methylphenyl)ethyl chloride, 19935-78-5; 1-phenylethyl chloride, 672-65-1; 1-(3-methoxyphenyl)ethyl chloride, 58114-05-9; 1-(3-bromophenyl)ethyl chloride, 19935-76-3; 1-(4-methylphenyl)ethyl bromide, 24344-85-2; 1-(3-nitrophenyl)ethyl bromide, 29067-55-8; 1-(4-methoxyphenyl)ethyl bromide, 55214-85-2; 1-(4-fluorophenyl)ethyl bromide, 65130-46-3; 1-(3-methylphenyl)ethyl bromide, 88563-82-0; 1-phenylethyl bromide, 585-71-7; 1-(3-methoxyphenyl)ethyl bromide, 88563-83-1; 1-(3-bromophenyl)ethyl bromide, 59770-98-8; 1-(4-nitrophenyl)ethyl chloride, 19935-75-2; 1-(4-nitrophenyl)ethyl bromide, 19935-81-0; 1-(4-nitrophenyl)ethyl tosylate, 82925-36-8; 1-(4-methylphenyl)ethyl pentafluorobenzoate, 88563-51-3; [1-(4-methylphenyl)ethyl]dimethylsulfonium bromide, 65130-40-7.

Supplementary Material Available: Salt effects and product compositions in Tables S-1, S-2, and S-3 (4 pages). Ordering information is given on any current masthead page.

General Base Catalysis of the Addition of Hydroxylic Reagents to Unstable Carbocations and Its Disappearance[1]

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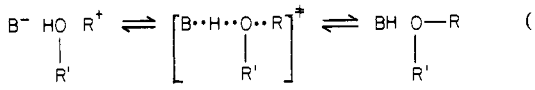
Abstract: General base catalysis of the addition of ROH is significant for 1-phenylethyl carbocations of moderate stability and is most important for weakly basic alcohols. The Brønsted slope for catalysis of the addition of trifluoroethanol to the 1-(4-methoxyphenyl)ethyl carbocation is $\beta = 0.08$. The development of positive charge on the attacking alcohol decreases with decreasing stability of the carbocation; this may be described by the interaction coefficient $p_{yy'} = \partial\beta_{\mathrm{nuc}}/-\partial\sigma$. The positive $p_{yy'}$ coefficient and small β correspond to a small component of proton transfer in the transition state for alcohol addition; in contrast, acetate catalysis of ROH addition to more stable electrophiles exhibits a negative $p_{yy'}$ coefficient that corresponds to a large component of proton transfer and a diagonal reaction coordinate on an energy contour diagram. It is concluded that the observed catalysis involves hydrogen bonding and represents the transition region between fully concerted, coupled general acid–base catalysis and specific acid catalysis with solvation of the proton in the transition state. Catalysis disappears with less stable cations when reaction with solvent and diffusion become competitive, with $k_s \sim 10^9$ s^{-1}, and the rate constant for base catalysis approaches a limiting value of $\sim 10^7$ M^{-2} s^{-1}. The absence of general base catalysis of alcohol addition corresponds to specific acid catalysis of alcohol expulsion to form an unstable carbocation in the reverse direction.

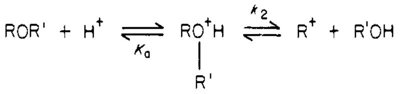
Most reactions that involve the addition or loss of water and alcohols are subject to general acid–base catalysis through the mechanism shown in eq 1. This class *n* mechanism involves



$$B^- \; \underset{R'}{HO} \; R^+ \rightleftharpoons \left[B\cdots H\cdots \underset{R'}{O}\cdots R\right]^{\ddagger} \rightleftharpoons BH \; \underset{R'}{O}{-}R \qquad (1)$$

catalysis of proton transfer to or from the nucleophilic reagent, with general base catalysis of proton removal from ROH in the addition direction and general acid catalysis of proton addition in the reverse direction. Structure–reactivity correlations have provided strong evidence that a number of these reactions are concerted, with significant contributions of both heavy atom movement and proton transfer in the transition state.[2-13]

This type of catalysis has been observed for several reactions in which carbocations are formed or react, including the hydrolysis of acetals and ortho esters and the addition of ROH to a phthalimidium ion.[3-5,9,10,14] However, other reactions in this group proceed with only specific acid catalysis for carbocation formation and with no catalysis of the addition of water or alcohols to the carbocation (eq 2).[15] We would like to know why this change



$$ROR' + H^+ \underset{K_a}{\rightleftharpoons} \underset{R'}{RO^+H} \overset{k_2}{\rightleftharpoons} R^+ + R'OH \qquad (2)$$

in mechansim takes place and what is the sequence of events as one mechanism changes, or "merges", into the other. Three factors are known that can be involved in these changes:

(1) There is a progressive increase in the Brønsted coefficient α (or a decrease in β in the addition direction) as the cation becomes less stable and the alcohol becomes more basic. When α becomes 1.0 (or β becomes 0) the reaction will usually become specific acid catalyzed (or uncatalyzed in the addition direction, eq 2). These changes can be described in terms of changes in the position of the transition state and reaction coordinate on an energy

