

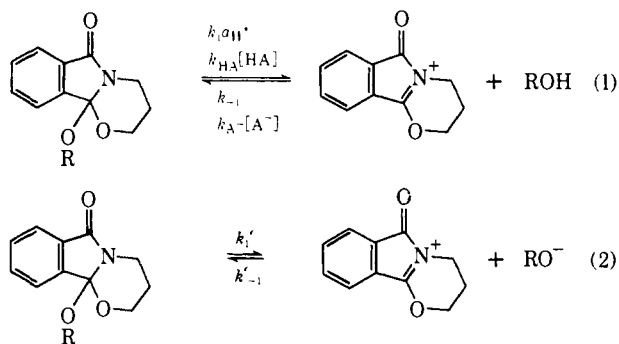
Mechanism of General Acid–Base Catalysis of the Breakdown and Formation of Tetrahedral Addition Compounds from Alcohols and a Phthalimidium Cation. Dependence of Brønsted Slopes on Alcohol Acidity¹

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Abstract: The formation and breakdown of tetrahedral addition compounds formed from alcohols and *N,O*-trimethylenephthalimidium cation are subject to general acid–base catalysis. The Brønsted coefficients for general acid catalysis of alcohol expulsion increase with increasing alcohol basicity from $\alpha = 0.49$ for trifluoroethanol to $\alpha = 0.74$ for ethanol. There is a corresponding change in the magnitude and direction of the effect of substituents in the leaving alcohol, from $\beta_{lg} = 0.24$ for catalysis by the proton to $\beta_{lg} = -0.23$ for catalysis by acetic acid. It is concluded that proton transfer and the formation and breakdown of the C–O bond are in some sense concerted. The mechanism and structure–reactivity relationships are discussed with the help of the Cordes equations and three-dimensional reaction coordinate–transition state diagrams. The reaction also proceeds through the uncatalyzed attack and elimination of alkoxide ion with $\beta_{lg} = -0.9$. The “carbon basicity” toward the phthalimidium ion is some 10^7 greater for alkoxide ions than for amines of the same basicity toward the proton, but for the uncharged species the exchange of hydrogen for carbon is some 40-fold more favorable for amines than for alcohols.

We describe here a study of structure–reactivity relationships in the general acid–base catalyzed (eq 1) and uncatalyzed (eq 2) formation and breakdown



of the tetrahedral addition compounds formed from *N,O*-trimethylenephthalimidium cation² and a series of aliphatic alcohols.

Experimental Section

Materials. Alcohols, with the exception of 2,2,2-trifluoroethanol (Aldrich Chemical Co., Puriss), were redistilled before use. The methanol and ethanol addition compounds were prepared by the addition of *N,O*-trimethylenephthalimidium perchlorate to a 1.5-fold molar excess of triethylenediamine or sodium acetate in the appropriate alcohol. Other alcohol addition compounds were prepared prior to each experiment by the addition of the phthalimidium perchlorate to a 1.5-fold molar excess of alcohol and of triethylenediamine in acetonitrile. The ethanol addition compound was also synthesized according to the procedure of Hünig and Geldern.² The ultraviolet spectrum and kinetic behavior of the synthetic product were identical with those of the adduct prepared in ethanol solution.

Kinetics. Kinetic measurements were carried out as previously described.^{3,4} Hydrolysis of the alcohol addition compounds was

followed by measuring the appearance of phthalimide absorption at 300 nm, at 25°, and ionic strength maintained at 1.0 with potassium chloride. The reactions were initiated by adding 0.03 ml of a solution of addition compound to approximately 2.7 ml of buffer to give a final concentration on the order of 3×10^{-4} M. Slow reactions were followed using concentrations of approximately $2-3 \times 10^{-3}$ M and gave linear absorbance changes for up to 4–5% of the total reaction. The absorbance of the product at time infinity was observed in these experiments by diluting aliquots of each solution in acid. Pseudo-first-order rate constants for these experiments were obtained by dividing the initial rate of absorbance change by the absorbance at time infinity minus the initial absorbance. The pH of each solution was determined at the end of the reaction.

Rate constants for catalysis by general acids were generally determined from five runs with buffer concentrations in the range 0.02–0.80 M at each of three different buffer ratios. Catalysis by acetate buffers of the hydrolysis of the methanol adduct was measured with 3–5 runs at each of five buffer ratios. The catalytic constants for the acids were obtained from the ordinate intercepts of plots of the observed catalytic constants against the fraction of the buffer in the basic form. No catalysis by the basic component of the buffer was observed. Rate constants for hydronium ion catalysis and pH-independent hydrolysis were obtained from the intercepts of the plots of rate constants against buffer concentration.

The pH values of solutions of chloroacetic and cyanoacetic acid buffers were adjusted to a constant value with hydrochloric acid to correct for the decrease in the concentration of the acid component of these strong acid buffers from ionization at low pH values. In order to correct for the variation in the pH of phosphate buffers with increasing concentration, rate constants were determined at five concentrations of buffer for each of three to five different buffer ratios and the rate constants at each concentration were plotted against pH. The rate constants at a given constant pH value at increasing buffer concentrations were then read off this plot. Rate constants for hydrolysis of the methanol and ethanol adducts were found to decrease with increasing concentration of *N*-methylimidazole buffers, presumably because of complexation of the buffer with the adduct.

The product of the hydrolysis of all of the alcohol adducts was identified as the phthalimide by ultraviolet spectroscopy.

Reaction of Alcohols with the Phthalimidium Cation. The relative rates of nucleophilic reaction of alcohols and water were determined from the ratios of alcohol adduct and hydrolysis product (phthalimide) formed after solvolysis of the phthalimidium ion in water–alcohol mixtures, by essentially the same technique as described previously for the reactions of amines.⁴ The phthalimidium ion was generated from the piperidine addition compound below pH 7.2 and from the imidazole adduct at pH 8.7–11.8. In

(1) Supported by grants from the National Science Foundation (GB 5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247). N. G. was a Predoctoral Fellow of the National Institutes of Health (GM 212).

