in anthracene (and probably DBA as well) must be due to energy transfer from T_n ($n > 2$) to the solvent. The T_2 energies of both donors lie well below the T_1 energy of benzene, i.e. 73.0[35] and 74.4[38] < 85 kcal/mol.[39] Clearly then, if T_n is long enough lived to undergo intermolecular energy transfer, it could conceivably undergo ISC back to the singlet manifold. However, our quenching experiments with 1,3-octadiene suggest that only T_2 is involved and that any contributions from other upper states (at least those generated by 467-nm excitation) are within the errors of these measurements.

Our results led to $k_2^{ET}\tau_{T_2}$ = 1.8 M^{-1} for 1,3-octadiene as quencher. From this value it is possible to estimate a value for τ_{T_2}: Since the T_2 state of DBA is close to the lowest triplet state of xanthone, we assume that energy transfer to 1,3-octadiene occurs with approximately the same rate constant in both systems. For the latter we measured[37] $k_9 \sim 1 \times 10^{10}$ M^{-1} s^{-1}. From this we estimate $\tau_{T_2} \sim$ 200 ps.

Conclusions

Our results lead to the following conclusions:

(i) Back intersystem crossing (TS) following dye-laser excitation (467 nm) of T_1 occurs with quantum yields of 0.17 and 0.09 in cyclohexane and benzene, respectively. Quite clearly T_2 participates directly in this process. T_n ($n > 2$) is sufficiently long lived to participate in intermolecular energy transfer to the solvent (benzene) in a process which we believe is responsible for the lower Φ_{TS} value measured in benzene; however, this state (T_n) does not need to be invoked as a direct participant in the TS process.

(ii) Despite the fact that triplet excitation at 467 nm results in the production of a T_n state with more than sufficient energy to induce C–Br cleavage, this process is relatively inefficient, occurring with $\Phi_{-Br} \sim 1.6 \times 10^{-3}$. This accounts for only ca. 4% of the triplets bleached in benzene.

(iii) Lifetimes can be estimated for T_2 from 1,3-octadiene quenching experiments and for T_n from benzene quenching data. These lead to $\tau_{T_2} \sim$ 200 ps and $\tau_{T_n} \sim$ 20 ps.

Acknowledgment. Thanks are due to S. E. Sugamori for technical assistance.

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General-Base Catalysis of Nucleophilic Substitution at Carbon[1]

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Abstract: The bimolecular reaction of [4-(trifluoromethyl)benzyl]methyl(4-nitrophenyl)sulfonium ion with trifluoroethanol is catalyzed by substituted acetate ions and other buffer bases in 50% trifluoroethanol–water (v/v) at 40 °C and ionic strength 0.5 M ($NaClO_4$). The Brønsted β value is 0.26, but there is no significant solvent deuterium isotope effect. The reactions with water and ethanol do not show catalysis and there is no catalysis of the reaction of (4-trifluoromethyl)benzyl bromide.

One of the curious problems of enzymology is the question of how enzymes catalyze simple displacement reactions. In addition to decreasing the requirement for entropy loss by induced intramolecularity, stabilization of the transition state by ionic and nonpolar interactions, and possibly compression, enzymes might catalyze displacement reactions by general-base catalysis of proton removal from hydroxylic nucleophiles in the transition state.[3-6] There is evidence for such general-base catalysis in nonenzymatic reactions for attack at sp^2 carbon (or the equivalent general acid catalysis in the reverse reaction),[7-9] for substitution on silanes,[10] and for displacement at sp^3 carbon in intramolecular reactions,[5,11-16] but it has not been reported for bimolecular displacement reactions at sp^3 carbon. We are interested in why this might be the case, and in order to characterize these reactions further, we have examined general-base catalysis of solvolysis in the presence of alcohols with different pK_a. General-base-catalyzed reactions of hydroxylic nucleophiles generally show an increased Brønsted β value with decreasing pK_a of the alcohol that is described by a positive interaction coefficient, $p_{xy'} = \partial\beta/-\partial pK_{nuc} = \partial\beta_{nuc}/-\partial pK_{BH}$, so that catalysis should be easier to detect with more acidic alcohols.[17]