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Table I. Effect of Methoxyacetate Anion on Partitioning of the 1-(4-Methoxyphenyl)ethyl Carbocation[a]

$[CH_3OCH_2CO_2^-]$,[b] M	k_{az}/k_{TFE}[c,d]	k_{az}/k_{H_2O}[c,d]	k_{az}/k_{MeOH}[c]
0	4950	2330	113
0.1	4560	2260	113
0.2	4130	2160	109
0.3	3760	2050	105
0.4	3390	1920	100
0.5	2980	1840	95

[a] Generated from 1-(4-methoxyphenyl)ethyl 3,5-dinitrobenzoate in 50:45:5 H_2O:TFE:MeOH (v/v/v) containing 0.01 M NaN_3 at 22 ± 2 °C and ionic strength 0.5, maintained with $NaClO_4$. [b] Sodium salt. [c] Dimensionless ratio of second-order rate constants. [d] Methanol lowers these values slightly compared with those in 50:50 TFE:H_2O.[20]

contour diagram that is defined by the structure-reactivity-coefficients.[2,3,5,7,10,13,16,17]

(2) There may be a change in the direction and nature, as well as the position, of this reaction coordinate. When a diagonal reaction coordinate that represents both proton transfer and heavy atom motion approaches the edge of such an energy contour diagram it is expected to become more vertical or horizontal and, eventually, will involve only heavy atom motion or proton transfer. Changes in the orientation and curvature of the saddle point are also expected to occur with large changes in reactant structure because of the complex nature of the energy surface.[12,18]

(3) There may be an approach to limiting rate constants or a change in rate-limiting step such that catalysis is no longer significant. For example, if the addition of ROH to a carbocation is diffusion controlled there will be no general base catalysis because the catalyst does not accelerate diffusion. In the reverse direction this situation corresponds to specific acid catalysis, because the leaving group has been protonated before its rate-limiting diffusional separation from the carbocation.[2,19]

We describe here a study of general base catalysis of the addition of alcohols to 1-phenylethyl carbocations. Approximate lifetimes of these carbocations are known, so that the disappearance of catalysis can be correlated with the carbocation lifetime as well as with structure-reactivity parameters.[20]

Experimental Section

Materials. Reagent grade inorganic salts, sodium acetate, and sodium formate were used without further purification. The procedures for purification of alcohols and carboxylic acids[21] and for the synthesis of the 1-phenylethyl derivatives[20] are described in previous papers.

Methods. Reaction solutions were prepared by mixing water at ionic strength 1.0, maintained with $NaClO_4$, with an equal volume of trifluoroethanol or a mixture of trifluoroethanol and other alcohols. Studies of catalysis by carboxylate anions were usually conducted with unbuffered solutions of the anion. The observed pH values of these solutions were recorded ~10 s after insertion of the electrode and it was shown that solutions adjusted to the same pH value by the addition of small amounts of sodium hydroxide ($\leq$0.3 mM) did not give significant amounts of reaction of the substrate with trifluoroethoxide ion.

The procedures for product separation and measurement by HPLC are given in the first two papers of this series.[20,21] Selectivity rate constant ratios for the partitioning of substituted 1-phenylethyl cations were calculated from the ratios of the reaction products and the concentrations of nucleophiles.[20]

Results

1-(4-Methoxyphenyl)ethyl derivatives react to form a carbocation intermediate that partitions between reaction with solvent and added nucleophiles.[20] The dependence on the concentration of added methoxyacetate anion of the partitioning of this carbocation intermediate between solvent components and azide ion in 50:45:5 (v/v/v) H_2O:TFE:MeOH is shown in Table I. The data are reported as dimensionless rate constant ratios in order to facilitate comparison of the relative molar reactivities of azide and solvent. Table II shows the dependence of k_{az}/k_{TFE} on the concentration of added acetate anion for the reactions of several meta-substituted 1-(4-methoxyphenyl)ethyl carbocations.

Table II. Effect of Acetate Concentration on the Partitioning of 1-(3-Substituted-4-methoxyphenyl)ethyl Carbocations[a]

$CH_3CO_2^-$,[b] M	k_{az}/k_{TFE}[c] 3-substituent H	Br	NO_2
0	5700	680	123[d]
0.095	4800	620	126
0.19	4300	570	128
0.29	3800	510	127
0.38	3300	470	126
0.48	2900	420	126

[a] In 50:50 TFE:H_2O (v/v) containing 0.025 M NaN_3 at 22 ± 2 °C and ionic strength 0.5 maintained with $NaClO_4$. [b] Sodium salt. [c] Dimensionless ratio of second-order rate constants. [d] The larger value of $k_{az}/k_{TFE} = 150$ obtained from measurements at higher azide concentrations[20] may reflect a specific salt effect.[23]

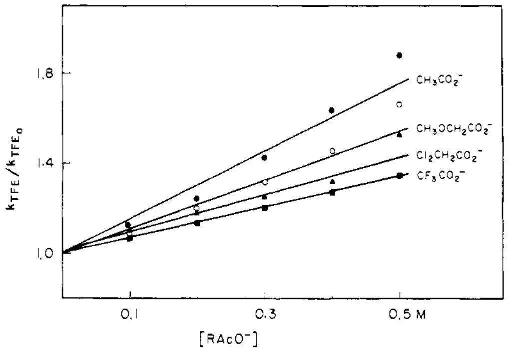

Figure 1. General base catalysis by carboxylate anions of the reaction between trifluoroethanol and the 1-(4-methoxyphenyl)ethyl cation in 50:45:5 (v:v:v) H_2O:TFE:MeOH at ionic strength 0.5 maintained with $NaClO_4$. The *y* axis gives the normalized yield of the trifluoroethyl ether calculated from the trifluoroethyl ether:azide adduct product ratio as described in the text.