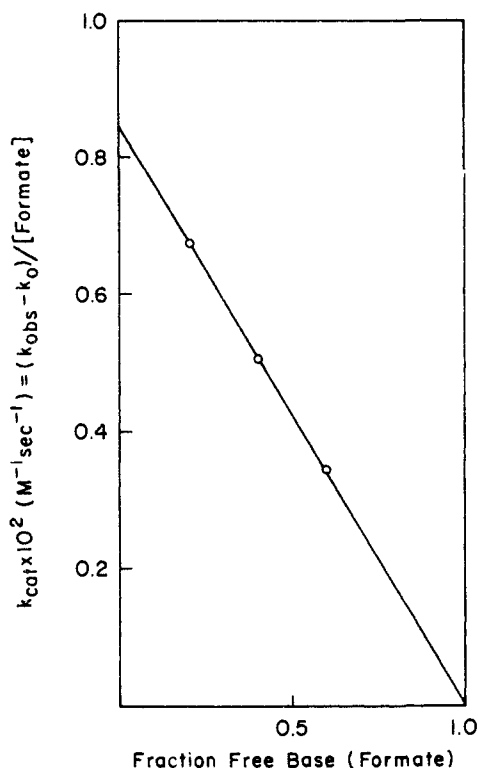
(2) S. Hünig and L. Geldern, *J. Prakt. Chem.*, **24**, 246 (1964).

(3) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 489 (1974).

(4) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 499 (1974).

Table I. Rate Constants and Brønsted α Values for the Breakdown of Alcohol Adducts Formed from *N,O*-Trimethylenephthalimidium Cation, at 25° and Ionic Strength 1.0 (KCl)

Alcohol adduct	pK _a , alcohol ^a	$k_{H_3O^+}$, M ⁻¹ sec ⁻¹	$k_{HA} \times 10^4, M^{-1} \text{sec}^{-1}$				Brønsted α
			ClCH ₂ - COOH	HCOOH	CH ₃ COOH	H ₂ PO ₄ ⁻	
Ethanol	16.0	24.6			4.67		0.74
Methanol	15.54	19.9	192	45	5.27	0.30	0.71
2-Chloroethanol	14.31	7.1	106	33	4.85		0.64
2-Propyn-1-ol	13.55	9.0	242	85	16.7		0.60
2,2-Dichloroethanol	12.89	3.7		72	18		0.53
2,2,2-Trifluoroethanol	12.43	4.2	480	147	52	5.5	0.49

^a Reference 5.**Figure 1.** Dependence on buffer composition of the catalytic constants for catalysis by formate buffers of the hydrolysis of the addition compound of 2-propyn-1-ol and *N,O*-trimethylenephthalimidium ion at 25° and ionic strength 1.0 (KCl).

each case the rate of hydrolysis of the amine adduct was at least 10^3 times faster than that of the alcohol adduct product. The concentration of alcohol adduct product was determined from the change in absorbance at 300 nm upon hydrolysis to phthalimide in acidic solutions, as described previously.⁴

The ratio of alcohol adduct to hydrolysis product is given by eq 3.

product ratio =

$$\frac{k_{ROH^0}[ROH] + k_{RO^-}[RO^-] + k_{ROH^B}[ROH][B]}{k_{H_2O}[H_2O] + k_{OH^-}[OH^-] + k_{H_2O^B}[H_2O][B]} \quad (3)$$

The experiments were carried out at low buffer concentrations, at which the buffer does not significantly affect the product ratio, so that the k^B terms could be neglected. It was shown that there was no significant effect of buffer concentrations up to 0.1 M on the product ratio in the lower pH region. Experiments in this region were carried out with 0.02–0.05 M buffer with a total of at least 24 experiments and at least two buffer ratios for the methanol and ethanol reactions, using acetate and phosphate buffers, at a series of different alcohol concentrations. The reaction of the anion is negligible at these pH values, so that the product ratios give the ratio k_{ROH^0}/k_{H_2O} directly. Experiments at higher pH values were carried out in triethylenediamine or quinuclidine buffers at 0.005–0.02 M with between 2 and 36 runs at concentrations of the different alcohols in the range 0.5–6.0 M. Under the conditions of

these experiments only the anion reactions are significant and the ratio k_{RO^-}/k_{OH^-} was calculated from the product ratio and the ionization constants of the alcohol.⁵ These experiments were carried out at ionic strength 0.002–0.01.

Results

Hydrolysis. Rate constants for the hydrolysis of a series of alcohol addition compounds of *N,O*-trimethylenephthalimidium cation, catalyzed by the proton and buffer acids, are summarized in Table I. The observed rate constants were found to increase linearly with increasing buffer concentration and plots of the observed catalytic constants against the fraction of the buffer in the basic form showed catalysis by only the acidic component of the buffer, as illustrated for catalysis of the hydrolysis of the 2-propyn-1-ol adduct by formic acid in Figure 1. Rate constants for catalysis by the proton were obtained from the slopes of (linear) plots against hydrogen ion activity of the ordinate intercepts from the plots against buffer concentration. At high pH values the dichloroethanol and trifluoroethanol adducts were found to undergo hydrolysis through a pH-independent reaction. The rate constants k_1' for this hydrolysis were obtained from the intercepts of the plots of rate constants against hydrogen ion activity and are summarized in Table II. The ethanol and methanol adducts were found to be stable for 12 hr in 0.01 M sodium hydroxide.

Upon addition to perchloric acid solutions at four concentrations in the range 7.0–9.9 M, the ethanol addition compound was found to undergo immediate hydrolysis to a product with absorption maxima, extinction coefficients, and rate constants for hydrolysis to phthalimide that are identical with those of authentic phthalimidium ion examined under the same conditions. Hydrolysis to the phthalimide gives isosbestic points at 305, 258, 245.5, and 238.5 nm. The phthalimide is the thermodynamically favored final product in the less concentrated acid solutions. These results show that the alcohol adduct undergoes cleavage to the phthalimidium ion, rather than ring opening to a new imidate that undergoes hydrolysis to phthalimide under these conditions.

Formation of Alcohol Addition Compounds. The rate constants for the attack of alcohols (k_{-1}) and alcoholate ions (k_{-1}') on the phthalimidium ion (Table II) were determined from the ratio of alcohol addition compounds and phthalimide hydrolysis products formed upon solvolysis in alcohol–water mixtures at neutral and alkaline pH values and from the known rate constants for attack of water and hydroxide ion.³ The

(5) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **81**, 1050 (1959); **82**, 795 (1960).

