THF seems to drive the equilibrium $F_K \rightleftharpoons F_C$ in favor of the kinetic form. To measure the extent of this reversal of the equilibrium, samples of the kinetic and cubane forms were used to prepare two NMR samples using THF as the solvent. The samples were kept at 20 to 25° in sealed NMR tubes, and spectra were obtained at convenient intervals. Whereas the NMR spectrum of the kinetic form in THF showed no change after several weeks, signals for the kinetic form slowly appeared in the sample of the cubane form after the same time period. Thus, the kinetic form is thermodynamically favored in THF.

Mixed CH_3MgOR Systems. A sample of unsolvated, kinetic methylmagnesium *tert*-butoxide was divided into two portions. One portion was dissolved in diethyl ether and placed in an nmr tube. To the other portion, a similar amount of unsolvated methylmagnesium isopropoxide (which appears to be the cubane form, although it was isolated under conditions which yielded the kinetic, linear oligomer form of methylmagnesium *tert*-butoxide) was added. This mixture was placed in a second NMR tube and also dissolved in diethyl ether. The room-temperature NMR spectra of these samples were obtained approximately 30 min after preparation and then at specific intervals of time for several days. Whereas, the pure *tert*-butoxy system contained only a small percent of *tert*-butoxy and methyl groups in cubane sites, the mixed system contained a large percentage of *tert*-butoxy and methyl groups in cubane sites.

Kinetic Methylmagnesium *tert*-Butoxide–Dimethylmagnesium. A sample of the solid product obtained by reacting 1 mol equiv of *tert*-butyl alcohol with 2 mol equiv of dimethylmagnesium in diethyl ether and removing solvent rapidly in vacuo was redissolved in diethyl ether and observed over a period of time. Its NMR spectrum initially showed only a sharp methyl rapid exchange signal. Over a period of days, the signals characteristic of the cubane form of methylmagnesium *tert*-butoxide appeared and slowly developed. Ultimately, the spectrum was consistent with a nonexchanging mixture of the cubane form of methylmagnesium *tert*-butoxide and dimethylmagnesium.

Acknowledgment. We thank the Fannie and John Hertz Foundation for a fellowship for G.E.P. and the National Science Foundation for generous support of this work.

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Hydrolysis of N,N-Disubstituted Imidate Esters

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Abstract: The influence of pH on the nature of the products of hydrolysis of six N,N-disubstituted imidate esters has been investigated. The yield of amine decreases invariably as pH is increased, but imidates derived from dimethyl- and diethylamine are converted to amine in unusually high yield in solutions as alkaline as pH 12.7. These findings are interpreted in terms of a recently suggested[7] mechanism involving tetrahedral addition intermediates which are not at equilibrium with respect to proton transport. The relevance of this work to the proposal[13] that orbital orientation controls the decomposition of tetrahedral intermediates is discussed.

The importance of understanding the mechanism of hydrolysis of imidate esters and its relation to the mechanism of ester aminolysis has been emphasized in a number of recent investigations, beginning with the study of thiazoline hydrolysis in 1959.[1-7] The observation that the products of imidate hydrolysis vary with pH has been a prominent element in the studies which have sought to identify the rate-determining steps in the aminolysis of esters.[4,7,8] Imidates derived from aliphatic alcohols and aliphatic and aromatic amines generally yield amines (and esters) on hydrolysis at low pH, and amides (and alcohols) at high pH.[4,8-10] The product transition occurs at pH 5.5-9.5, depending mainly on the basicity of the resident amine, which has varied in the range of pK_a = 1-10. Imidates, derived from phenols,[3,7,11] and thioimidates[12] yield largely amides through most of the pH range, although some of them form amines below pH 2-3. With the exception of imidates derived from very weakly basic amines (di- and trinitroaniline, *p*-toluenesulfonamide),[6] the hydrolysis of most imidate esters does not produce amines in significant yield at pH $>$10.

In a recent publication, Deslongchamps et al.[13] reported that several cationic imidate esters were converted in high yield to amines during hydrolysis at basic pH. These reactions were carried out usually in mixed aqueous-organic solvents of uncertain pH, and sometimes in the presence of carbonate buffers, which are known to increase markedly the yield of amine produced on hydrolysis of some imidates.[9,14] The importance of these observations for the mechanism of imidate hydrolysis, particularly with respect to the properties of the tetrahedral intermediates formed in these reactions, led us to reexamine the hydrolysis of certain cationic imidate esters in predominantly aqueous solution, over a range of pH values. The results which are presented in this paper confirm and extend the observations of Deslongchamps et al.[13] that some imidate esters derived from basic amines afford mostly amines upon hydrolysis in alkaline solutions.

Results

Kinetic measurements of the hydrolysis of six cationic imidate esters (**1–6**) were made in 0.5% acetonitrile–water (μ = 0.5, KCl), at 30°, by spectrophotometric means. The unsymmetrical *N*-methyl-*N*-ethyl imidate **4** consisted mainly of one isomer ($>$85%) to which the structure shown

Table I. Rate Constants for Hydrolysis of Imidates[a]

Imidate	pH	$k_1 \times 10^4$, sec^{-1}	k_2,[b] M^{-1} sec^{-1}
1	5.4–12.7	0.21	1600
2	6.4–12.6	0.022	320
3	7.0–12.7	0.01[c]	59
4	7.0–12.6	0.03[d]	630
5	1.0–9.0	1.87	5500
5[e]	3.7–9.6	6.0[f]	(3×10^{-11})[g,h]
6	3.0–9.2	0.39	1100

[a] 30°, $\mu = 0.5$. [b] Calculated using $K_\mathrm{w} = 10^{-14}$. [c] Upper limit; k_1 is 16% of the lowest value of k_obsd. [d] Upper limit; k_1 is 5% of the lowest value of k_obsd. [e] In 50% acetonitrile–water. [f] May include small buffer effect (0.04 M formate, pH 3.7). [g] $k_\mathrm{obsd} = 0.126$ sec^{-1} at pH 9.6 (0.02 M triethylenediamine buffer). [h] Value of k_2' in $k_\mathrm{obsd} = k_1 + k_2'/[\mathrm{H}^+]$. Note that $k_2 = k_2'/K_\mathrm{w}$.