Catalysis of the addition of trifluoroethanol by a series of substituted acetate ions is illustrated in Figure 1. Similar catalysis has been observed for addition reactions of other carbocations.[4,14] The upward curvature in the plots may represent a specific salt effect that arises from the substitution of acetate for perchlorate ion at constant ionic strength.[22,23] The effect of added acetate anion on the partitioning of several meta-substituted 1-(4-methoxyphenyl)ethyl carbocations is shown in Figure 2. The ordinate of Figures 1 and 2, k_{TFE}/k_{TFE_0}, is equal to the observed value of k_{TFE}/k_{az} at a given carboxylate concentration divided by k_{TFE}/k_{az} in the absence of carboxylate anion. Thus, increasing k_{TFE}/k_{TFE_0} values reflect the increasing reactivity of trifluoroethanol relative to azide (Tables I and II).

The decrease in k_{az}/k_{TFE} values reported in Tables I and II could be due to an increase in k_{TFE} or a decrease in k_{az}. We conclude that general base catalysis by carboxylate anions of the trifluoroethanol reaction with 1-(4-methoxyphenyl)ethyl cation is primarily responsible for the decrease in k_{az}/k_{TFE} values because the magnitude of the dependence of k_{az}/k_s on carboxylate concentration changes with the solvent species (k_{az}/k_{TFE}, k_{az}/k_{MeOH}, k_{az}/k_{H_2O} values in Table I), with the basicity of the carboxylate

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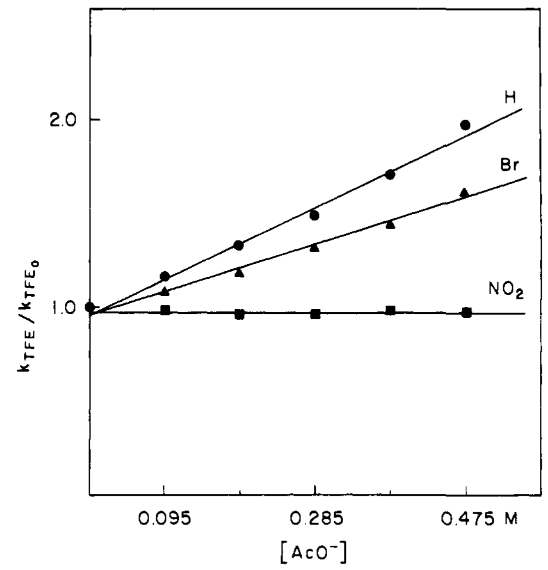


Figure 2. General base catalysis by the acetate anion of the reaction of trifluoroethanol with 1-(3-substituted-4-methoxyphenyl)ethyl cations in 50:50 (v:v) TFE:H_2O at ionic strength 0.5 maintained with $NaClO_4$. The *y* axis gives the normalized yield of the trifluoroethyl ether calculated from the trifluoroethyl ether:azide adduct product ratio as described in the text.

Table III. Rate Constants for General Base Catalysis of the Reaction of Trifluoroethanol with the 1-(4-Methoxyphenyl)ethyl Cation[a]

base	pK_a[b]	k_B/k_{TFE},[c] M^{-1}	k_B,[d] $M^{-2}\,s^{-1}$
$CH_3CO_2^-$	4.8	1.6	1.6×10^6
HCO_2^-	3.8	1.1	1.1×10^6
$CH_3OCH_2CO_2^-$	3.5	1.2	1.2×10^6
$Cl_2CHCO_2^-$	1.3	0.8	0.8×10^6
$CF_3CO_2^-$	0.2	0.7	0.7×10^6
H_2O	−1.8		3.6×10^4 [e]

[a] Generated from 1-(4-methoxyphenyl)ethyl 3,5-dinitrobenzoate in 50:45:5 (v/v/v) H_2O:TFE:MeOH at 22 ± 2 °C and ionic strength 0.5 maintained with $NaClO_4$. [b] In water (Jencks, W. P., and Regenstein, J. In "Handbook of Biochemistry and Molecular Biology", 3rd ed.: Fasman, G. D., Ed.; CRC Press: Cleveland, 1976; Physical and Chemical Data, Vol. 1, pp 305–351. [c] Calculated from the increase in trifluoroethyl ether formation with increasing base concentration (Figure 1). [d] A value of 1×10^6 $M^{-1}\,s^{-1}$ for k_{TFE} was calculated from $k_{az}/k_{TFE} = 5000$ and an estimated rate constant of $k_{az} = 5 \times 10^9$ $M^{-1}\,s^{-1}$. [e] $k_{TFE}/[H_2O]$.

anion (Figure 1), and with the stability of the carbocation (Table II and Figure 2). This behavior is not easily explained as a specific salt effect on the diffusional rate constant k_{az}, but is consistent with the expected structure–reactivity effects on general base catalysis of the reaction of solvent with an unstable carbocation, as discussed below.