Table II. Rate and Equilibrium Constants for the Reactions of Alcohols with *N,O*-Trimethylenephthalimidium Cation at 25°

Alcohol	k_1 , M^{-1} sec^{-1}	k_{-1} , M^{-1} sec^{-1}	k_1' , sec^{-1}	k_{-1}' , $M^{-1} sec^{-1}$	K_{eq}^a	$K_{eq}'^b M$
Ethanol	24.6	3.7	$3.3 \times 10^{-8}^c$	5×10^7	6.65	$6.7 \times 10^{-16}^d$
Methanol	19.9	5.3	$4.4 \times 10^{-8}^c$	4×10^7	3.78	$1.1 \times 10^{-16}^d$
2,2-Dichloroethanol	3.7	1.0	8.5×10^{-8}	1.7×10^7	3.7^d	5×10^{-13}
2,2,2-Trifluoroethanol	4.2	0.62^e	8.4×10^{-8}	3.3×10^7	6.7^d	2.5×10^{-12}

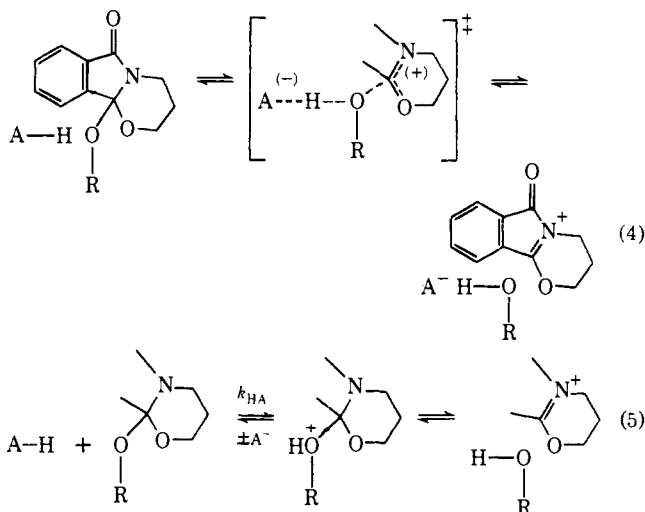
^a $K_{eq} = [ROH][PI^+]/[Ad][H^+] = k_1/k_{-1}$. ^b $K_{eq}' = [RO^-][PI^+]/[Ad] = k_1'/k_{-1}'$. ^c Calculated from $k_1' = k_{-1}'/K_{eq}'$. ^d Calculated from $K_{eq}' = K_{eq}K_{diss}^{ROH}$. ^e Calculated from $k_{-1} = k_1/K_{eq}$.

phthalimidium ion was usually generated *in situ* from the piperidine or imidazole addition compounds. Similar results were obtained by the direct addition of phthalimidium perchlorate in acetonitrile to alcohol-water solutions at alcohol concentrations up to 6 *M*. Acetate buffers (50% anion) at concentrations up to 0.2 *M* were found to have no effect on the product ratio with methanol and ethanol, but quinuclidine buffers at pH 11.8 increase the methanol adduct/phthalimide ratio by twofold at 0.2 *M*.

The equilibrium constants K_{eq} for the neutral reactions of ethanol and methanol (eq 1) were calculated from the rate constants k_1 and k_{-1} in the two directions. The equilibrium constants K_{eq}' for the reactions of the anions of dichloroethanol and trifluoroethanol (eq 2) were calculated from the rate constants k_1' and k_{-1}' in the two directions. The two equilibrium constants are related by the acid dissociation constant of the alcohol, $K_{eq}' = K_{eq}K_{diss}^{ROH}$, so that the remaining equilibrium constants were readily calculated (Table II). The rate constants k_1' for ethanol and methanol and k_{-1} for dichloroethanol and trifluoroethanol, which were not measured directly, were calculated from the equilibrium constants and the rate constants for the reaction in the opposite direction (Table II).

Discussion

General Acid-Base Catalysis. The following evidence supports the conclusion that the acid-base catalyzed elimination and addition of alcohols occurs through a "concerted" (eq 4), as opposed to a stepwise (eq 5), mechanism of general acid-base catalysis.



(1) The Brønsted plots for general acid catalysis of the hydrolysis of the addition compounds have slopes of 0.49–0.74 (Figure 2). The stepwise mechanism

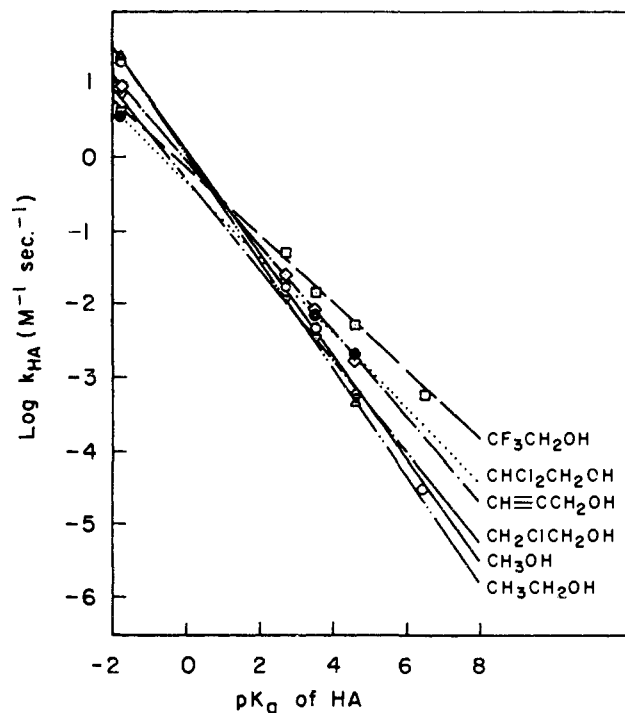


Figure 2. Brønsted plots for the general acid catalyzed breakdown of the 2,2,2-trifluoroethanol (\square), 2,2-dichloroethanol (\bullet), 2-propyn-1-ol (\diamond), 2-chloroethanol (∇), methanol (\circ), and ethanol (\triangle) addition compounds of the phthalimidium cation at 25° and ionic strength 1.0 (KCl).

could exhibit general acid catalysis if the proton transfer step (k_{HA} , eq 5) is rate determining and a value of α other than 0 or 1.0 could be observed for such a mechanism if the pK_a of the catalyst is close to that of the substrate.⁶ However, the pK_a values of the conjugate acids of the phthalimidium addition compounds are expected to be on the order of 8.4 units lower than the corresponding pK_a values for the parent alcohols.⁴ Consequently, a value of $\alpha = 1.0$ would be expected for this thermodynamically unfavorable proton transfer step from catalysts of $pK = -1.7$ to 7,⁶ and the observed values of $\alpha = 0.49$ –0.74 rule out the mechanism of eq 5.

(2) The calculated rate constants for protonation of the addition compound are inadequate to account for the observed reaction rate. Assuming that the pK_a of the conjugate acid of an ether is the same as that of water⁷ and that the substituent effect of the trifluoroethyl group is the same for the ionizations of ROH and

(6) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).

(7) In fact, simple ethers are half-protonated only at $H_0 = -6.4$, although the ratio $\log ([BH^+]/[B])$ gives a slope of only 0.32–0.35 when plotted against $-H_0$: D. G. Lee and R. Cameron, *Can. J. Chem.*, 50, 445 (1972).