We report here that buffer bases catalyze the reaction of [4-(trifluoromethyl)benzyl]methyl(4-nitrophenyl)sulfonium tetrafluoroborate, **1**, with trifluoroethanol, but not with ethanol or water, in the solvent. This substrate was choosen because there is some evidence that benzyl compounds with electron-withdrawing substituents[18] and sulfonium ions[16,19] have unusually large amounts

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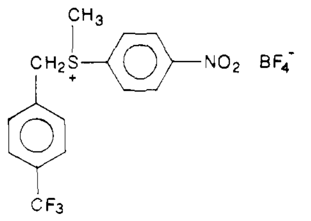

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of bond formation to the nucleophile in the transition state, which would increase the acidity of the transition state and the likelihood of detecting catalysis. No catalysis was observed with Br^- as the leaving group. The reactions were followed by determining the effect of buffer bases on the yields of alcohol and ethers compared with that of the nitrate, in the presence of NO_3^-, because attack of this nucleophile is not subject to general-base catalysis.

Experimental Section

Materials. Reagent-grade inorganic salts and trifluoroethanol (99+%, Aldrich) were used without further purification. 4-(Trifluoromethyl)benzyl bromide (Aldrich) was shown to be >99% pure by HPLC and was used as received. 4-Nitrobenzyl bromide was recrystallized from ethanol (mp 98–99.5 °C) and was shown to be >99% pure by HPLC. 4-Nitrothiophenol (80% from Aldrich) was recrystallized from ethanol (mp 75–77 °C). Water was glass-distilled.

4-(Trifluoromethyl)benzyl 4-nitrophenyl sulfide was prepared as follows. In a dry 100-mL round-bottom flask was placed 0.287 g (7.2×10^{-3} mol) of NaH (60% suspension in mineral oil). After washing of the mixture twice with 6-mL portions of anhydrous pentane, the sodium hydride was slurried in 6 mL of dry tetrahydrofuran. To this slurry was added with stirring 0.789 g (5.1×10^{-3} mol) of 4-nitrothiophenol in 10 mL of tetrahydrofuran. To this red solution was added with stirring 0.959 g (4.0×10^{-3} mol) of 4-(trifluoromethyl)benzyl bromide. To the orange solution was added ~5 mL of methanol to decompose any remaining sodium hydride. The solution was filtered and the solvent was removed under reduced pressure to give 1.18 g of an amber oil that eventually solidified. HPLC analysis showed the product to be >90% pure: NMR ($CDCl_3$) δ 8.1 (d), 7.5 (d), 7.6 (d), 7.3 (d), (8 aromatic protons), 4.3 (s, 2). The mass spectrum has a parent ion with $m/e = 313$ that is consistent with the structure of 4-(trifluoromethyl)benzyl 4-nitrophenyl sulfide.

[4-(Trifluoromethyl)benzyl]methyl(4-nitrophenyl)sulfonium tetrafluoroborate, **1**, was prepared by dissolving 1.18 g of 4-(trifluoromethyl)benzyl 4-nitrophenyl sulfide in 12 mL of dry acetonitrile and adding 0.796 g (5.4×10^{-3} mol) of trimethyloxonium tetrafluoroborate. After stirring of the mixture for 1 h, the CH_3CN was removed under reduced pressure to give a brick red solid (mp 82–87 °C dec) that was >96% pure by HPLC: NMR (acetone) δ 8.4 (d, 4), 7.7 (d, 4), 5.4 (m, 2), 3.7 (s, 3).

Product Analysis. Reaction products were analyzed by high-performance liquid chromatography (HPLC) with a Waters Associates reverse-phase 5-μm NOVA-PAK C_{18} chromatography column, which was pressurized in a Waters Radial Compression Module. Separation of the components of the reaction mixture was accomplished by gradient elution with acetonitrile–water mixtures ranging from 52:48 to 58:42 (v/v) CH_3CN/H_2O, containing 0.05 M tetrabutylammonium phosphate (Waters Associates PIC-A reagent). Peak areas were obtained by electronic integration of their UV absorbance at 222 nm with a Waters Model 730 data module.