If k_{az} values are constant with increasing carboxylate concentration, then Figures 1 and 2 depict the increasing reactivity of trifluoroethanol due to catalysis of the trifluoroethanol reaction by carboxylate anions. The rate constant ratios k_B/k_{TFE} (M^{-1}) reported in Table III were calculated from the slopes of the lines in Figure 1. Absolute values for the rate constant k_B were calculated from an estimated value of k_{TFE} as described in footnote *d* to Table III.

A k_B/k_{TFE} value of 1.4 M^{-1} was observed for the acetate-catalyzed reaction in 50:50 TFE:H_2O at an acetate/acetic acid buffer ratio of 3. This is in agreement with the value in Table III and shows that the reaction of trifluoroethanol is not catalyzed by the acid component of the buffer.

The addition of phenol to the 1-(4-methoxyphenyl)ethyl carbocation was also found to be catalyzed by acetate buffers, with a 2-fold increase in the concentration of the phenyl ether product in the presence of 0.5 M buffer, 75% base.

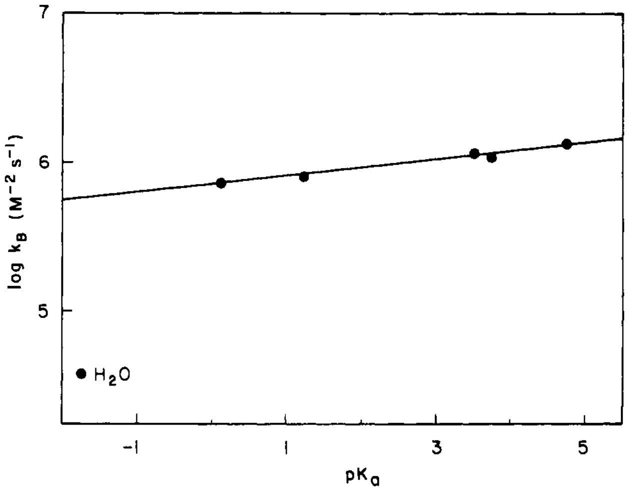
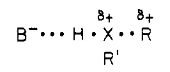


Figure 3. Brønsted plot for general base catalysis of the reaction of trifluoroethanol with the 1-(4-methoxyphenyl)ethyl cation in 50:45:5 (v:v:v) H_2O:TFE:MeOH.

Discussion

Brønsted Plot and Electrostatic Effects. Rate constants for general base catalysis of the addition of trifluoroethanol to the 1-(4-methoxyphenyl)ethyl carbocation, k_B, from the slopes of Figure 1 follow a Brønsted plot with $\beta = 0.08$, shown in Figure 3. The negative deviation of $10^{1.2}$ for the water-catalyzed reaction is similar to the deviations for catalysis by the proton of the hydrolysis of acetals and ortho esters, which is the same reaction mechanism in the reverse direction (eq 1, $B^- = H_2O$).[5,9] There is a similar value of $\beta = 0.09$ and a similar negative deviation of the rate constant for water in general base catalysis of the addition of water to the carbocation derived from 4-methylacetophenone dimethyl ketal.[24]

These deviations may be explained by an electrostatic effect. There is an electrostatic stabilization of the transition state by anionic catalysts, 1, that does not exist in the reference ionization



$$B^- \cdots H \cdot \overset{\delta+}{\underset{R'}{X}} \cdot\cdot \overset{\delta+}{R}$$

1

reaction in which the proton has moved into the bulk solvent.[9,25] However, other reactions of this class show no such deviation or electrostatic effect.[4,6,13] The available data suggest that it is important when the proton is almost completely transferred to the substrate, with a large α or small β, and when there is a large amount of O–C bonding in the transition state, so that a positive charge develops adjacent to the anion. The rate will then be increased by electron-donating substituents on the alcohol, with positive values of β_{nuc} and β_{lg}. This is likely to be more important for basic alcohols, which frequently have a relatively large development of positive charge in this class of reaction (corresponding to a negative coefficient, $p_{y'} = \partial\beta_{nuc}/-\partial pK_{nuc}$).[12] Thus, it provides an explanation for the negative deviations of the rate constants for catalysis by the proton when basic alcohols and phenols are expelled from formaldehyde hemiacetals and benzaldehyde methyl phenyl acetals.[5,8] The small or nonexistent negative deviations for less basic leaving groups result in a compression of the range of rate constants for the different leaving groups and a decrease in the value of β_{lg} for catalysis by the proton in these reactions.