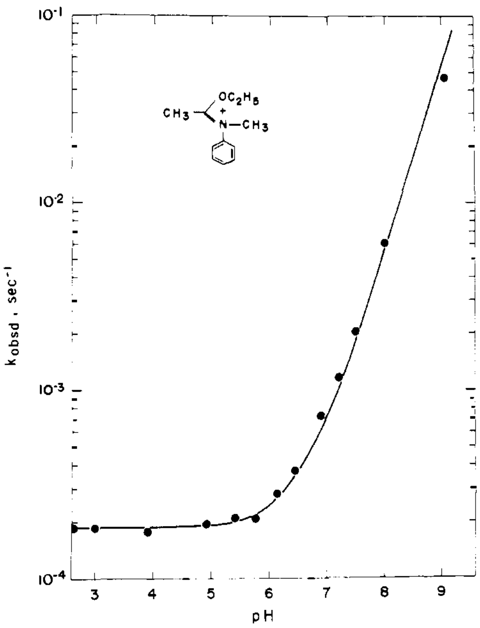


Figure 1. pH-rate profile for hydrolysis of **5** at 30°, $\mu = 0.5$. Curve is calculated from eq 1 using constants of Table I.

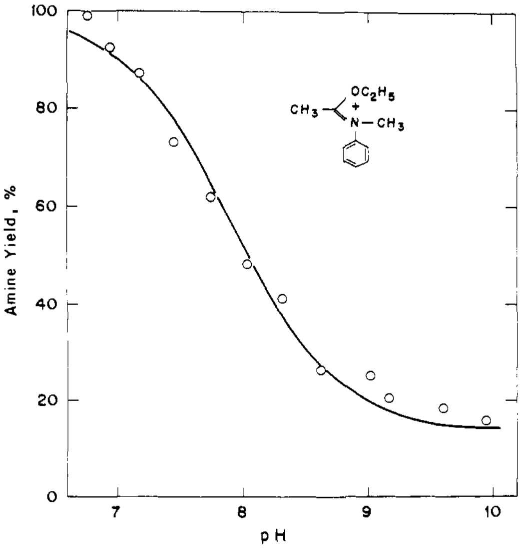
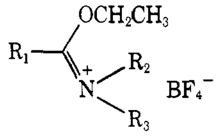


Figure 2. Product-pH profile for hydrolysis of **5** in 0.5% CH_3CN-H_2O. Curve is calculated from eq 2 using constants of Table II.



1, $R_1 = R_2 = R_3 = CH_3$

2, $R_1 = CH_3$; $R_2 = R_3 = C_2H_5$

3, $R_1 = CH_3$; $R_2 = R_3 = i\text{-}C_3H_7$

4, $R_1 = R_2 = CH_3$; $R_3 = C_2H_5$

5, $R_1 = R_2$ (or R_3) $= CH_3$
R_3 (or R_2) $= C_6H_5$

6, $R_1 = C_6H_5$; $R_2 = R_3 = CH_3$

was assigned on the basis of its NMR spectrum (see Experimental Section). The other unsymmetrical imidate **5** appeared to consist solely of one isomer, the structure of which is not known. No kinetic evidence was obtained for the presence of more than one isomer of **4** or **5** during the course of hydrolysis; syn-anti isomerization is either very slow or very rapid with respect to the rate of hydrolysis, the former being more likely.[15]

As expected for cationic imines,[4,12b,16] the kinetics of the hydrolysis of imidates **1-6** follow a simple rate law (eq 1)

$$k_\mathrm{obsd} = k_1 + k_2[\mathrm{OH}^-] \qquad (1)$$

which includes terms for addition of water and hydroxide ion to the $C{=}N^+$ bond. Rate data were extrapolated to zero buffer concentration when necessary. The low concentration of buffers used (usually <0.08 M) caused small increases in rate (<50% over the rate extrapolated to zero buffer concentration), presumably as a result of general-base catalysis of the addition of water to the cationic center.[1b,8] At pH 10.5-12.7, the rapid reaction rates required the use of the stopped-flow technique. A typical pH-rate profile is shown in Figure 1, and rate constants are summarized in Table I. In some cases, the contribution of the water reaction to the total observed rate at the lowest pH examined was small and is estimated as an upper limit only. With **5**, which was studied in solutions as acidic as pH 1, no rate decrease was seen at the low end of the pH scale. Such decreases in rate have been observed with many imines and result sometimes from a change in rate-determining step as pH is varied,[1a,16a] and sometimes from activity coefficient effects.[4] With all six imidates, k_obsd increased linearly with $[\mathrm{OH}^-]$ in the range of pH 8-13. No indication was seen of a rate term proportional to $[\mathrm{OH}^-]^2$, as has been reported in the hydrolysis of a bicyclic 1,3-dihydrooxazinium salt.[17]

The hydrolysis of **5** was also studied in 50% acetonitrile-water. The threefold rate increase in k_1 is consistent with the expected effect of decreasing dielectric constant on a reaction where dispersal of charge occurs in the transition state. In the pH range where k_obsd is proportional to $[\mathrm{OH}^-]$, the observed rate in 0.5% CH_3CN is about twice that determined in 50% CH_3CN-H_2O at the same measured pH value. In terms of hydroxide ion activity, the rate constant k_2 probably increases markedly in the presence of 50% acetonitrile since it is likely that the ion product of water, and hence a_{OH^-}, decreases appreciably with added organic solvent.[18] An increase in k_2 is expected for a reaction where disappearance of charge takes place in the transition state.