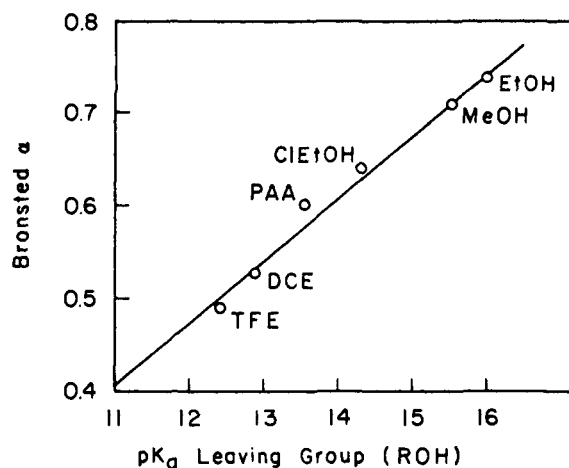
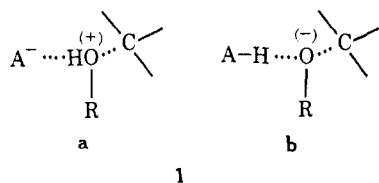


Figure 3. Dependence of the Brønsted α values for general acid catalyzed breakdown of alcohol addition compounds on the basicity of the leaving alcohol.

$RR'OH^+$, the pK_a of the conjugate acid of the trifluoroethanol adduct is on the order of $-1.74 - 8.4 - 3.6 = -13.7$. Assuming a diffusion-controlled rate constant of $10^{10} M^{-1} sec^{-1}$ for the reaction of this species with acetate ion, the rate constant for protonation of the adduct by acetic acid ($pK_a = 4.6$) is then $5 \times 10^{-9} M^{-1} sec^{-1}$, well below the observed rate constant of $5.5 \times 10^{-4} M^{-1} sec^{-1}$ for the acetic acid catalyzed breakdown of this adduct. Thus, the stepwise mechanism of eq 5, with rate-determining protonation of the addition compound, cannot account for the observed reaction rate.

(3) The rate constants for the acetic acid catalyzed breakdown increase with electron-withdrawing substituents on the leaving alcohol (Table I). This is inconsistent with a mechanism involving protonation of the leaving alcohol as the only process taking place in the rate-determining step. In a modification of the mechanism of eq 5, proton transfer and carbon-oxygen cleavage occur in separate steps, but the transition state for carbon-oxygen cleavage is stabilized by hydrogen bonding to the catalyst, as shown in **1a** and **1b**. Al-



though we are reluctant to speculate on the detailed mechanism of coupling of the various bond-forming and -breaking processes, we believe that the data are inconsistent with mechanisms **1a** and **1b**, so that a fully concerted mechanism is required. Mechanism **1a** involves stabilization of a cationic protonated leaving alcohol by hydrogen bonding to the conjugate base of the catalyst. Since this mechanism requires the development of positive charge on the leaving oxygen atom, it is inconsistent with the observed stabilization of the transition state of the acetic acid catalyzed reaction by electron-withdrawing substituents in the alcohol. Mechanism **1b** involves stabilization of the leaving oxyanion by hydrogen bonding to the acid form of the catalyst. The negative charge development on the leaving oxygen atom is inconsistent with the

observed stabilization of the transition state of the proton-catalyzed reactions by electron-donating substituents in the alcohol. The gradual change in the Brønsted α value and the reversal of the direction of the substituent effect on the leaving group with changing acid strength (Figure 2) are difficult to reconcile with mechanisms that involve double potential well hydrogen bonds, such as **1a** and **1b**; a single well hydrogen bond corresponds to a concerted mechanism.

With acids of intermediate strength, for which the effect of substituents in the alcohol is small or zero, the negative charge development on the leaving oxygen atom from cleavage of the carbon-oxygen bond must be closely balanced by positive charge development from partial proton transfer so that there is little or no change in the net charge on the leaving group in going from the reactants to the transition state. Since the average Brønsted α value of 0.62 implies a considerable amount of proton transfer, this means that there must be a corresponding amount of C-O bond cleavage; both processes have probably proceeded about halfway or slightly more toward completion, as indicated in the transition state of eq 4.

The substituent effects are also inconsistent with a mechanism of hydrolysis in which the rate-determining step involves endocyclic cleavage. Such a mechanism would give an oxocarbenium ion involving this alcohol as the immediate product and would be inhibited by electron-withdrawing substituents. The directly observed formation of the phthalimidium ion as the initial product in acid solution (see Results) and the known preferred exocyclic cleavage of acetals⁸ provide additional evidence supporting the mechanism of exocyclic cleavage shown in eq 4.

Structure-Reactivity Relationships and Catalysis.

The most interesting result of this work is the progressive increase in the value of the Brønsted coefficient from $\alpha = 0.49$ to $\alpha = 0.74$ as the substituents on the leaving alcohol become relatively electron donating (Figure 3). It is this increase that is responsible for the reversal of the order of reactivity of the different alcohol addition compounds with changing strength of the catalyzing acid (Figure 2). At the risk of appearing anthropomorphic, the transition state evidently adjusts itself to take advantage of the easier protonation of more basic oxygen atoms, so that there is a greater amount of acid catalysis for the more basic alcohols. Conversely, one can say that a more acidic catalyst leads to the development of a more cationic transition state that "takes advantage" of the greater proton-donating ability of the catalyst. Both of these changes are in the opposite direction from what one might initially expect from the considerations of Leffler and Hammond,⁹ which predict that the proton transfer should occur with an earlier transition state for a more basic oxygen atom and a stronger acid catalyst. The observed behavior is clearly a consequence of the linking of the proton transfer and C-O bond cleavage processes and may be described as a substituent effect perpendicular to the reaction coordinate.¹⁰

(8) B. Capon, *Chem. Rev.*, **69**, 407 (1969); J. Lehman, E. Pfeiffer, and H. Reinshagen, *Chem. Ber.*, **102**, 2748 (1969); A. Kankaanperä and K. Mikkilä, *Suom. Kemistilehti B*, **41**, 42 (1968); A. Kankaanperä, *ibid.*, **43**, 133 (1970).

(9) J. E. Leffler, *Science*, **117**, 340 (1953); G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(10) E. R. Thornton, *J. Amer. Chem. Soc.*, **89**, 2915 (1967).

