardized as previously described.[7] Oxygen-18 enriched water (1.724% ^{18}O) was obtained from Miles Laboratories, Inc. Published procedures were used for the preparation of 2,6-dimethylbenzamide[8] and the methyl and ethyl esters of 2,6-dimethylbenzoic acid.[9,10]

The imidates were prepared by O-alkylation[2] of 2,6-dimethylbenzamide with trimethyloxonium and triethyloxonium borofluorate,[11] followed by treatment with sodium carbonate.

Methyl 2,6-dimethylbenzimidate (I) had: bp 51° (0.6 mm); NMR (CCl_4, Me_4Si τ 2.7–3.3 (4 H, m, ArH and NH), 6.21 (3 H, s, OCH_3), 7.78 (6 H, s, CH_3).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.56; H, 8.24; N, 8.57.

Ethyl 2,6-dimethylbenzimidate (II) had: bp 57° (0.5 mm); NMR (CCl_4, Me_4Si) τ 2.7–3.3 (4 H, m, ArH and NH); 5.73 (2 H, q, J = 7 Hz, CH_2); 7.75 (6 H, s, $ArCH_3$); 8.70 (3 H, t, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.63; H, 8.57; N, 7.94.

Product Analysis. With both imidates, the hydrolysis in all acids up to 60% H_2SO_4 produced a uv spectrum within experimental error superimposable on the spectrum of 2,6-dimethylbenzamide in the same acid. Gas chromatography, however, detected small traces of 2,6-dimethylbenzoate ester. Quantitative analysis was therefore carried out by GC by addition of an external standard (bibenzyl) to the ether extract of a neutralized product solution. A flame-ionization detector gave a linear response, and the relationship between peak areas of product and standard was determined from synthetic mixtures. Yields of amide were reproducible to within ±5%; for the ester, the relative reproducibility was considerably worse. Analysis was performed on a Carlo-Erba Model 61 chromatograph, with a column (2 m × 6 mm) of 30% Carbowax 20M on Chromosorb P operating at 180°.

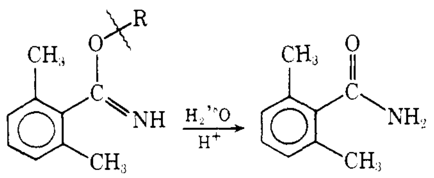
Position of Cleavage. The imidates were allowed to hydrolyze in oxygen-enriched water containing 1% added concentrated sulfuric acid. The amide product was isolated by extraction and purified by recrystallization. This was analyzed on an AEI Model Ms 902 mass spectrometer equipped with a Vacuumetrics ratiometer. The ratio of the mass peaks at 149 and 151 was determined and compared with the similar ratio determined for unlabeled amide.

Kinetics. Hydrolysis rates were measured by observing the spectral change at 245–260 mμ on a Cary 14 spectrophotometer. The technique of sealed ampoules in an oil bath was used.[12] All runs were made in at least duplicate. Infinity absorbances were found to be stable up to 65% H_2SO_4, and rate constants were determined by least-squares treatment of ln ($A - A_\infty$) vs. time data.

Results

Products of Hydrolysis. The general conclusion is that there is a virtually quantitative conversion of imidates I and II to 2,6-dimethylbenzamide at all acidities. A very small amount (less than 1%) of the appropriate 2,6-dimethylbenzoate ester accompanies this, the yield decreasing as the acidity is increased. In Table I are listed the amounts of these products obtained after complete hydrolysis and determined by GC analysis. Under reaction conditions, the amide is stable up to 65% H_2SO_4. For the esters, further hydrolysis becomes a problem above 30% H_2SO_4.

Position of Cleavage. Hydrolysis of the unlabeled imidates in oxygen-enriched water produces unlabeled 2,6-dimethylbenzamide (Table II). Thus, as before,[2] this product must be arising with cleavage of the oxygen–alkyl bond.



Kinetics of Hydrolysis. Excellent first-order plots were observed for the hydrolysis of the two imidates up to 65% H_2SO_4. (Above this point, extensive decomposition occurs.) Pseudo-first-order rate constants as a function of temperature and acidity are presented in Table III. The reproducibility in these values is of the order of ±2%.

Activation Parameters. Activation parameters as determined from plots of log k_{obsd}/T vs. $1/T$ are listed in Table IV. For I, values were obtained over a range of acidity but show little variation.