The ratio k_2/k_1 of the rates of hydroxide to water attack on the imidates varies from 2.9×10^7 to 1.5×10^8 M^{-1}, which is comparable to the values found with other imidate esters.[9] The effect of N-methylation on the rates of addition of water to imidates and related compounds is variable. Ethyl *N*-phenylacetimidate[9] is hydrolyzed 41 times more rapidly than **5**, while ethyl *N*-phenylthiobutyrimidate[12a] reacts 13 times faster than its *N*-methyl derivative.[12b] Ethyl *N*-methylacetimidate,[10] 2-methyl-Δ^2-thiazoline,[16a] and 2-methylbenzoxazole[19] are five to six times more reactive than their *N*-methyl derivatives[19,20] but *N*-methylbenzophenone imine[16b] is hydrolyzed only 1.5 times faster than the corresponding *N*,*N*-dimethylimmonium salt. Whereas conversion of ethyl benzimidate[21] to the ethyl *N*,*N*-dimethylbenzimidate cation reduces its rate of hydrolysis by a factor of 2 only, similar N,N-dimethylation of ethyl thioacetimidate causes a 100-fold decrease in the rate of hydrolysis.[12a,16c]

Hydrolysis Products. The products of hydrolysis of **5** were determined over the range of pH 1-10. The amine yield were corrected at each pH for buffer effects, which were not large. The use of bifunctional buffers[14] (CO_3^{2-}, HPO_4^{2-}) was avoided. The yield of amine decreases from 100% at low pH to a value of about 14% approached asymptotically at high pH (Figure 2). The dependence of amine yield on pH seems to obey fairly well a simple sigmoid function with a transition at pH 7.9. The effect of pH on the products of hydrolysis of **5** is similar to those reported for a number of other imidates derived from aniline[8,9] or aliphatic amines,[4,9] although the yield of amine at high pH is significantly greater than previously observed. Care was taken to avoid contamination of reagent solutions by atmospheric carbon dioxide, to eliminate the possibility that the nonzero yield of amine at high pH resulted from the effect of adventitious bicarbonate ion.

A similar variation of amine yield with pH is observed after hydrolysis in 50% acetonitrile-water. The effect of the organic solvent is to shift the product-pH curve by about 1.3 pH units to the alkaline side. There also seems to be a decrease in the amine yield at high pH, which approaches 5%.

The influence of pH on the amine yield obtained from the aliphatic imidates **1-4** was studied in the range of pH 8.0-12.7. All four compounds exhibit a decrease in amine yield as pH increases (Figure 3). The following features of the pH-product profile are of interest. (a) The amine yield reached asymptotically below pH 8 is high, but is probably less than 100% even with **1** or **2**, and falls to 60% with the diisopropyl imidate **3**. Most imidates derived from aliphatic alcohols and basic amines are converted to nearly 100% amine at pH values near neutrality, although the hydrolysis of 1-benzylimino-2,3-dihydroisobenzofuran gave approximately 70% amine at pH 6-7.[22] (b) The amine yield reached asymptotically at pH >12 is unusually high with **1**, **2**, and **4**. This is in contrast to the behavior of most imidates which form little or no amine at high pH[4,8,9] and is in agreement with the less detailed observations of Deslongchamps et al.[13] with several quaternary imidates. (c) The hydrolysis products vary with pH according to a simple sigmoid dependence (eq 2, where P^0 is the asymptotic value of the amine yield at low pH, and P^- is the asymptotic

$$\text{amine yield} = \frac{P^0 + P^-K''/[H^+]}{1 + K''/[H^+]} \qquad (2)$$

value of the amine yield at high pH), with a transition in products at pH = pK'' = 10.3-10.6. Although the data for **4** exhibited appreciable experimental scatter, it is assumed that they also are described by eq 2. The values of P^0, P^-, and K'' used with eq 2 to calculate the curves in Figures 2 and 3 are presented in Table II. The product-transition pH values of 10.2-10.6 are the highest which have been reported in imidate hydrolysis. At pH <10.5, the hydrolyses of **1-4** were carried out in dilute borate buffers (0.02-0.08 *M*), which are not expected to have a significant effect on the nature of the products. Increasing borate buffer concentration from 0.008 to 0.08 *M* (pH 9.3) did not change the yield of amine formed from **2**. Hydrolysis of **2** in 0.01 *M* borate (pH 10.04) gave 81.5% amine; when pH was maintained constant at 10.0 by use of the pH stat in the absence of added buffer, the yield was 81.3%. At pH >10.5, NaOH buffers were used.

Table II. pH Dependence of Amine Yield from Imidates[a]

Imidate	$P^0 \times 100$	$P^- \times 100$	pK''
1	96.3	78.4	10.2
2	86	72	10.3
3	60	6	10.6
4	92	80	10.3
5	100	13.6	7.9
5[b]	100	5	9.25

[a] Constants refer to eq 2; see also eq 3 and 4. [b] In 50% acetonitrile-water.