General acid catalysis in the cleavage direction is not enforced by the absence of a barrier for leaving group expulsion after protonation of the leaving oxygen atom in this system. The value of $k_H = 0.06$ $M^{-1}\,s^{-1}$ for the proton-catalyzed cleavage of the C–O bond of 1-(4-methoxyphenyl)ethyl alcohol[20] and a value of k_2

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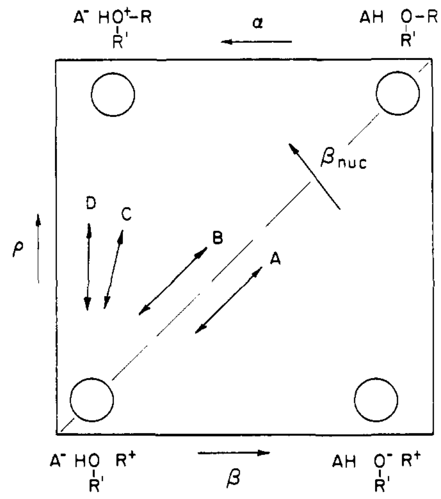

Figure 4. Reaction coordinate–energy contour diagram for general base catalysis of the addition of alcohols to 1-phenylethyl carbocations. The x and y axes represent proton transfer and C–O bond formation as measured by β and ρ, respectively. A diagonal axis, y', represents charge development on the oxygen atom, as measured by β_{nuc}. The reaction coordinates A–D are discussed in the text and the energy contour lines are omitted.

$\geq 10^{13}$ s^{-1} if there is no barrier for the cleavage step after protonation (eq 2) gives $K_a = k_2/k_H = >10^{14}$ M or pK_a = <-14, which is far below the pK_a of protonated alcohols. The pK_a of protonated ethanol is -1.94.[26]

Transition-State Structure. There is a progressive change in the nature of the transition state with changing stability of the electrophile in this class of reactions. These changes are manifested in structure–reactivity parameters and may be described by the reaction coordinate–energy diagram of Figure 4, which has separate axes for proton transfer and for C–O bond formation or cleavage. The transition from general acid–base catalysis to specific acid catalysis of C–O cleavage (no catalysis of alcohol addition) as the electrophile becomes less stable is shown by the reaction coordinates A–D in Figure 4.

The increase in catalysis with more acidic alcohols (Table I) corresponds to a larger value of β for more acidic alcohols and to a smaller dependence of log k_B on the pK_a of the alcohol, β_{nuc}, for stronger base catalysts. This may be described by a positive value of the interaction coefficient $p_{xy'} = \partial\beta/-\partial\,\mathrm{p}K_{\mathrm{nuc}} = \partial\beta_{\mathrm{nuc}}/-\partial\,\mathrm{p}K_{\mathrm{BH}}$,[18] which is characteristic of this class of reactions.[2-5,9,10,13,27] The rate constants in Tables I and III for catalysis of the addition of trifluoroethanol and methanol by methoxyacetate ion and by water correspond to a value of $p_{xy'} = 0.03$. This coefficient typically gives rise to a crossing of the Brønsted lines for alcohols of different pK_a, so that trifluoroethanol becomes more reactive than less acidic alcohols with basic catalysts. This is not observed in these reactions; an extrapolation of the data indicates that it would occur only with strongly basic catalysts.

The positive $p_{xy'}$ coefficient corresponds to a reaction coordinate in Figure 4 with an important vertical component in the transition state.[12,18] An electron-withdrawing substituent on the alcohol raises the energy of the cation in the upper left corner and lowers the energy of the alcohol anion in the lower right corner of the diagram, as shown by the arrows in the corners of Figure 5A. The transition state will then tend to slide downhill perpendicular to the reaction coordinate, toward the lower energy region in the right corner, and to move uphill parallel to the reaction coordinate, toward the top of the diagram. The resultant of these movements shifts the transition state toward the right and results in a larger β value for proton removal from the more acidic alcohol, as shown in Figure 5A.

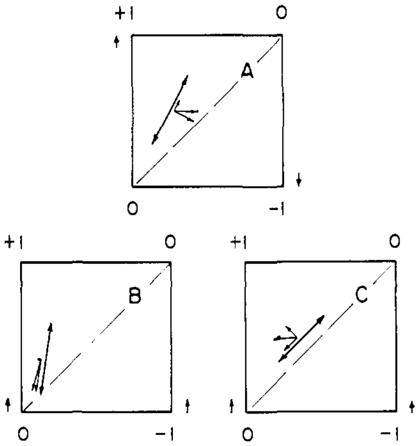

Figure 5. Reaction coordinate diagrams similar to Figure 4 to illustrate the effects on the position of the transition state of (A) an electron-withdrawing substituent in ROH, (B) an electron-withdrawing substituent on the carbocation with a predominantly vertical reaction coordinate, and (C) the same as (B) but with a diagonal reaction coordinate. The numbers show the formal charge on the alcohol oxygen atom.

The interaction between the alcohol and the electrophile is opposite in direction for the reactions of 1-phenylethyl carbocations and the acetate-catalyzed reactions of formaldehyde. The selectivity of carbocations toward alcohols decreases as the carbocation becomes more reactive, with a decrease in the dependence of log k on the pK_a of the alcohol, β_{nuc}, from 0.50 for the 4-dimethylamino to 0.22 for the 4-phenoxy-substituted cation. This corresponds to a simple "Hammond" effect and a positive value of the interaction coefficient $p_{yy'} = \partial\beta_{\mathrm{nuc}}/-\partial\sigma = \partial\rho/-\partial\,\mathrm{p}K_{\mathrm{nuc}}$.[12] For a Hammett correlation modified according to Yukawa and Tsuno and ρ normalized for ρ_{equib}, the value of $p_{yy'}$ is 0.1.[21] The decrease in the secondary α-deuterium isotope effect with more acidic leaving groups, from $k_H/k_D = 1.11$ for p-methoxyphenol to 1.06 for p-nitrophenol, in the proton-catalyzed hydrolysis of 2-(p-substituted-phenoxy)tetrahydrofurans corresponds to a positive $p_{yy'}$ coefficient for the same kind of reaction in the reverse direction.[28]