Discussion

Effect of Ortho Substituents. The goal of this research, to block the acyl addition and thus favor attack at the alkyl position, has been achieved, to a degree of 99% and greater. Amide, not ester, is the predominant product and arises through O-alkyl bond cleavage.

The retarding effect of the 2,6-dimethyl substituents on water attack at the acyl carbon can be calculated by assuming that the small amount of ester product observed arises from that reaction. For example, the rate of hydrolysis of I via acyl addition (in 12.3% H_2SO_4 at 86.1°) is $0.007 \times k_{obsd} = 7.8 \times 10^{-7}$ sec^{-1}. In 12.5% H_2SO_4 at 85.2°, the unhindered methyl benzimidate hydrolyzes[2] at a rate of 1.14×10^{-2} sec^{-1}. Assuming that this rate applies solely to acyl addition and neglecting the small temperature and acidity differences, the retardation by the 2,6-dimethyl substituents amounts to ca. 15,000. This can be compared with the effect of 2,6-dimethyl substituents on the base hydrolysis of methyl benzoate; a rate decrease of ca. 10^5 can be estimated from available rates and activation parameters.[13]

On the other hand, the substituents appear to have had little effect on the alkyl substitution reaction. For methyl benzimidate, a rate constant of ca. 2×10^{-6} sec^{-1} was estimated[2,14] for hydrolysis by this pathway in 65% H_2SO_4. Short extrapolation of the data obtained here suggests that the rate constant for the 2,6-dimethyl compound is ca. 3×10^{-6} sec^{-1}.

Evidence for $A_{Al}2$ Mechanism. The results obtained with imidates I and II place the $A_{Al}2$ mechanism for imidate hydrolysis on a firmer ground. Particularly conclusive is the observation that the 2,6-dimethyl substituents do exert the predicted effect in terms of the products, again with the appropriate bond cleavage. In addition, there are three mechanistic criteria which supply further evidence.

The involvement of a water molecule in the rate-determining step for the reaction is suggested from the way the rate varies as a function of acidity (Figure 1), showing a steady decrease as the acidity is increased. As shown on the same figure, a similar behavior is observed for the acyl addition reaction.[2,15] Such a rate decrease can be explained in the following way. Imidate esters are fully protonated even in the most dilute acids used in this study,[16] and therefore increases in acidity merely serve to decrease the water available for nucleophilic attack by decreasing the water activity.

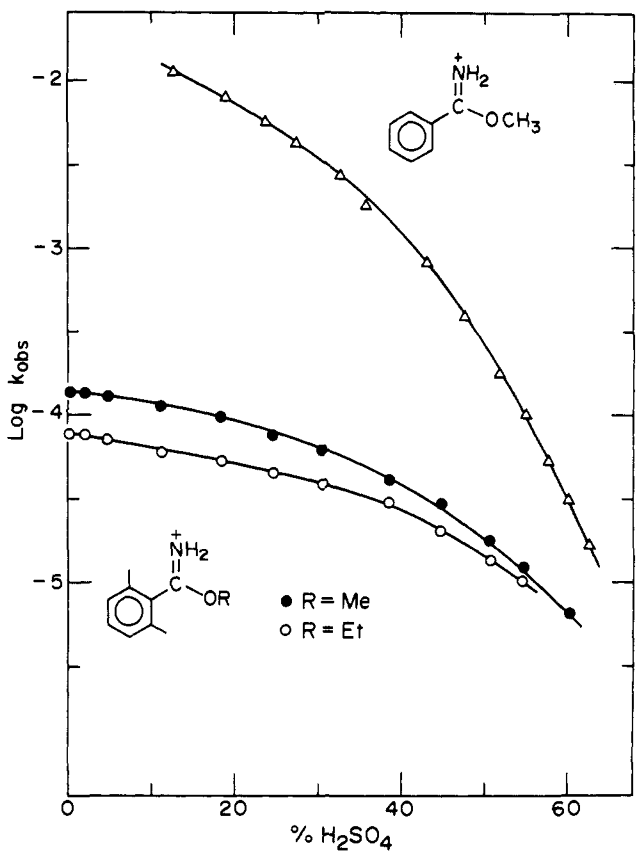


Figure 1. Rates of benzimidate hydrolysis as a function of acidity. Data for methyl benzimidate at 85.2° taken from ref 2. Data for 2,6-dimethylbenzimidates at 86.1°.