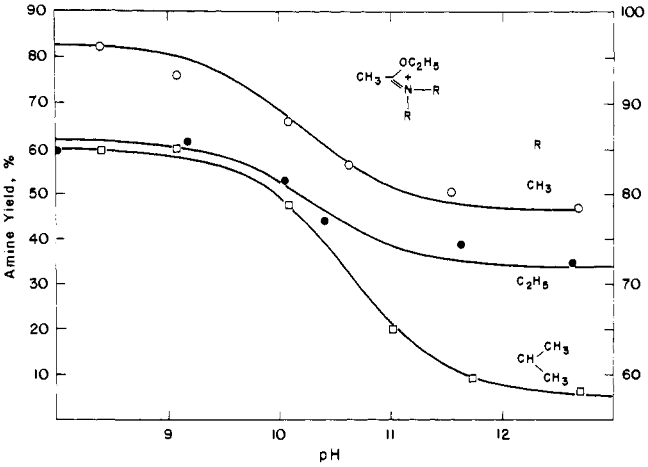
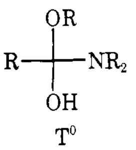


Figure 3. Product-pH profile for hydrolysis of alkyl imidates **1-3**. (○) **1** and (●) **2**, right ordinate. (□) **3**, left ordinate. Curves are calculated from eq 2 using constants of Table II.

Hydrolysis of the benzimidate **6** at pH <8 gave about 90% amine, and the yield decreased to 82% at pH 9.7. The high yield of amine is in general agreement with the report[13] that basic hydrolysis of **6** under unspecified conditions produced >98% amine. The product data obtained with **6** in the present study are limited and possibly of low precision. For these reasons, they are considered to be preliminary and are not used in the discussion that follows.

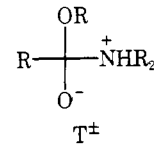
Discussion

Several previous studies have established that the hydrolysis of imidate esters proceeds via tetrahedral addition intermediates, the principal line of evidence being the independent effects of pH and general acid-base catalysts on the rates and products of hydrolysis.[4,5,8-10] Early reaction mechanisms postulated the existence of several ionic species of the addition intermediates, believed to be in acid-base equilibrium. The variation in products with pH was thus explained by proposing that a neutral (T^0), or, more likely, zwitterionic ($T^{\pm}$) intermediate expelled amine; at higher pH, ionization to the anionic species T^- resulted in the expulsion of alkoxide ion with the consequent formation of amide as the main product. More recently, cogent arguments have been presented to support the suggestion that



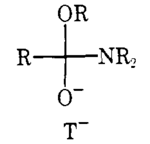
$$R-\overset{OR}{\underset{OH}{C}}-NR_2$$

T^0



$$R-\overset{OR}{\underset{O^-}{C}}-\overset{+}{N}HR_2$$

$T^{\pm}$

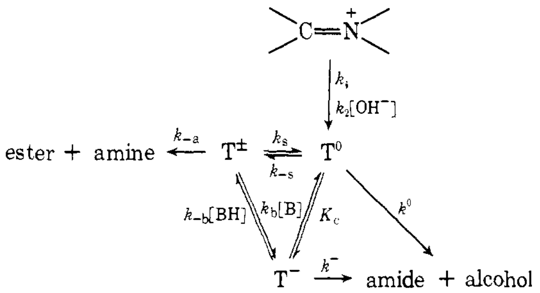


$$R-\overset{OR}{\underset{O^-}{C}}-NR_2$$

T^-

the intermediates are not always at equilibrium with respect to proton transfer; proton-transport steps may become product determining in imidate hydrolysis and rate determining in the aminolysis of esters.[7,23a] In what follows, the results of the present study are interpreted in terms of the mechanism suggested by Satterthwait and Jencks[7] for the hydrolysis of alkyl imidates (Scheme I).

Scheme I



The rate-determining step of alkyl imidate hydrolysis is proposed to be the addition of water or hydroxide ion to form T^0. The sole precursor of amine is $T^{\pm}$. Amide may be formed either from T^0 (step k^0) or via T^- (step k^-) to which T^0 is rapidly converted at high pH. T^0 is converted to $T^{\pm}$ by a proton switch mechanism (k_s, k_{-s}). In the absence of added buffer, B = OH^-.[23b] Assuming a steady state in the intermediates, and further[7] that $k_{-a} \gg k_b[B] + k_s$, the mole fraction of amine produced is given by eq 3, which is

$$\text{amine yield} = \frac{k_{-b} + k_{-s}[H^+]/K_c}{(k_{-b} + k^-) + (k_{-s} + k^0)[H^+]/K_c} \quad (3)$$

of the form of eq 2. The partitioning ratio P^0 which gives the amine yield at low pH is given by $k_{-s}/(k_{-s} + k^0)$ and depends on the relative rates of alcohol expulsion from T^0 and of the proton switch to $T^{\pm}$. The partitioning ratio P^-, which describes the yield of amine at high pH, is equal to $k_{-b}/(k_{-b} + k^-)$ and depends on the relative rates of alkoxide ion departure from T^- and of protonation of T^- to $T^{\pm}$. The pH value at which the product transition occurs is given by $[H^+] = K'' = K_c(k_{-b} + k^-)/(k_{-s} + k^0)$. In the extreme case where $P^0 \simeq 1$ and $P^- \simeq 0$; i.e., where the products of hydrolysis are exclusively amine at low pH and amide at high pH, $K'' = k^-K_c/k_{-s}$.[7]