This kind of interrelationship is described by eq 6 and 7. These equations are derived, as described by

$$(pK_i - pK_j)_{1g} = c_5(\alpha_i - \alpha_j)_{cat} \quad (6)$$

$$(pK_2 - pK_1)_{cat} = c_5(\beta_1 - \beta_2)_{1g} \quad (7)$$

Cordes for similar interrelationships,¹¹ from the Brønsted equation for general acid catalysis and from eq 8, which describes the change in observed rate with

$$\log(k_i/k_j) = \beta_{1g}(pK_i - pK_j)_{1g} \quad (8)$$

changing pK_a of the leaving group. When there is no proton transfer the sign of β is expected to be negative; *i.e.*, electron-withdrawing substituents increase leaving group ability. According to eq 6 the value of the Brønsted coefficient α_j will decrease as electron-withdrawing substituents are added to the leaving group to decrease pK_j when the coefficient c_5 is positive. This is in agreement with the observed decrease in α from 0.74 to 0.49 as the pK of the leaving alcohol is decreased from 16 to 12.4 and corresponds to a value of $c_5 = 14$ ($1/c_5 = 0.07$).¹² It follows from eq 7 that as the catalyst becomes a stronger acid (pK_1 decreases) the value of β_1 for the leaving group increases (or becomes less negative). This is in accord with the observed reversal of substituent effect with changing acid strength; *i.e.*, the change in the value of β_{1g} from -0.23 for catalysis by acetic acid to 0.24 for catalysis by the proton. This change corresponds to the value of $c_5 = 14$ in eq 7.

Three-dimensional energy contour diagrams with separate axes for motion of the proton and cleavage of the carbon–oxygen bond are helpful in visualizing these structure–reactivity interrelationships (Figure 4).^{13,14} Although these diagrams have been drawn based on known or extrapolated equilibrium and rate constants, they obviously should not be taken too seriously or literally in view of the complexity of the reaction.¹⁵ Starting with the uncharged addition compound A in the upper right-hand corner of the diagram, the reaction can proceed through a stepwise mechanism involving the uncatalyzed elimination of alcoholate ion to give the intermediate I^- in the lower right corner, followed by proton transfer to give the final products PI^+ , the phthalimidium ion, and free alcohol, in the lower left corner. The alternative stepwise mechanism involves proton transfer first to give the protonated adduct I^+ in the upper left corner, followed by carbon–oxygen bond cleavage to give products. In the concerted mechanism the proton transfer and C–O cleavage take place more or less simultaneously and the reaction follows the lowest energy path diagonally across the diagram. The driving force for the catalyzed reaction is the avoidance of the unstable intermediates I^- and I^+ and the transition states leading to their formation and breakdown. The diagrams in Figure 4

(11) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 4319 (1962).

(12) In comparing different reactions it is desirable to use $1/c_5$, which increases, rather than c_5 , which decreases, with increasing sensitivity to changing pK of the leaving group or catalyst.

(13) R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970); J. E. Critchlow, *J. Chem. Soc., Faraday Trans 1*, **68**, 1774 (1972).

(14) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

(15) The contour lines and numbers in the diagrams are based on observed or estimated values of $\log k$ or $\log K$ and a molar standard state and are only meant to provide an indication of the way the surface changes with changing substituents; more exact treatments should probably be based on a mole fraction standard state.

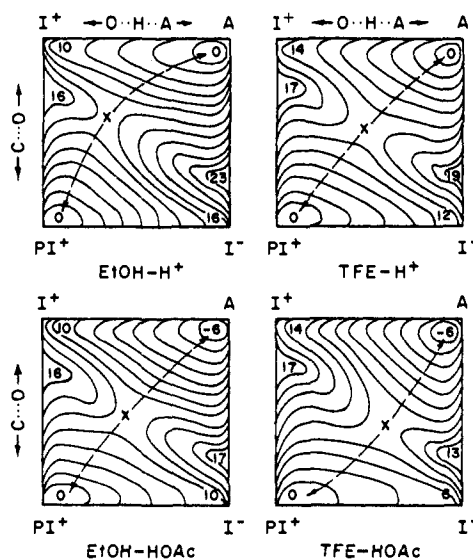
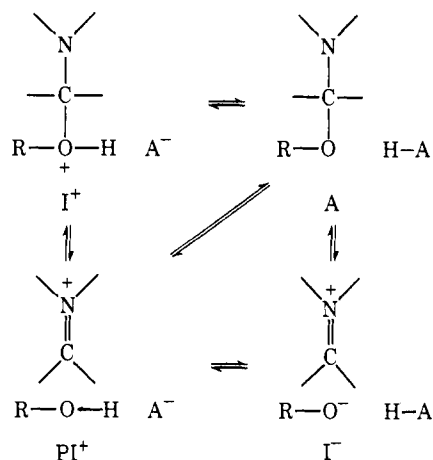


Figure 4. Energy contour diagrams to describe the reversible reaction of the phthalimidium ion with ethanol and trifluoroethanol catalyzed by the proton and by acetic acid. The vertical axes describe the amount of C–O bond formation or cleavage and the horizontal axes describe the amount of proton transfer.



have been drawn assuming that there is no energy barrier for a proton transfer that is strongly favored thermodynamically, but that there is a significant energy barrier for C–O bond cleavage and formation (the latter assumption is consistent with extrapolations of the available structure–reactivity data in this system). However, similar conclusions are reached if the “intermediates” are assumed to have a finite lifetime.¹⁴

This reaction provides a particularly favorable system for the demonstration of this kind of interaction of substituent effects because there is little difference in the charge on the oxygen atom in the starting material and the product alcohol, but there is a full positive or negative charge on this atom in the two intermediates I^+ and I^- . Substituents on the alcohol will, therefore, have a larger effect on the stability of transition states in which this oxygen atom bears a partial positive or negative charge than on the stabilities of starting materials and products. The addition of an electron-withdrawing substituent to the alcohol will destabilize the intermediate bearing the positive charge and raise the energy of the upper left-hand region of the diagram; it will also stabilize the anionic intermediate and lower the energy of the lower right region of the diagram.

The effect of these changes will be to shift the position of the valley through which the reaction coordinate passes toward the lower right corner of the diagram. This will shift the position of the transition state in the saddle point of the valley in the same direction, perpendicular to the reaction coordinate, so that it occurs at a point less far along the axis for proton transfer (from right to left). This illustrates the prediction of eq 6 with $c_3 = 14$ and is in agreement with the decrease in the value of α for general acid catalysis from 0.74 to 0.49 in going from the ethyl to the trifluoroethyl alcohol addition compound.

Electron-withdrawing substituents are also expected to give rise to an increase in the amount of C–O bond cleavage in the transition state, so long as the reaction coordinate is truly diagonal. Although we have not observed such a change, we do not have sufficient data to exclude a moderate effect of this kind. The curvature of the surface in the region of the saddle point may be smaller in the direction for proton transfer than for carbon–oxygen cleavage (*i.e.*, the barrier for proton transfer is likely to be less than that for C–O cleavage), so that the change in the amount of C–O bond cleavage would be relatively small.