Kinetics. Reaction mixtures for solvolysis measurements in 50% aqueous trifluoroethanol (v/v) at 40 ± 0.2 °C and ionic strength maintained at 0.5 M with $NaClO_4$ were prepared by combining 12.5 mL of a trifluoroethanol solution of **1** (~8×10^{-3} M), which also contained ~10^{-4} M *p*-chlorobenzaldehyde, with 10.4 mL of 1.2 M $NaClO_4$ and 2.1 mL of H_2O. The solution was shaken and approximately 3 mL was placed in several 4-mL HPLC sample vials. The vials were closed tightly with Teflon-sealed caps. After temperature equilibration in a constant-temperature bath at 40 ± 0.2 °C, the samples were removed at intervals, quenched in ice, and analyzed by HPLC. The *p*-chlorobenzaldehyde was used as an internal standard to calibrate injection volumes and concentrations. Pseudo-first-order rate constants for solvolysis were obtained by monitoring the appearance of alcohol product, P, as a function of time. The rate constant was obtained from a semilogarithmic plot of $(P_\infty - P_T)$ against time with nine data points covering 2.5 half-lives. The P_∞ values obtained after 10 and 12.5 half-lives were the same within experimental error. The same first-order rate constant was observed by monitoring the appearance of the ether product.

Pseudo-first-order rate constants for the reactions of **1** with trifluoroethanol and water were obtained from product analysis by HPLC, as described in the Results section. Solvolysis of **1** in 50% aqueous trifluoroethanol gave 4-(trifluoromethyl)benzyl alcohol and 4-(trifluoromethyl)benzyl trifluoroethyl ether in a ratio of 94.2 ± 0.4:5.8 ± 0.4 (the average result of 17 samples with standard deviations of the mean).

The rate constants for general-base catalysis by buffers were also determined from product analysis by HPLC. Reaction mixtures were prepared as follows. Known volumes of buffer (1.2 M in base), 1.2 M sodium perchlorate, and 0.6 M sodium nitrate were combined in a 4-mL HPLC vial to give a total volume of 1.5 mL. To this was added 1.5 mL of a freshly prepared trifluoroethanol solution of **1** (~8×10^{-3} M). The final solution was 0–0.4 M in buffer base and 0.1 M in sodium nitrate and had an ionic strength of 0.5 M. After incubation in a constant-temperature bath at 40 ± 0.2 °C for approximately 24 h, the samples were analyzed by HPLC, as described above. Plots of the trifluoroethyl ether product area (R–OTFE) relative to the area of the nitrate product ($R-NO_3$) against base concentration, [B], showed a linear increase in $[R-OTFE]/[R-NO_3]$ with increasing base concentration; 10 base concentrations were usually examined for each buffer. Duplicate injections generally agreed within <5%. Several complete experiments were also run in duplicate and gave slopes that also agreed within <5%. It was shown that the ratio $[R-OTFE]/[R-NO_3]$ did not change during the course of the experiment. For CF_2HCOO^- as a base a solution of 1.2 M CF_2HCOO^- in a buffer of 0.02 M $CH_3OCH_2COO^-$ and 0.005 M CH_3OCH_2COOH was used as the stock buffer solution. The values of $[R-OTFE]/[R-NO_3]$ were corrected for any increase in R–OTFE caused by the methoxyacetate, which was determined in separate experiments. For CF_3COO^- as a base no acidic species was present. Solvent deuterium isotope effects were determined by the same procedure with solutions containing 89% exchangeable deuterium; the 11% protium was derived from acetic acid and trifluoroethanol.

HPLC analysis showed only the expected products from attack at the benzylic carbon of **1** except for a small peak corresponding to 4-(trifluoromethyl)benzyl 4-nitrophenyl sulfide, from attack at the methyl group of **1**, and two other small peaks (<6%) that were not identified.

Measurements of pH were made with an Orion Research Model 701A pH meter at 25 °C and a glass combination electrode containing saturated potassium chloride, standardized with aqueous buffers. Values of pK_a in 50% aqueous trifluoroethanol (v/v) were determined from the apparent pH of dilute buffer solutions at ionic strength 0.5 M ($NaNO_3$). The values of apparent pH were corrected by adding 0.263, which was determined from measurements of the pH of 0.05, 0.01, 0.003, and 0.001 M HCl solutions in 50:50 (v/v) TFE/HOH. For several buffers the values of pK_a determined at two different buffer ratios agreed within ±0.03 pH unit. The pK_a values of CF_3COOH and HCF_2COOh were determined by extrapolation of a plot of pK_a in TFE:HOH against the pK_a values in HOH[20] of cyanoacetic acid, methoxyacetic acid, acetic acid, and cacodylic acid; the line is defined by pK_a TFE/HOH = 0.97 pK_a HOH − 0.23.