A positive $p_{yy'}$ coefficient corresponds to a transition state in which there is only a small component of proton transfer and a reaction coordinate that is close to vertical, as shown by C in the energy diagram of Figure 4.[12] A substituent with a larger σ value will destabilize the carbocation and raise the energy of the bottom edge of the diagram, as indicated by the two vertical arrows in Figure 5B. This shifts the position of the transition state toward the position of higher energy along (parallel to) the reaction coordinate and toward the position of lower energy perpendicular to the reaction coordinate. For a reaction coordinate that is largely vertical the first effect will predominate and there will be less bond formation to the attacking alcohol in the transition state and a smaller value of β_{nuc}, as shown in Figure 5B.

Figure 5C shows that for a more diagonal reaction coordinate, with a larger component of proton transfer, the same destabilization of the carbocation will cause a larger movement of the transition state perpendicular to the reaction coordinate, so that the transition state moves in the opposite direction with respect to charge development on the alcohol and there is an increase in β_{nuc}. Positive charge development on the alcohol increases from the lower right to the upper left corner of the diagram, so that a movement of the transition state to the left corresponds to an increase in positive charge development that arises from a smaller amount of proton removal from the attacking alcohol. This is observed for the acetate-catalyzed reaction of alcohols with formaldehyde, which exhibits a change in α-secondary deuterium isotope effect with different alcohols that corresponds to a negative $p_{yy'}$ coefficient and a nearly diagonal reaction coordinate with a

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large component of proton transfer as shown in B of Figure 4.[12]

These interaction coefficients are related by eq 3, in which $p_{y'} = \partial\beta_{\text{nuc}}/-\partial \text{p}K_{\text{nuc}}$.[12,18] A positive $p_{y'}$ coefficient corresponds to

$$p_{yy'} = p_{y'} + p_{xy'} \qquad (3)$$

a Hammond effect for addition of the alcohol. According to eq 3 the diagonal reaction coordinate B corresponds to a positive value of $p_{xy'}$, a negative value of $p_{yy'}$, and a more negative value of $p_{y'}$. This negative value of $p_{y'}$ corresponds to an "anti-Hammond" effect and is consistent with the upward curvature that is commonly observed in general acid–base catalyzed reactions with more stable electrophiles; it is sufficient to give U-shaped curves in plots of log *k* against $\text{p}K_{\text{ROH}}$ for the general base catalyzed addition of alcohols to formaldehyde.[8] This upward curvature corresponds to a movement of the transition state perpendicular to the reaction coordinate, toward the upper left corner, with increasing $\text{p}K_{\text{ROH}}$ when there is a large component of proton transfer and the reaction coordinate is diagonal (B in Figure 4).

There is no evidence for curvature in plots of log *k* against $\text{p}K_{\text{ROH}}$ for the addition of alcohols to 1-phenylethyl carbocations.[21] This corresponds to a value of $p_{y'} \sim 0$ and is consistent with the positive values of both $p_{xy'}$ and $p_{yy'}$ for this reaction, according to eq 3. It is also the behavior that is expected from the more vertical reaction coordinate C for the reactions of the 1-phenylethyl carbocations.

Finally, there is a tendency for reactions that generate a more stable carbocation to exhibit smaller values of α.[2,3,5,10,13,16–18] This trend represents a positive value of the coefficient $p_{xy} = \partial\alpha/\partial\sigma = \partial\rho/-\partial \text{p}K_{\text{BH}} = \partial\beta/-\partial\sigma$. The small value of $\beta = 0.08$ for catalysis of trifluoroethanol addition to the 1-(4-methoxyphenyl)ethyl cation corresponds to the large value of $\alpha = 0.92$ and a large amount of proton transfer in the transition state for alcohol expulsion in the reverse direction. The values of α are in the range 0.40–0.49 for the expulsion of alcohols to generate the much more stable amidinium ion.[13]

These changes can be described by the reaction coordinates A, B, C, and D in Figure 4. The general base catalyzed attack of ROH on an amidinium ion occurs through a nearly diagonal reaction coordinate with a large component of proton transfer, A, that is located a little below the center of the diagram. As the cation becomes less stable there is movement to the left with a decrease in β, as shown in transition state B. This is observed for the addition of alcohols to a phthalimidinium ion[4] and to formaldehyde,[8] for example. These reactions appear to represent concerted proton transfer and formation or cleavage of bonds to heavy atoms. The reaction coordinate for addition to the 1-(4-methoxyphenyl)ethyl carbocation is close to the left wall of the diagram and cannot move appreciably further without disappearance of catalysis. Its direction has changed to approach the vertical, so that there is only a small component of proton transfer, as shown in C. This change in direction may simply be a consequence of the approach to the edge of the diagram. Reaction coordinate D represents specific acid catalysis, with no movement of the proton in the transition state, as is observed for the hydrolysis of some acetals.[15]

The catalysis in the 1-phenylethyl system could be accounted for simply by hydrogen bonding of the base to the attacking alcohol in the transition state. Class *n* catalysis of nucleophilic attack by hydrogen bonding has been observed for the addition of anilines to carbon dioxide[25] and bisulfite ion to ketones.[29] The data do not permit a decision as to whether proton transfer is concerted with C–O bond formation in the reactions of 1-phenylethyl carbocations.