As earlier, there is no correspondence between the pH of the product transition (pK'') and the pH where the rate law indicates a change from water to hydroxide ion attack on the imidate. With the aliphatic imidates **1-4**, the change in products takes place completely in a pH range where $k_{obsd} = k_2[OH^-]$. In the case of **5**, pK'' = 7.9, while the contributions of the two terms of eq 1 are equal at pH 6.5. There is thus no parallel between the contribution of the hydroxide term to the rate-limiting step and the proportion of amide product, such as was found with phenyl imidates.[7]

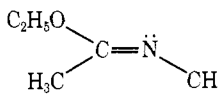
The observation[13] of high amine yields in alkaline solution in the hydrolysis of an imidate could be due either to an unusually high value of pK'' since P^0 is frequently near one, or to a high value of P^-. The pK'' values of 10.2-10.6 obtained in the present work are only slightly higher than those of 8.5 and 9.8 reported[9,10] for imidates derived from basic primary amines. It would seem that the explanation for the high yields of amine formed from imidates **1**, **2**, and **4** in alkaline solution must be sought in the factors which control the partitioning of T^-.

Deslongchamps et al.[13] have offered the hypothesis that the proper orientation of lone-pair orbitals on the oxygen atoms of the tetrahedral intermediate specifically facilitates the cleavage of the carbon-nitrogen bond. According to this theory, substituents in the imidate govern its conformation, which is maintained initially in the tetrahedral intermediate formed by addition of hydroxide ion. Recent quantum mechanical calculations appear to support the view that two lone-pair orbitals disposed antiperiplanar to the C-N bond would lead to its cleavage in preference to cleavage of the C-OR bond.[24]

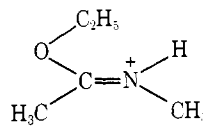
It is possible to explain the results of the present study without assuming that orbital orientation governs the rate of cleavage of the C-N bond in a tetrahedral intermediate. To the extent that the mechanism of Scheme I is valid, the yield of amine at high pH (i.e., at pH > pK'') depends on the relative rates of processes k_{-b} and k^-, i.e., on the partitioning of T^- between protonation on nitrogen and expulsion of alkoxide ion. Conversion of **1** to **3** should have little effect on the electron density in the nitrogen atom,[25] and hence little electronic influence on k^-, but steric or solvation effects resulting from the presence of bulky hydrophobic groups may reduce the rate of protonation k_{-b}, and thereby diminish the amine yield. Alternatively, there is no significant change in the rate of protonation of T^- to $T^{\pm}$, but the conformation of T^- is affected by the introduction of bulky groups on nitrogen; this conformational effect leads to an increase in k^- and a decrease in amine yield. Note that this conformational effect is suggested to accelerate the departure of alkoxide ion, without affecting the already very rapid amine expulsion from $T^{\pm}$ (step k_{-a}) or the rate of the preceding step k_{-b}. In summary, if the rate of protonation (by water) of the nitrogen atom of T^- is kinetically significant, orbital-orientation effects on the rate of cleavage of the C-N bond may not be important in determining the yield of amine in the hydrolysis products.

It has been suggested, however, that when *water* is the proton donor, the expulsion of amine from T^- may be concerted with proton transfer from water to the nitrogen atom of T^-.[7] If this is the case, then orbital orientation could well affect the rate of C-N bond cleavage and hence the yield of amine product. It does not seem possible to rule out this alternative at present.

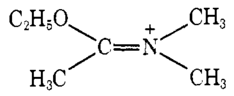
The yield of amine (P^0) at pH < pK'' depends on the competition between the proton switch (k_{-s}) and the expulsion of ethanol (k^0), and arguments similar to those above may be made here as well, again without necessarily invoking a change in the rate of cleavage of the C-N bond.



(*E*)-7



(*E*)-7-H



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The complete pH-product profile for ethyl *N*-methylacetimidate **7** is not available, but this compound is hydrolyzed at pH 10.6 to 38% amine,[10] i.e., much less than is obtained from the corresponding *N,N*-dimethyl imidate **1**. On the basis of the orbital-orientation theory,[13] it might be expected that the *N,N*-dimethyl imidate would yield less amine than the monomethyl derivative. The imidate **7** exists primarily in the *E* configuration.[26] If protonation in alkaline solution is more rapid than syn-anti isomerization,[27] the protonated imidate **7**-H is more likely than **1** to exist initially in the *E* configuration shown, i.e., with the lone-pair orbitals of the ethereal oxygen suitably disposed for expulsion of amine. The fact that **1** yields more amine than **7** suggests that factors other than orbital orientation should be considered.

Use was made of the approach outlined by Fox and Jencks[29] to estimate the pK_a values relating the various species of the tetrahedral intermediates derived from **1** and **5**.[30] The values of these equilibrium constants, combined with the experimentally determined values of P^0, P^-, and pK'', and the assumption that $k_b = 10^{10}\ M^{-1}\ sec^{-1}$,[28] were sufficient to calculate estimates of all the constants of Scheme I for the hydrolysis of **1** (Table III). The same procedure could not be applied to **5** since it became apparent that the calculated value of k_s was of the same order of magnitude as the rate of proton transfer from $T^{\pm}$ to H_2O. Thus, the assumption could not be made that the favored pathway from $T^{\pm}$ to T^- at relatively low pH proceeds solely via proton switch to T^0. Inclusion in Scheme I of the additional pathway

$$T^{\pm} \underset{k_{-b'}(H^+)}{\overset{k_{b'}}{\rightleftharpoons}} T^-$$

and application of the steady state approximation lead to eq 4–7, for the pH dependence of the amine yield, the amine yield at low pH, the amine yield at high pH, and the pH of the product transition, respectively.