Results

The benzylsulfonium compound **1** undergoes solvolysis with a rate constant of $k_{sol} = (2.4 \pm 0.2) \times 10^{-5}\ s^{-1}$ in 50% aqueous trifluoroethanol (v/v), ionic strength 0.5 M ($NaClO_4$), at 40 ± 0.2 °C, determined by analysis of the alcohol and the trifluoroethyl ether products by HPLC. This rate constant and the ratio of the alcohol and trifluoroethyl ether products give rate constants of $k_{HOH} = 2.3 \times 10^{-5}\ s^{-1}$ and $k_{TFE} = 1.4 \times 10^{-6}\ s^{-1}$ for the reactions with water and trifluoroethanol, respectively; the corresponding second-order rate constants are 8.3×10^{-7} and $2.0 \times 10^{-7}\ M^{-1}\ s^{-1}$. A similar experiment in the presence of 0.1 M $NaNO_3$ under the same conditions gave a rate constant for reaction with NO_3^- of $k_{NO_3} = 1.0 \times 10^{-4}\ M^{-1}\ s^{-1}$, which was obtained from the ratio of the $R-NO_3/R-OH$ peak areas determined by HPLC.

Figure 1 shows that the ratio of products formed from trifluoroethanol and nitrate ion, $[R-OTFE]/[R-NO_3]$, increases with increasing concentration of the buffer base when the buffer concentration is increased at constant buffer ratio and ionic strength 0.5 M. The product ratios were determined by HPLC. There is significant catalysis of the reaction with trifluoroethanol

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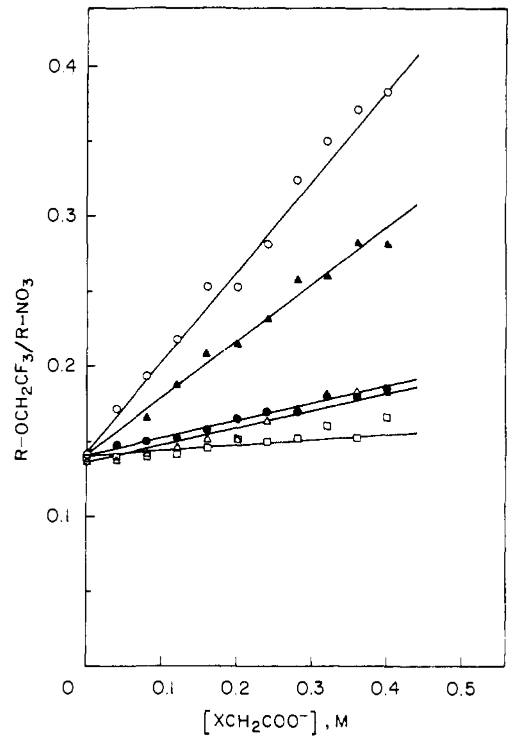

Figure 1. General-base catalysis by carboxylate anions of the reaction between trifluoroethanol and [4-(trifluoromethyl)benzyl]methyl(4-nitrophenyl)sulfonium tetrafluoroborate, **1**, at 40 °C in 50% aqueous trifluoroethanol (v/v), 0.1 M in $NaNO_3$ at ionic strength 0.5 M ($NaClO_4$). The *y* axis gives the ratio of trifluoroethyl ether and nitrate products. The bases are as follows: CH_3COO^- (○), $CH_3OCH_2COO^-$ (▲), $NCCH_2COO^-$ (△), F_2CHCOO^- (●), CF_3COO^- (□). The buffer ratios were B/A = 4.0 except for CF_2CHCOO^- and CF_3COO^-, which were present as the anion.

by acetate and methoxyacetate ions and a small amount of catalysis by cyanoacetate and difluoroacetate; however, the slopes for these weaker bases are small and give unreliable rate constants. Similar experiments with cacodylate buffers gave slopes of 1.4 and 1.1 with buffer ratios of B/A = 4 and 1.1, respectively; trifluoroethylamine buffers gave a slope of 2.0 ($B/BH^+ = 3$). The constant value of the intercept at different pH values shows that there is no significant reaction of trifluoroethoxide anion under the conditions of these experiments. The nitrate derivative was shown to be stable under the conditions of the experiments.