Table V. Entropies of Activation of Bimolecular Acid-Catalyzed Reactions

Substrate	$\Delta S^{\ddagger}$	Mechanism	Ref
Ethyl acetate[a]	−23	$A_{Ac}2$[c]	*d*
Acetamide[a]	−37	$A_{Ac}2$	*d*
Benzoic acid (exchange)[a]	−30	$A_{Ac}2$	*d*
Benzamide	−16	$A_{Ac}2$	*e*
Methyl benzoate[a]	−16	$A_{Ac}2$	*f*
Methyl benzimidate (dilute acid)	−16	$A_{Ac}2$	*e*
Methyl benzimidate (65% H_2SO_4)	−11	Mixed	*e*
Methyl 2,6-dimethylbenzimidate	−8	SN2	This work
Ethylene oxide[a]	−6	SN2	*d*
Aziridine	−7	SN2	*g*
Diethyl ether[a]	−9	SN2	*d*
Trimethylsulfonium[b]	−7	SN2	*h*

[a] These substrates exist in their unprotonated form so that $\Delta S^{\ddagger}$ must also contain a contribution from the protonation step. [b] Not acid catalyzed. [c] Used in the general sense of a acid-catalyzed acyl-addition reaction. [d] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, **1**, 1 (1963). [e] C. R. Smith, Ph.D. Thesis, University of Toronto, 1971. [f] K. Yates and M. F. Goldman, unpublished results. [g] J. F. Bunnett, R. L. McDonald, and F. P. Olsen, *J. Am. Chem. Soc.*, **96**, 2855 (1974). [h] C. G. Swain, W. D. Burrows, and B. J. Schowen, *J. Org. Chem.*, **33**, 2535 (1968).

The bimolecularity is also suggested by the entropy of activation (−6 to −9 eu). Normally negative entropies of activation are associated with bimolecular acid-catalyzed (A-2) reactions, zero or positive entropies of activation with unimolecular acid-catalyzed (A-1) reactions.[18,19] In this case, the $\Delta S^{\ddagger}$ values are somewhat less negative[20] than has come to be expected for A-2 reactions of carboxylic acid derivatives. A-2 reactions of noncarboxylic acid derivatives have been noted before to show this same tendency to less negative $\Delta S^{\ddagger}$ values.[18] The observation here suggests that it is not the type of substrate that is responsible for these trends, but rather the type of reaction. This point is illustrated in Table V, where $\Delta S^{\ddagger}$ values are listed for a number of simple bimolecular reactions (in all cases but one, A-2). These can be separated into two classes, reactions involving the formation of a tetrahedral intermediate and reactions involving a direct displacement on a cationic species. The trend is apparent; the former hydrolysis generally shows a significantly more negative entropy of activation. As will be shown

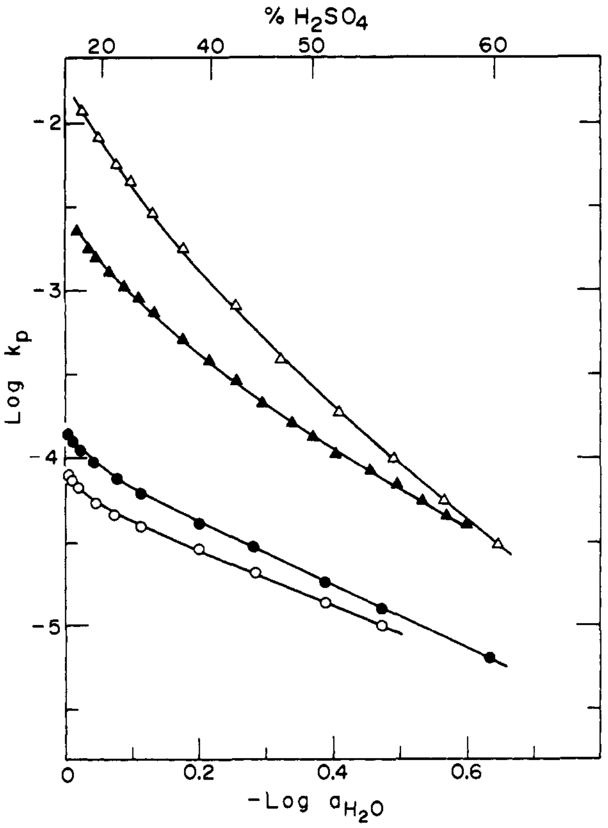


Figure 2. Hydration plots of acid-catalyzed hydrolysis: (○) II; (●) I; (▲) benzamide (ref 12); (△) methyl benzimidate (ref 2). For the imidates, $\log k_p = \log k_{obsd}$; for benzamide, $\log k_p = \log k_{obsd} - \log (h_a/h_a + K_{SH^+})$. Temperature: (○), (●) 86.1°; (▲), (△) 85.0°. Water activity refers to same temperature (ref 12).