A decrease in the acidity of the catalyzing acid HA will raise the energy of the entire left-hand side of the diagram relative to the right-hand side (Figure 4, lower diagrams). This will have the same effect of tending to move the saddle point toward the lower right-hand corner by raising the energy of I^+ relative to I^- , but will also tend to move the transition state toward the lower left-hand corner by raising the energy of PI^+ relative to A and causing the transition state to occur later along the reaction coordinate from A to PI^+ . The latter effect is a "Hammond effect," parallel to the reaction coordinate, but may be smaller than the former, perpendicular, effect because of a smaller curvature of the surface in the direction perpendicular to the reaction coordinate. Both effects predict an increase in the degree of C–O bond cleavage. The shift perpendicular to the reaction coordinate, toward I^- , leads to an increase in the development of negative charge on this atom in the transition state as the catalyzing acid becomes weaker (Figure 4). The shift in the position of the transition state along the diagonal between A and PI^+ results in little or no change in the charge on the leaving oxygen atom, since the oxygen carries no net charge in either A or $PI^+ \cdot ROH$. These changes are in agreement with eq 7 and with the observed change in β_{lg} from 0.24 for catalysis by the proton to -0.23 for catalysis by acetic acid.

The more or less concerted mechanism for general acid catalysis of alcohol elimination in this reaction is made possible by the extreme instability of the protonated intermediate I^+ , which would be formed in a stepwise mechanism of acid catalysis. In acetal hydrolysis there is only a single electronegative atom on the central carbon atom, in addition to the leaving oxygen atom, so that protonation by the solvated proton is relatively easy and the stepwise mechanism (specific acid catalysis) is ordinarily favored. When this proton transfer is made more difficult, by the addition of electron-withdrawing substituents in acetals, or in ortho esters, the concerted mechanism becomes significant; it is also favored by stabilization of the product

oxocarbenium ion, analogous to PI^+ , as predicted by the diagrams.^{13,14,16} For a substrate of sufficiently low basicity the protonated "intermediate" will be too unstable to exist; *i.e.*, it will not correspond to a potential minimum with a significant activation energy for decomposition, so that a stepwise mechanism of specific acid catalysis is impossible.

The reverse reaction involves general base catalysis of the addition of alcohol to the phthalimidium ion and must proceed through the same transition state as the elimination reaction (eq 4). Since there is no significant effect of substituents on the equilibrium constant K_{eq} for the overall reaction (Table II) the effect of substituents in the alcohol on the rate of the addition reaction will be the same as in the breakdown direction. However, the effect of substituents in the catalyst will be reversed, because the catalyst undergoes a change in charge of 1.0 and $\beta = 1 - \alpha$. The interrelationships between the substituent effects are given by eq 9 and 10,

$$(pK_t - pK_j)_{nuc} = c_5(\beta_j - \beta_t)_{cat} \quad (9)$$

$$(pK_2 - pK_1)_{cat} = c_5(\beta_1 - \beta_2)_{nuc} \quad (10)$$

in which the pK_a of the alcohol is taken as a measure of the nucleophilic reactivity of the alcohol in the absence of proton transfer and β_{nuc} is a measure of the sensitivity of the reaction rate to the pK_a of the alcohol.¹⁷ The same value of c_5 holds for these equations as for eq 6 and 7. Equation 9 predicts that the reaction of a stronger nucleophile (increased pK_j) will proceed with less proton removal by the base catalyst (decreased β_j). This result is required by the experimental results in the reverse direction and the relationship $\beta = 1 - \alpha$. Equation 10 predicts that a reaction catalyzed by a stronger base (increased pK_2) will show a smaller increase in rate with increasing basicity of the nucleophile (decreased β_2). This is in accord with the increase in rate with increasing basicity of the nucleophile for the water-catalyzed reaction (k_{-1} , Table II) and the opposite dependence on nucleophile basicity for the acetate-catalyzed reaction, calculated from the data of Tables I and II. Since the equilibrium constant is independent of nucleophile basicity, the values of β_{nuc} must be 0.24 and -0.23 for the water-catalyzed and acetate-catalyzed reactions, respectively. These relationships may be visualized in the diagrams of Figure 4 by following the reaction from the lower left to the upper right corner of each diagram.

The Uncatalyzed Elimination and Addition of Alkoxide Ion. As the strength of the acid catalyst is decreased the energy of the left-hand side of the diagrams of Figure 4 will increase until a point is reached at which proton transfer from the catalyst to the leaving alkoxide ion confers no significant advantage or is thermodynamically unfavorable. When this is the case, a concerted mechanism that follows a diagonal path through the center of the diagram is no longer possible, in accordance with a recently proposed rule,¹⁸

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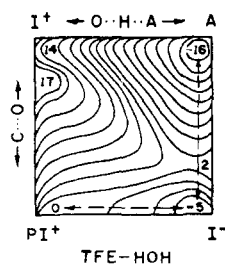
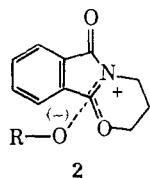


Figure 5. Energy contour diagram describing the reversible reaction of the phthalimidium ion with trifluoroethanol in the presence of the weak acid water. The reaction will proceed through the lowest energy, stepwise path with the intermediate formation of the trifluoroethoxide ion.

and the reaction will proceed by a stepwise mechanism through I^- , with the uncatalyzed elimination and addition of alkoxide ion (eq 2, Figure 5). The energy surface in Figure 5 goes downhill from left to right for any amount of C-O cleavage so that proton transfer from the catalyst is thermodynamically unfavorable for the starting materials and the product and, presumably, for the transition state as well. This situation is expected to hold for acid catalysis of the elimination reaction by water, so that the "water" reaction in fact represents the uncatalyzed expulsion and addition of alkoxide ion.¹⁹ In the addition direction this reaction involves the reversible ionization of the alcohol to the corresponding alcoholate ion followed by rate-determining attack on the phthalimidium ion; *i.e.*, the Brønsted β value is 1.0.

The properties of the "water" alkoxide reaction are in accord with this interpretation. In contrast to the acid-catalyzed reaction, the rate constants k_{-1}' for the uncatalyzed expulsion of alkoxide ion increase sharply with decreasing pK of the leaving group (Table II) and the slope, β_{lg} , of a plot of $\log k$ against pK_a is approximately -0.9 , suggesting a transition state that closely resembles products (Figure 6). The rate constants for alkoxide attack have a correspondingly small sensitivity to nucleophile basicity with a value of $\beta_{nuc} = 0.1$, suggesting an early transition state (Figure 6); the equilibrium constants K_{eq}' (Table II) are directly proportional to alkoxide basicity. Furthermore, the rate constants for the reaction fall more than two orders of magnitude above the extrapolated Brønsted plots for the general acid catalyzed reactions. The mechanism of the reaction is, therefore, formulated according to the transition state 2.