Rate constants for general base catalysis by buffer bases of the reaction with trifluoroethanol were calculated from the dependence of the product ratio on base concentration and the known values of k_{TFE} and k_{NO_3}, according to eq 1. The results are summarized in Table I.

$$[R\text{-}OTFE]/[R\text{-}NO_3] = (k_{TFE} + k_B[TFE][B^-])/(k_{NO_3}[NO_3^-]) \quad (1)$$

Figure 2 shows that there is no catalysis by acetate of the reaction with water in 1:1 TFE/H_2O (solid circles) or with ethanol in 50:33:17 H_2O/TFE/EtOH (triangles) with a buffer ratio of B/A = 0.33. There is actually a small decrease in the yield of the ethyl ether product with increasing buffer concentration, although the catalysis of the reaction with trifluoroethanol was the same as in 1:1 TFE/H_2O. The second-order rate constant for the reaction with ethanol is 10^{-5} M^{-1} s^{-1}. It was shown that the acetate product resulting from nucleophilic attack of acetate anion on **1** is stable under the conditions of this experiment. An increase in the $[R\text{-}OH]/[R\text{-}NO_3]$ ratio was observed with increasing concentrations of trifluoroethylamine buffer, which corresponds to a value of $k_B = 3.8 \times 10^{-6}$ M^{-2} s^{-1} for catalysis of hydrolysis.

There is no detectable catalysis of the reaction of trifluoroethanol with 4-(trifluoromethyl)benzyl bromide, as shown by the open circles in Figure 2.

Table I. Rate Constants for General-Base Catalysis of the Reaction of Trifluoroethanol with [4-(Trifluoromethyl)benzyl]methyl(4-nitrophenyl)sulfonium Tetrafluoroborate[a]

base	pK_a[b]	buffer ratio (B/A)	10^7k_B, M^{-2} s^{-1}
$CH_3CO_2^-$	4.46 (4.6)	4.0	8.9
		0.33	7.0
$CH_3OCH_2COO^-$	3.25 (3.33)	4.0	5.5
$NCCH_2COO^-$	2.06 (2.23)	4.0	1.6
F_2CHCOO^-	0.79 (1.05)	100% base[c]	1.8
CF_3COO^-	0 (0.23)	100% base	0.6
$(CH_3)_2AsO_2^-$	5.79 (6.16)	4.0	20
		1.0	16
$CF_3CH_2NH_2$	4.38 (5.7)	3.0	29
H_2O	(−1.74)		0.07[d]

[a] In 50:50 trifluoroethanol/water (v/v) at 40 °C in 0.1 M $NaNO_3$ and ionic strength 0.5 M ($NaClO_4$). [b] Determined in 50% aqueous trifluoroethanol at 25 °C and ionic strength 0.5 M as described in the Experimental Section. The pK_a values in water at 25 °C and ionic strength 1.0 M[20] are given in parentheses. [c] In methoxyacetate–methoxyacetic acid buffer with B/A = 0.02/0.005. [d] Obtained by dividing the pseudo-first-order rate constant for the reaction of trifluoroethanol by [TFE] and [HOH].

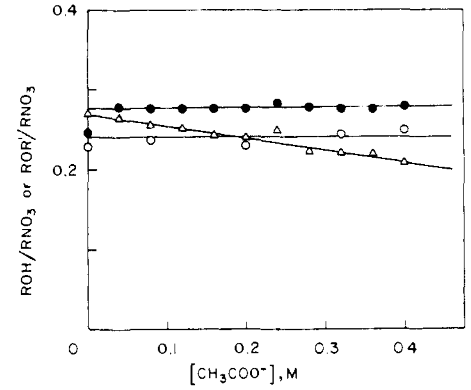

Figure 2. The dependence on $[CH_3COO^-]$ of the yield of ROH (●) and ROEt (△) from the reaction of water (B/A = 0.33; 1:1 HOH/TFE) and ethanol (B/A = 4.0; 50:33:17 HOH/TFE/EtOH) with **1** at 40 °C, ionic strength 0.5 M ($NaClO_4$). The open circles show the yield of R-OTFE product for the reaction of 4-(trifluoromethyl)benzyl bromide under the same conditions as for **1** (B/A = 4.0).