$$\text{amine yield} = \frac{[H^+]\left[k_{-b'} + \dfrac{k_{-s}}{K_c}\right] + k_{-b}}{[H^+]\left[k_{-b'} + \dfrac{k_{-s} + k^0}{K_c}\right] + k_{-b} + k^-} \tag{4}$$

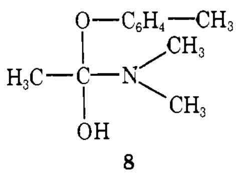
$$P^0 = \frac{k_{-b'} + \dfrac{k_{-s}}{K_c}}{k_{-b'} + \dfrac{k_{-s} + k^0}{K_c}} \tag{5}$$

$$P^- = \frac{k_{-b}}{k_{-b} + k^-} \tag{6}$$

$$K'' = \frac{k_{-b} + k^-}{k_{-b'} + \dfrac{k_{-s} + k^0}{K_c}} \tag{7}$$

As for **1**, eq 5–7, together with the estimated pK_a values for the intermediates derived from **5**, and the assumption[28] that $k_b = 10^{10}\ M^{-1}\ sec^{-1}$ and $k_{-b'} = 5 \times 10^{10}\ M^{-1}\ sec^{-1}$ allowed the calculation of the constants for the hydrolysis of **5** (Table III).

The value of k^0 is about 10^5 smaller than that for the expulsion of phenolate ion from **8**,[7] which seems reasonable



8

when the pK_a values of *p*-cresol (10.2) and of ethanol (15.9) are compared. The rate constant k^- for expulsion of ethoxide from **5** is nearly 3000 times smaller than the corresponding constant for **1**, reflecting the much reduced electron density in the aniline derivative. The rates k_s for the proton switch may be compared with the values of 10^6 to $10^7\ sec^{-1}$ estimated for k_s in the intermediate formed by addition of hydrazine to ethyl acetate.[7] When the basicity of the resident amine is significantly reduced, the decreasing value of k_s and the increasing rate of proton transfer from $T^{\pm}$ to H_2O ($k_{b'}$) result in the diminishing importance of the proton switch mechanism as the predominant pathway of interconversion of T^0 and $T^{\pm}$.

The aminolysis of esters of basic alcohols in the absence of buffer catalysis may thus involve one of the following sequential changes in rate-determining step as pH increases: (a) rate-limiting breakdown of T^- (step k^-), followed by a rate-limiting proton switch which converts $T^{\pm}$ to T^0 (step k_s), and finally, at high pH, the rate-limiting abstraction of a proton to convert $T^{\pm}$ to T^- directly (e.g., in the reaction of ethyl acetate with hydrazine);[7] (b) same as a, except that the proton-switch step at intermediate pH is replaced by proton transfer from $T^{\pm}$ to water; this sequence is expected in aminolysis reactions of weakly basic amines such as anilines; (c) the breakdown of T^- is essentially rate determining throughout the entire alkaline pH range; this mechanism is anticipated for reactions such as that between dimethyl- or diethylamine and ethyl acetate which, for reasons not well understood, give tetrahedral intermediates which expel mainly amine at all pH values.

Table III. Rate and Equilibrium Constants for the Hydrolysis of Imidates 1 and 5[a,b]

Constants	1	5
$pK_{b'}, M$	10.9	6.1
pK_c, M	13	12.3
pK_e, M	5.8	1.1
K_s	130	1.6×10^6
k^-, sec^{-1}	2.2×10^6	8×10^2
k^0, sec^{-1}	6×10^2	
k_s, sec^{-1}	2×10^6	1.9×10^4
k_{-a}, sec^{-1}	$>10^8$	$>10^8$

[a] Constants refer to Scheme I and ref 30. [b] $K_s = k_s/k_{-s}$.

Experimental Section[34]

Methyl[α-(ethoxy)ethylidene]phenylammonium tetrafluoroborate (5)[35] was prepared in a manner analogous to that used in the alkylation of *N*-methyl thionbutyranilide.[12b] A suspension of 4.6 g (24.2 mmol) of triethyloxonium tetrafluoroborate[36] in ether was introduced into a dry flask and the ether removed in vacuo. The residue was dissolved in 10 ml of dry CH_2Cl_2 and cooled to 0°. A solution of 3.6 g (24.2 mmol) of *N*-methylacetanilide in 4 ml of CH_2Cl_2 was added dropwise with exclusion of moisture. The reaction mixture was kept at 0° for 1 hr, then at room temperature for 1 hr. On addition of dry ether and seeding, a crystalline mass was obtained, which was recrystallized from petroleum ether-CH_2Cl_2: mp 90–92° (61% yield); ir (Nujol) 6.10 μ ($C{=}N^+$); uv (1% CH_3CN-H_2O) no λ_{max} at >220 mμ (ϵ_{220} ~6200); NMR ($CDCl_3$) δ 1.58 (t, 3 H, CH_2CH_3), 2.38 (s, 1 H, C–CH_3), 3.58 (s, 1 H, N–CH_3), 4.77 (q, 2 H, CH_2CH_3). The NMR spectrum gave no evidence of a second isomer.

Anal. Calcd for $C_{11}H_{16}NOBF_4$ (265.07): C, 49.83; H, 6.08; N, 5.29. Found: C, 50.25; H, 6.16; N, 5.27.

The same general procedure was used for the synthesis of the symmetrically N,N-disubstituted imidate salts **1–3** and **6**.