Comparison of Amines and Alcohols as Attacking and Leaving Groups. The interpretation of the mechanism of acyl transfer reactions is complicated by the fact that observed rate constants frequently include the equilibrium constants for formation of a tetrahedral addition intermediate and are affected by varying amounts of resonance stabilization of the starting material. The phthalimidium system is of particular interest in that it

(19) The alkoxide ion is, of course, solvated by water.

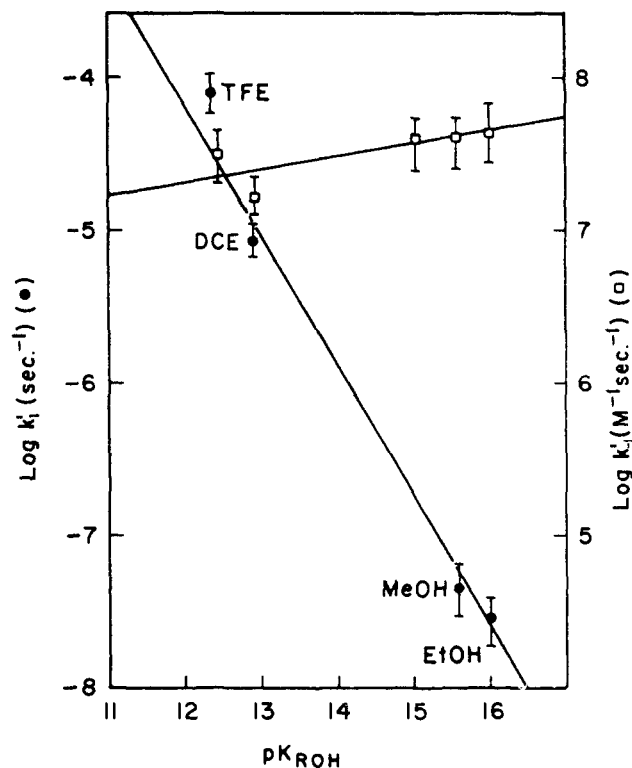


Figure 6. Dependence on the pK_a of the alcohol of the first-order rate constants for uncatalyzed alcohol-adduct breakdown (\bullet) and the second-order rate constants for nucleophilic attack of alkoxide anions on the phthalimidium cation (\square).

makes possible a comparison of rates, equilibria, and mechanisms for the addition and elimination of amines and alcohols under conditions in which the driving force arising from the phthalimidium nucleus is a constant and there is no resonance stabilization of the addition product. The conclusions may be summarized as follows.

(1) As noted previously,⁴ the leaving ability of a protonated secondary amine is approximately 10^5 greater than that of an alkoxide ion of the same pK . This suggests that alkoxide ion expulsion will ordinarily be the rate-determining step in the uncatalyzed aminolysis of esters. The transition states for the expulsion of alkoxide ions and protonated amines resemble products, with values of β_{lg} of approximately -0.9 .

(2) The rate constants for the attack of alkoxide ions on the phthalimidium cation (Table II) are about 30-fold larger than those for amines of comparable pK .⁴ Although one is tempted to ascribe this difference to an electrostatic effect, such an explanation is not correct in its simplest form because the electrostatic effect should be accounted for in the reference reaction, the addition of the cation H^+ . The smaller steric requirements of the alkoxide ion may facilitate its attack. The transition states for the attack of both amines and alkoxide ions occur early along the reaction coordinate, with values of β_{nuc} of approximately 0.1.

Methoxide and ethoxide ions are tenfold more effective than hydroxide ion as nucleophilic reagents toward the phthalimidium ion. This difference is similar to that observed for reactions of saturated carbon compounds,²⁰ but is smaller than that for *p*-nitrophenyl

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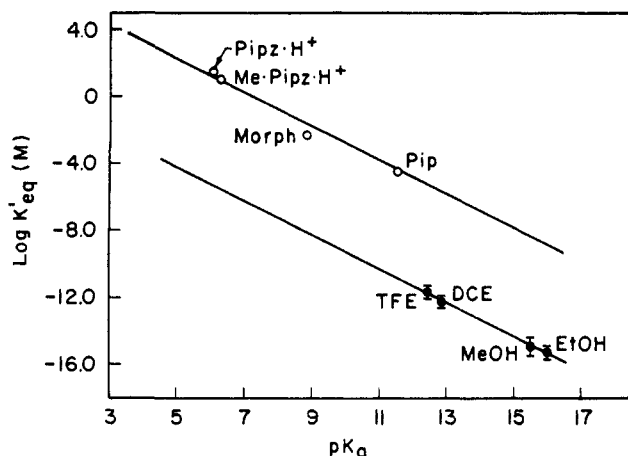
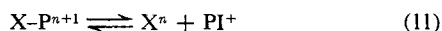


Figure 7. Dependence on leaving group pK of the logarithms of the equilibrium constants, K'_{eq} , for breakdown of alcohol (●) and protonated amine (see ref 4) (○) addition compounds at 25°.

acetate²¹ and in nucleophilic aromatic substitution.²² The reactivities of uncharged ethanol and methanol toward the phthalimidium ion are larger by factors of 3.7 and 5.3, respectively, compared to water. This is smaller than the corresponding difference of 20–30-fold for the equilibrium addition of alcohols and water to the carbonyl group²³ and the relative rates of reaction with benzyl bromide.²⁰ It is similar to the relative reactivities toward acetic anhydride²⁴ and in nucleophilic aromatic substitution,²² but is larger than toward acetyl chloride,²⁵ carbonium ions,²⁶ and oxocarbenium ions,²⁷ which show no enhanced reactivity of alcohol compared to water; in fact, the reactivity of water is significantly larger than that of alcohols toward carbonium ions. A full explanation of these differences is obviously not simple, but the enhanced reactivity of alcohols relative to water with the more selective electrophiles may reflect a special stabilization of water through cooperative hydrogen bonding²⁸ and/or stabilization of the transition states and products of alcohol addition by hydrophobic–van der Waals interactions.

(3) As required by the differences in the rate constants in the two directions, the equilibrium constants for the breakdown of the alcohol addition compounds to alcoholate ions (Figure 7) are some 10^7 smaller than those for the breakdown of addition compounds formed from amines of comparable pK (in the absence of proton transfer). The reactions involve a change of charge of 1.0 on the alcohol or amine (eq 11) and the



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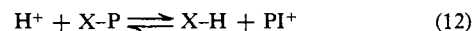
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equilibrium constants are proportional to the basicity of the leaving or attacking group with β values of -1.0 . Again, the difference between amines and alkoxide ions is not a simple electrostatic effect because the reference protonation reaction involves the same change in charge. The reactions may be written as the exchange of a phthalimidium group for a proton according to eq 12, in which X–H is ROH or $R_2NH_2^+$.