Table VI. Calculated[a] Proportions of Acyl and Alkyl Substitution for Methyl Benzimidate at 85°

% H_2SO_4	Acyl addition, %	Alkyl substitution, %
65	82[b]	18[b]
60	88	12
50	95	5
35	98.6	1.4
25	99.1	0.9
12.5	99.4	0.6

[a] See text. [b] Taken from ref 2.

later, this observation is entirely consistent with the types of transition states involved in the two classes of reactions.

Finally, the decrease in rate on substitution of the O-methyl group by ethyl is consistent with the displacement at that group. In dilute acid, the rate difference between the two is 1.8 (at 86.1°). This value is somewhat greater than that observed in the hydrolysis of alkyl halides and tosylates ($k_{Me}/k_{Et} = 1.02-1.3$)[22] but may reflect the greater crowding in these imidates. Any mechanism involving formation of a carbonium ion as an explanation for the observed products and cleavage must be ruled out, however.

"r" Hydration Plots. As noted, the rate of hydrolysis of I and II decreases with increasing acidity. One approach to the study of such rate-acidity variations has been in terms of the hydration differences between transition state and starting material, i.e., the "w" treatment[23] or "r" treatment.[24] Previously, linear "r" plots have been observed for ester hydrolysis,[24,25] but the plots for amides[12], ureas,[26] and imidates[2] showed considerable curvature. Figure 2 depicts such plots for imidates I and II, as well as comparison plots for methyl benzimidate[2] and benzamide.[12] For the three imidates, these take the form of $\log k_{obsd}$ vs. $\log a_{H_2O}$ since the substrates are fully protonated at all acidities. For the amide, a protonation correction is necessary. Again considerable curvature is observed, particularly in the more dilute acids. In fact all four plots are very similar in shape, although not in slope. Thus we can conclude that curvature in "r" plots appears to be the general case for nitrogen-containing carboxylic acid derivatives, regardless of the nature of the reaction. This is an important observation; some workers have ascribed the nonlinearity of the "r" plots for amide hydrolysis to two competing bimolecular reactions.[27]

Acyl Addition vs. Alkyl Substitution. The observation of imidates that hydrolyze by alkyl substitution at all acidities permits a comparison of the two mechanisms for imidate hydrolysis in acid solutions. A particularly striking difference involves the more pronounced decrease in rate observed with the acyl-addition reaction as the acidity is increased (Figure 1). For example, the rate decrease with I on going from 12.3 to 60.3% H_2SO_4 is 17; for methyl benzimidate, a factor of 370 is involved, and this must be a lower limit since, in the more concentrated acids, there is a contribution from the other reaction.

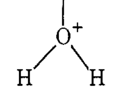
This observation illustrates why, with the unhindered benzimidates, acyl addition does give way to alkyl substitution in the more concentrated acids. For example, assuming that the $A_{Al}2$ hydrolysis of methyl benzimidate has an acidity dependence similar to that for the 2,6-dimethyl compound, the ratio of the two reactions at various acidities can be estimated using the previously estimated value[2] in 65% H_2SO_4 (this requires a slight extrapolation of our data). This is shown in Table VI and does predict, as is observed,[2] that acyl addition predominates to greater than 99% in dilute acids.

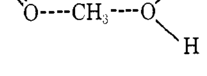
What remains is to explain the difference. For both schemes, the rate can be expressed in terms of activity coefficients by an identical equation. Since the effect is independent of the imidate, its origin must lie in the transition-state activity-coefficient term. In particular the transition state leading to acyl addition must be more salted-out by increasing acidity than the transition state leading to alkyl substitution.

$$k_{obsd} = k_0 \frac{f_s a_{H_2O}}{f_\ddagger}$$

Two related effects can be pictured to account for this. Both are based on recent suggestions[28] outlining the factors important in determining activity coefficient behavior of cationic species. For our purposes these are the extent of charge delocalization and the possibilities for specific hydrogen-bonding interactions of the type $O^+—H\text{---}OH_2$. For the former, increased delocalization results in less salting-out with increasing acidity since the requirement for solvent stabilization of the charge is lower. For the latter, such interactions will give rise to an increased salting-out with increasing acidity, because of the decrease in water activity.