Dimethyl[α-(ethoxy)ethylidene]ammonium Tetrafluoroborate (1). Addition of dry ether on completion of reaction yielded a mass of hygroscopic colorless crystals. The product was purified by repeated trituration with fresh batches of dry ether; remaining traces of solvent were removed in vacuo at room temperature: NMR ($CDCl_3$ containing 2 drops of dimethyl-d_6 sulfoxide) δ 1.46 (t, 3 H, CH_2CH_3), 2.52 (s, 3 H, C-CH_3), 3.25 (s, 3 H, N-CH_3), 3.38 (s, 3 H, N-CH_3), 4.55 (q, 2 H, CH_2CH_3).

Anal. Calcd for $C_6H_{14}NOBF_4$ (203.00): C, 35.50; H, 6.95; N, 6.90. Found: C, 34.69; H, 6.67; N, 7.02.

Diethyl[α-(ethoxy)ethylidene]ammonium Tetrafluoroborate (2). Addition of ether gave an oil which was purified as for **1**: NMR ($CDCl_3$) δ 2.53 (s, 3 H, C-CH_3), 4.62 (q, 2 H, OCH_2CH_3).

Anal. Calcd for $C_8H_{18}NOBF_4$ (231.05): C, 41.60; H, 7.85; N, 6.06. Found: C, 41.76; H, 7.74; N, 6.30.

Diisopropyl[α-(ethoxy)ethylidene]ammonium Tetrafluoroborate (3). On completion of reaction, the solvent was removed in vacuo, and the crystalline residue was recrystallized from ethanol-ether: mp 121–123°; NMR ($CDCl_3$) δ 2.58 (s, 3 H, C-CH_3).

Anal. Calcd for $C_{10}H_{22}NOBF_4$ (259.11): C, 46.34; H, 8.50; N, 5.41. Found: C, 45.87; H, 8.24; N, 5.73.

Dimethyl[α-(ethoxy)benzylidene]ammonium Tetrafluoroborate (6) was obtained as a viscous liquid: NMR ($CDCl_3$) δ 1.40 (t, 3 H,

CH_2CH_3), 3.24 (s, 3 H, N-CH_3), 3.55 (s, 3 H, N-CH_3), 4.26 (q, 2 H, CH_2CH_3).

Ethylmethyl[α-(ethoxy)ethylidene]ammonium Tetrafluoroborate (4). The hydrofluoroborate salt of ethyl *N*-ethylacetimidate was prepared by treatment of distilled *N*-ethylacetamide with triethyloxonium tetrafluoroborate as described for the preparation of **5**: NMR ($CDCl_3$) δ 2.52 (s, 3 H, C-CH_3), 4.62 (q, 2 H, OCH_2CH_3) [reported[37a] for ethyl *N*-ethylpropionimidate·HBF_4: δ 4.61 (OCH_2CH_3)]. The free base was obtained by shaking the solid salt with a mixture of ether and saturated NaCl solution containing 1 equiv of KOH at 0°. The ethereal phase was dried over K_2CO_3, and the imidate free base was purified by distillation (73% yield): bp 115-116° (lit.[37a] 113°); NMR ($CDCl_3$) δ 1.82 (s, 3 H, C-CH_3).

A solution of ethyl *N*-ethylacetimidate in dry CH_2Cl_2 was added dropwise to an equimolar suspension of trimethyloxonium tetrafluoroborate[37b] in refluxing CH_2Cl_2. The reaction mixture became homogeneous as reaction proceeded. Purification as for **1** gave the partially crystalline product **4**: NMR ($CDCl_3$) δ 2.56 (s, 3 H, C-CH_3), 3.25 (s, 3 H, N-CH_3), 3.75 (q, 2 H, NCH_2CH_3), 4.60 (q, 2 H, OCH_2CH_3). The observation of distinct long-range coupling between the N-CH_3 and C-CH_3 groups suggests that **4** possesses the structure with the N-CH_3 trans to the C-CH_3.[26] The NMR spectrum indicates the presence of 10-15% of the isomer with the N-CH_3 group (δ 3.38, sharp singlet with no sign of splitting) cis to the C-CH_3 group.

Anal. Calcd for $C_7H_{16}NOBF_4$ (217.03): C, 38.74; H, 7.39; N, 6.45. Found: C, 38.55; H, 7.25; N, 6.64.

Dimethylamine hydrochloride (mp 170-172°), **diethylamine hydrochloride** (mp 224-226°), and **diisopropylamine hydrochloride** (mp 215-217°) were recrystallized from ethanol-ether.

Kinetic Measurements. The purifications of acetonitrile and imidazole have been described.[8] β-Dimethylaminopropionitrile, *N*-methylmorpholine, and triethylamine were distilled prior to use. Other buffers and inorganic salts were of reagent grade and were used without further purification. Freshly boiled, glass-distilled water was used to make up all solutions for rate determinations and product analyses of reactions at pH >7. The solvent used for the kinetic studies was 0.5% acetonitrile-water for all reactions with $t_{1/2}$ > 10 sec, i.e., at pH <10, except for a limited series of experiments with **5** in 50% CH_3CN-H_2O. All rate and product determinations were performed with ionic strength maintained at 0.5 *M* (KCl) and T = 30.0°. Buffers used were HCl, formate, acetate, succinate, imidazole, phosphate, β-dimethylaminopropionitrile, *N*-methylmorpholine, Tris, borate, triethylenediamine, carbonate, and NaOH in the appropriate pH ranges. Buffer concentrations were usually 0.02-0.08 *M* (three to four concentrations at each pH), and rate constants were extrapolated to zero buffer concentration. To initiate reaction, a small volume (ca. 15 μl) of a concentrated solution of imidate in acetonitrile was added to 3 ml of buffer previously equilibrated in the water-jacketed cell holder of a Cary Model 15 spectrophotometer, equipped with automatic sample-changer assembly. The final concentrations were 10^{-3} *M* for **1-4** and 1-2 × 10^{-4} *M* for **5** and **6**. The rate of hydrolysis of **5** was followed by the change in absorption at 230 mμ for reactions at pH <4, and at 240-242 mμ for higher pH. The hydrolysis of **6** was followed at 235 mμ. A decrease in absorption at 225 mμ provided a convenient means of measuring the rate of disappearance of the aliphatic imidates **1-4**.[4]