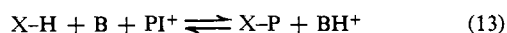
The equilibrium constant for eq 12 is the ratio of the dissociation constants of the adduct and of X–H and is 10^7 times larger for amines than for alcohols. In other words, when the comparison is made for compounds of comparable acidity but different charge type the affinity of oxygen toward carbon relative to hydrogen is some 10^7 times larger than that of nitrogen. This may be regarded as an enhanced stability of $R_2NH_2^+$ relative to ROH or of RO–P relative to R_2NH-P^+ .

If, however, the comparison is made for the *uncharged* compounds, with X–H = ROH and R_2NH , the result is quite different. The equilibrium constants for the uncharged species indicate that the amine addition compounds⁴ are more stable than the alcohol addition compounds (Table II) by a factor of approximately 40. This is somewhat less than the factor of approximately 100 that favors amine over alcohol addition to aromatic aldehydes and an additional 30-fold less than the comparable factor for addition to formaldehyde.²³ Thus, if one compares carbon and hydrogen basicity of nitrogen and oxygen at constant pK but different charge type, oxygen exhibits a relatively larger carbon basicity, but if the comparison is made at constant charge type but different pK nitrogen exhibits a relatively larger carbon basicity. The difference appears also in the greater acidity of R_2NH-P^+ compared to $R_2NH_2^+$ brought about by the strongly electron-withdrawing character of the phthalimide group.

The amine adducts are stable only because the amine can lose a proton after addition to the phthalimidium ion, and addition compounds formed from tertiary amines are not stable in water. The products of the addition of basic alkoxide ions are stable, but the addition compounds formed from weakly basic oxyanions break down rapidly because, in contrast to weakly basic amines, they cannot undergo loss of a proton to give a stable product. Extrapolation of the equilibrium and rate constants for the more basic alkoxides indicates, for example, that the equilibrium constant K'_{eq} and the rate constant k_1' for the breakdown of the acetate adduct are on the order of $10^{-4} M^{-1}$ and 500 sec^{-1} , respectively.

(4) The *mechanism* of the uncatalyzed attack and expulsion of amines and of alkoxide ions (eq 11) is the same and, in spite of the large difference in the rate of leaving group departure, the transition states resemble the phthalimidium ion and free nucleophile and are indistinguishable. The alkoxide ion is expelled directly, whereas the amine is converted to the protonated form in a rapid equilibrium step in order that the free amine may be expelled. However, alcohol attack and expulsion can also occur through a mechanism of general acid–base catalysis in which proton transfer

occurs more or less simultaneously with C-O bond formation or cleavage (eq 13, X = RO⁻). The compar-



able mechanism for protonated amines (X = R₂NH⁻) would require proton removal from an amine cation during attack and proton addition to a protonated amine during amine expulsion and is not observed, presumably because there are no free electron pairs on the

nitrogen atom to make such a mechanism feasible. The equilibrium proton transfer mechanism (specific acid catalysis of adduct breakdown) is favored for free amines (X = R₂N⁻) as a consequence of the much larger basicity of nitrogen than of oxygen, and it is apparent that an extrapolation of the dependence of α on p*K* (Figure 3) from the p*K*_a values of 12-16 for alcohols to 30-35 for amines predicts an α value of 1.0 for amines.

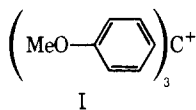
Reactions of the Tri-*p*-anisylmethyl Cation with Primary and Secondary Amines¹

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Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106. Received June 8, 1973

Abstract: The tri-*p*-anisylmethyl cation, R⁺, reacts with aliphatic primary and secondary amines to give derivatives of tri-*p*-anisylmethylamine. Amine nucleophilicity decreases with increasing bulk of substituents and with decreasing basicity, but the decrease is relatively small when the amine contains -I groups such as aryl, amino, or alkoxy. The reaction order is first with respect to most amines, and in these reactions there is no general base catalysis. Typical second-order rate constants are: MeNH₂, 6.3 × 10⁴; PhCH₂NH₂, 4.7 × 10⁴; *t*-BuNH₂, 54; H₂NNH₂, 3.2 × 10⁵ l. mol⁻¹ sec⁻¹. The reaction with pyrrolidine and 2-methylpyrrolidine is general base catalyzed, because the initially formed ammonium ion can lose R⁺, or a hydrogen ion to a general base, at similar rates. The rate constant for the initial attack of pyrrolidine upon R⁺ is 6.4 × 10⁶ l. mol⁻¹ sec⁻¹. Tri-*p*-anisylmethylamine decomposes readily in dilute acid. Kinetic salt effects upon the reaction of R⁺ with ammonia can be explained in terms of salt effects upon the activity coefficient of ammonia.

The reactivity of trivalent carbocations toward nucleophiles has been extensively studied. Much of the work has been done using triphenylmethyl dye cations (e.g., Crystal Violet and Malachite Green) which react relatively slowly with nucleophiles,²⁻⁵ but more reactive cations have been studied by several groups.⁶⁻¹¹ Ritchie has suggested that general base catalysis may be kinetically important in reactions of the less reactive cations with water;¹² but general base catalysis has not as yet been observed in reactions of the tri-*p*-anisylmethyl cation (R⁺, I),^{7-9,11} and the small deute-



(1) Support of this work by the National Science Foundation is gratefully acknowledged.

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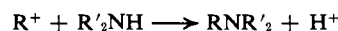
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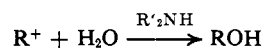
rium kinetic solvent isotope effect suggests that slow proton transfers are not important for attack of water.⁷ Consistently the reaction of R⁺ in the presence of tertiary amines is much slower than with primary amines.

Our present work was intended to test this point further by using sterically hindered amines, and also to differentiate between two reaction paths by product examination.

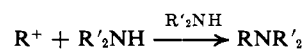
Nucleophilic attack



General base catalysis of water reaction



General base catalysis of amine reaction



In two cases, reaction with pyrrolidine and its 2-methyl derivative, we found evidence for general base catalysis of amine attack, but it seems that it is not important in most reactions of I.

Experimental Section

Materials. The amines were generally commercial samples and most of them were purified by distillation. Methylamine, dimethylamine, and trimethylamine were purified as their hydrochlorides using extraction with CHCl₃ followed by recrystallization.¹³ 2-Methylpyrrolidine was prepared from 5-methyl-2-pyr-

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