Catalysis by hydrogen bonding, with a largely vertical reaction coordinate, C, provides a transition region and a pathway for "merging" of the mechanisms for specific acid catalyzed cleavage (or uncatalyzed addition, eq 2) and for fully concerted general acid–base catalysis of the expulsion and addition of ROH. There is no sharp line that separates general base catalysis by hydrogen bonding from stabilization of the transition state by solvation of the developing positive charge. Hydrogen bonding to a catalyzing base in the addition direction corresponds to hydrogen bonding by the basic component of the acid catalyst after proton transfer to the leaving RO– group in the cleavage direction. Therefore, there is also no sharp dividing line that separates specific acid catalysis from general acid catalysis with such hydrogen bonding in the transition state. The presence or absence of significant catalysis will depend on the amount of positive charge development in the transition state and the resulting stabilization of this charge by hydrogen bonding to the basic component of the catalyst.

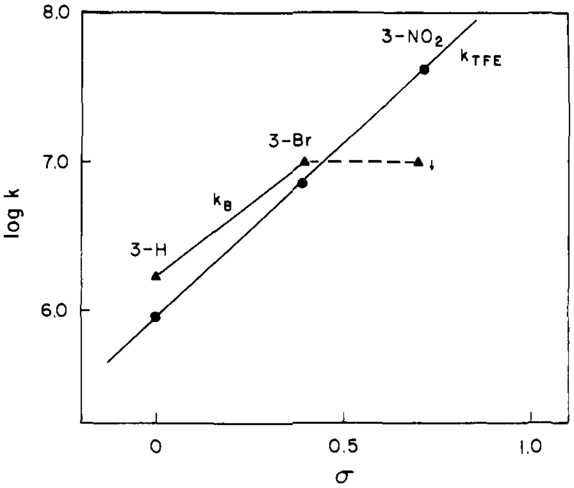

Figure 6. Hammett plots for the uncatalyzed (k_{TFE}, $\text{M}^{-1}\ \text{s}^{-1}$) and the acetate anion catalyzed (k_{B}, $\text{M}^{-2}\ \text{s}^{-1}$) reactions of trifluoroethanol with 1-(3-substituted-4-methoxyphenyl)ethyl cations in 50:50 (v:v) TFE:H_2O.

The Disappearance of Catalysis. The decrease and then disappearance of catalysis when electron-withdrawing substituents are added to 1-phenylethyl carbocations (Figure 2) corresponds to a sharp break in the Hammett plot for the base-catalyzed reaction as the cation becomes less stable, as shown in Figure 6. No catalysis is detected with the 3-nitro-4-methoxy-substituted cation and there is also no catalysis with the 4-methyl-substituted compound.[21]

The decrease in β and in positive charge development on the attacking alcohol that are described by the interaction coefficients $p_{xy} = \partial\beta/-\partial\sigma$ and $p_{yy'} = \partial\beta_{\text{nuc}}/-\partial\sigma$ contribute to this decrease and disappearance of catalysis, but the principal cause is an approach to limiting rate constants for reaction of the cation with solvent components. This is also responsible for a sharp drop in the selectivity of solvent components in the uncatalyzed reactions of the same carbocations.[21]

Evidently, the reactivity of those solvent molecules that are hydrogen bonded to acetate ion is not large enough to give detectable catalysis with these unstable carbocations. A significant fraction of the reaction of the 1-(4-methylphenyl)ethyl carbocation with solvent and azide occurs before it diffuses out of the solvent cage in which it is formed, through a preassociation mechanism, and this must also be the case for the 3-nitro-4-methoxy-substituted cation, which has an almost identical lifetime.[20] If the association constant for formation of a productive complex that contains acetate ion is $K_{\text{as}} = 0.1\ \text{M}^{-1}$, only 5% of the bond cleavage events will have $\text{AcO}^-{\cdot}\text{HOR}{\cdot}\text{R}^+$ in a reactive position in the presence of 0.5 M acetate ion and catalysis within the complex will not be significant. The limiting assumption that each acetate ion binds indiscriminately to one solvent proton gives 11% of the acetate ions in the species $\text{AcO}^-{\cdot}\text{HOTFE}$ and a limiting second-order rate constant of $\leq 6 \times 10^8\ \text{M}^{-1}\ \text{s}^{-1}$ for the reaction of this species with the 1-(3-nitro-4-methoxyphenyl)ethyl carbocation. This rate constant is about an order of magnitude below that for azide ion. There is presumably a larger requirement for correct positioning and entropy loss in the transition state for this hydrogen-bonded pair than for azide ion, which results in a lower limiting rate constant. The early approach to limiting rate constants for the uncatalyzed reaction of methanol also suggests that at least part