The fast reaction rates of **1-4** at pH 10-12.7 were measured with a Durrum-Gibson stopped-flow spectrophotometer, with a 20-mm light path. These reactions were carried out in purely aqueous medium and were initiated by mixing equal volumes of a dilute imidate solution in 0.5 *M* KCl, acidified to about pH 4, with the appropriate buffer solution (at μ = 0.5).

Fast and moderately slow reactions were followed to completion, and rates were calculated from the slopes of semilogarithmic plots of absorbance change vs. time. Rate constants for very slow reactions were calculated by means of a modified Guggenheim treatment.[38]

At pH >8, small changes in pH resulting from buffer dilutions cause significant changes in k_{obsd} owing to the importance of the $k_2[OH^-]$ term (eq 1). Assuming that buffer effects are negligible, k_2 values calculated separately at each buffer concentration were found to be essentially constant.

Product Analysis. The yield of amine produced during the hydrolysis of **5** was measured by colorimetric determination of *N*-methylaniline, using a modification[12b] of the method of Sawicki et al.[39] Product analysis was carried out after >6 half-lives of reaction, on reaction mixtures identical with those used in the kinetic studies.

The yield of amine formed from imidates **1-4** or **6** after >6 half-lives of reaction was measured colorimetrically as previously described for dimethylamine.[12b] The hydrochlorides of dimethyl-, diethyl-, or diisopropylamine were used as standards. Under the usual assay conditions, a 1-ml aliquot containing amine at 1 × 10^{-4} *M* gave an absorbance of about 0.40 at 540 mμ. Owing to the sensitivity of the colorimetric assay, the final concentration of the imidate in reaction mixtures intended for product analysis was 2 × 10^{-4} *M*, in 1% acetonitrile-water, except for reactions at pH >10, which contained no acetonitrile. Fast reactions were mixed in the stopped-flow spectrophotometer; the effluents of about ten consecutive mixings were pooled and analyzed for amine.

Acknowledgment. This research was supported by a grant from the National Science Foundation. We are grateful to Professor W. P. Jencks for preprints of unpublished material.

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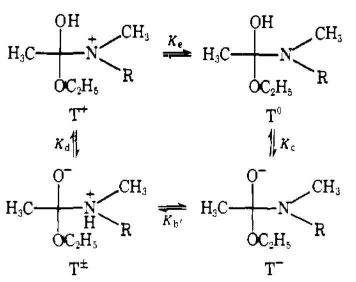

(30) R = CH_3: pK_e based on pK_a for $(CH_3)_3N$ = 9.69 (30°);[31] σ_I for OH = OC_2H_5 = 0.25;[25] pK_d and pK_c based on pK_a for C_2H_5OH = 15.9,[32] σ_I for $N^+H(CH_3)_2$ = 0.7,[25] σ_I for $N(CH_3)_2$ = 0.10.[33] R = C_6H_5: pK_e based on pK_a for $C_6H_5N(CH_3)_2$ = 5.0 (30°);[31] pK_c based 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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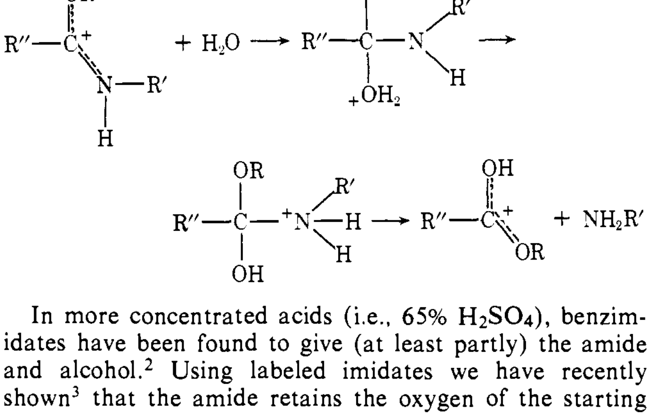
Abstract: Methyl and ethyl 2,6-dimethylbenzimidate hydrolyze at all acidities via a reaction analogous to $A_{Al}2$ carboxylate ester hydrolysis. The product of hydrolysis is principally (>99%) 2,6-dimethylbenzamide, and this arises with cleavage of the alkyl carbon-oxygen bond. Other factors consistent 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.

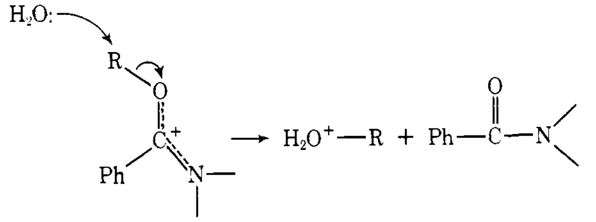
The hydrolysis of imidate esters generally proceeds through a tetrahedral addition intermediate[1] and has therefore seen considerable investigation because of the information that can be obtained regarding this important species. These compounds can in principle hydrolyze in two directions, giving either 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