In acyl addition, a transient intermediate species is being formed,[29] and the transition state might then be expected to resemble this fairly closely [‡ (addition)]. The $A_{Al}2$ hydrolysis is an SN2 displacement, and its transition state should not be nearly as advanced [‡ (substitution)]. By this rea-


‡ (addition)


‡ (substitution)

soning, ‡ (addition) has both a less delocalized positive charge and a greater requirement for hydrogen bonding of the above type since there is a larger buildup of positive charge on the oxygen of the attacking water. From the previous discussion, these two related effects must result in its greater salting-out.

Even if ‡ (substitution) were fully product-like (amide + $CH_3O^+H_2$), ‡ (addition) would be expected to be relatively salted-out since it contains two additional electronegative groups ($-NH_2$ and $-OCH_3$) in the vicinity of the positive charge. These would inductively destabilize the cation and force a greater requirement for solvent stabilization of the $^+O-H\cdots OH_2$ type.

Significantly, entropies of activation, not only for the imidates but also in general for bimolecular acid-catalyzed reactions, are in accord with the above discussions. In particular it was shown previously (Table V) that $\Delta S^\ddagger$ values for SN2-type reactions were significantly less negative than $\Delta S^\ddagger$ values for reactions involving a tetrahedral intermediate. This again can be explained in terms of a lower solvation requirement in the transition states for the substitution reactions, i.e., less restrictions of solvent molecules.

These same effects are mirrored, although to a much smaller extent, in a comparison of the two imidates of this study. The O-ethyl compound shows a slightly shallower acidity dependence (Figure 1), and also a slightly more positive entropy of activation. This suggests that the extra methyl group results in a smaller hydration requirement for the transition state. This can be attributed either to a steric hindrance to solvation or to an increased stabilization of the delocalized positive charge.

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Role of Water in the Hydrolysis of BH_4^- [1]

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Abstract: The rate law for the hydrolysis of BH_4^- in Me_2SO as a solvent has the form of that for a general-acid catalyzed reaction. Rate coefficients for H^+, H_2O, and 2,6-dinitrophenol are 0.74 ± 0.15, $1.5 \pm 0.2 \times 10^{-2}$, and 0.19 ± 0.4 M^{-1} sec^{-1}, respectively. That for water is six powers of ten *larger* than the comparable quantity in H_2O, but that for H^+ is six powers of ten *smaller*. It is postulated that proton transfer from hydronium ion to BH_4^- in water uses a water molecule as a proton relay. The H^+ rate coefficient in Me_2SO is much smaller because Me_2SO cannot function as a relay, and because of the instability of the structure $Me_2SO\cdots H\cdots HBH_3^+$.

Previous work on the hydrolysis of BH_4^- by aqueous acid (eq 1) has shown that the loss of the first hydrogen determines the overall rate, that the reaction

$$H^+ + BH_4^- + 3H_2O \longrightarrow 4H_2 + B(OH)_3 \qquad (1)$$

is first order in BH_4^- and first order in H^+, and that, in acidic solution, the product of the rate-determining step is H_2BH_3.[2] Solvent isotope effects have suggested that, in aqueous solution, a water molecule is intimately involved in the rate-determining step for the reaction with H^+, probably acting as a relay for the proton.[3] The purpose of this study was to test that suggestion by examining the reaction in nearly dry dimethyl sulfoxide (Me_2SO).

Dilute solutions in Me_2SO are well suited to such a study because H_2O is very nearly an ideal solute in Me_2SO up to at least 1.2 M,[4] and H^+ is only slightly hydrated in the concentration range of the present study.[5] A proton-transfer reaction, using water as a relay in aqueous solution, should be many powers of 10 slower in nearly anhydrous Me_2SO than in water as a solvent, because Me_2SO is not able to serve such a function. By contrast, ordinary A-SE2 reactions, which do not involve water in the rate-determining step, show rates only one to two powers of ten slower in Me_2SO than in water as a solvent and, in nearly anhydrous solution, their H^+ rate coefficients *decrease* slightly with increasing water concentration.[6,7] It should, therefore, be

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