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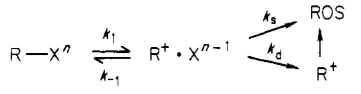
of the reaction occurs through clusters of solvent molecules with a low entropy.[21]

We conclude that, in the reverse direction, catalysis of alcohol expulsion by buffer acids disappears at approximately the point at which the carbocation reacts with the solvent or a leaving alcohol to a significant extent before diffusion occurs. For the hydrolysis of substituted benzaldehyde diethyl acetals this point is apparently reached with the 4-chlorobenzaldehyde derivative.[10]

As the stability of the cation decreases the reaction with solvent can occur either by a preassociation mechanism without diffusion, k_s in eq 4, or through rate-limiting diffusion away from the leaving



(4)

group, k_d. General acid–base catalysis must disappear when diffusion is rate limiting in these reactions, because buffers do not accelerate diffusion.[2,19] The requirements for rate-limiting diffusional separation are stringent, so that it is not often observed. The requirements are that $k_{-1} > k_d > k_s$; i.e., the leaving group must be a good nucleophile and the solvent must react more slowly than diffusion occurs; the intermediate must also have a significant lifetime, with $k_{-1} < 10^{13}$ s^{-1}. This is consistent with the behavior of the pH-independent cleavage reactions of 2-(aryloxy)tetrahydropyrans[30] and benzaldehyde ethyl arylthiol acetals,[31] in which ArO^- and ArS^-, respectively, are the leaving groups. It is less likely to be of major significance when an alcohol is the leaving group in hydroxylic solvents, because of the requirement for a considerably larger value of k_{-1} compared with k_s. However, the increase in the α-secondary deuterium isotope effect for the hydrolysis of benzaldehyde dimethyl acetal in the presence of increasing concentrations of dioxane has been attributed to rate-limiting diffusional separation of methanol.[32] When the carbocation becomes less stable the intermediate $R^+ \cdot X^{n-1}$ will cease to have a significant lifetime so that the initial product of a dissociative mechanism must have the leaving group in an unreactive position, such as a solvent-separated pair. The reverse, addition reaction can still be diffusion controlled in this situation.

When the carbocation becomes still less stable, so that substitution occurs through a concerted bimolecular displacement reaction with no intermediate, general acid–base catalysis is also not observed. This presumably reflects the small sensitivity of these reactions to the basicity of the nucleophile and the small advantage that can be expected from catalysis in an early transition state. If catalysis is not significiant for normal S_N2 displacement reactions it certainly will not be significant for concerted substitution reactions that proceed through an open, "exploded" transition state, which have even less positive charge development on the attacking reagent than ordinary displacement reactions. General base catalysis is observed in some intramolecular displacement reactions, presumably because of the smaller requirement for loss of entropy in the transition states of these intramolecular reactions.[33]

In all of these cases the disappearance of general acid–base catalysis corresponds to a change to a reaction mechanism in which the attack of ROH is not subject to catalysis and the cleavage of ROR′ in the reverse direction is subject to specific acid catalysis (eq 2). Thus, the mechanism of catalysis is determined to a significant extent by the lifetime of the carbocation intermediate.

Registry No. 1-(4-Methoxyphenyl)ethyl carbocation, 18207-33-5; 1-(3-bromo-4-methoxyphenyl)ethyl carbocation, 88510-80-9; 1-(3-nitro-4-methoxyphenyl)ethyl carbocation, 88510-81-0; trifluoroethanol, 75-89-8.

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Nucleophilic Substitution at Vinylic Carbon: The Importance of the HOMO–HOMO Interaction

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Abstract: A theoretical treatment of the stereochemical course of nucleophilic addition to alkenes is presented. On the basis of frontier molecular orbital theory and ab initio molecular orbital calculations, it is concluded that nucleophilic substitution with simple alkenes involves a concerted one-step mechanism. The developing anticarbanion rotates syn to the leaving group with the lowest lying σ* orbital, with concomitant inversion of the carbanion at C_β and expulsion of the leaving group. This overall process results in retention of configuration of the alkene. With substituents at C_β capable of stabilizing the incipient carbanion, addition of the nucleophile affords a planar, freely rotating carbanion, resulting in stereoconvergence of the alkene being formed. Poor leaving groups may also result in alkene stereoconvergence as a consequence of a loss of rotational selectivity to the best leaving group in a late transition state. The importance of the four-electron interaction (HOMO–HOMO) in determining the energetics and the relative position of the transition state on the reaction coordinate is discussed by invoking a three molecular orbital, four-electron model. The net effect of the four-electron interaction in the presence of a third higher lying empty orbital is to lower the enthalpy of activation.

The addition–elimination reaction of a nucleophile (e.g., RS^-, Cl^-, NH_2R, etc.) involving a carbon–carbon double bond is an intriguing process because ostensibly it involves the interaction of two nucleophilic species. The reaction typically occurs with an alkene bearing a substituent with lone pairs of electrons that would tend to increase the apparent nucleophilicity of the double bond. Recent experimental studies on nucleophilic vinylic substitution[1] have addressed one of the most important mechanistic questions remaining: Is the overall substitution reaction a single-step or a multistep process? In general, vinyl halide substitution occurs with nearly complete retention of configuration[2a,b]

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