The fact that trifluoroethylamine, an uncharged base, is a slightly more effective catalyst than anionic oxygen bases of comparable pK_a shows that the catalysis does not represent an electrostatic interaction of the anions with the cationic substrate or a salt-induced medium effect.[21] The small decrease in the catalytic constants for acetate and cacodylate ions as the fraction of acid in the buffer increases (Table I) may represent a medium effect or hydrogen bonding of the acid to the catalyzing base. In one experiment the addition of 0.5 M acetamide was found to have no effect on the $[R\text{-}OTFE]/[R\text{-}NO_3]$ ratio in the absence of added salt.

There is no detectable solvent deuterium isotope effect on the acetate-catalyzed reaction of trifluoroethanol. Experiments with an acetic acid–acetate buffer (B/A = 4), in which 89% of the exchangeable solvent hydrons were deuterium, gave slopes of 0.59 and 0.61 in plots of $[R\text{-}OTFE][R\text{-}NO_3]$ against $[B^-]$ and a rate constant for acetate of $k_B = 8.7 \times 10^{-7}$ M^{-2} s^{-1}. This rate constant does not differ significantly from the value of 8.9×10^{-7} M^{-2} s^{-1} for the reaction in H_2O (Table I).

Similar experiments showed an increase in the reaction of trifluoroethanol with 4-nitrobenzyl bromide in the presence of substituted acetate anions, similar to that observed with **1**. However, the data were not reproducible and showed scatter with

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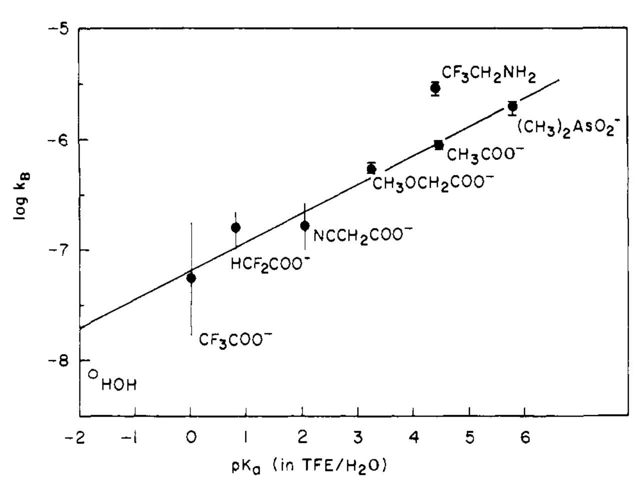


Figure 3. Brønsted plot for general-base catalysis of the reaction of trifluoroethanol with [4-(trifluoromethyl)benzyl]methyl(4-nitrophenyl)-sulfonium tetrafluoroborate in 50% aqueous trifluoroethanol at 40 °C and ionic strength 0.5 M ($NaClO_4$).

increasing buffer concentrations. It was found that exposure to sunlight of a solution of 4-nitrobenzyl bromide in 50% aqueous trifluoroethanol with 0.5 M $NaClO_4$ at room temperature greatly increased the rate of 4-nitrobenzyl bromide disappearance and the yield of trifluoroethyl ether product. In some of the reactions with this compound an additional peak was detected by HPLC that coeluted with 4-nitrobenzaldehyde.

Compounds of this class are known to undergo radical S_NR1 substitution reactions.[22,23] The 4-nitrobenzaldehyde may be formed from the reaction of 4-nitrobenzyl radical with oxygen to give 4-nitrobenzyl hydroperoxide,[23] which decomposes to 4-nitrobenzaldehyde.[24] It was shown that **1** and 4-(trifluoromethyl)benzyl bromide in 50% aqueous trifluoroethanol at ionic strength 0.5 M ($NaClO_4$) are stable for 72 h when exposed to sunlight at room temperature and that identical product yields were obtained from **1** in the presence and absence of light.

Discussion

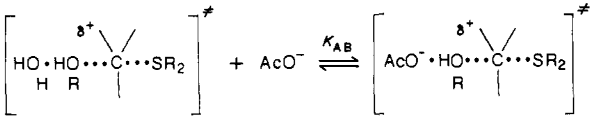
The observed catalysis of the reaction of trifluoroethanol with **1** by anionic and uncharged buffer bases has most of the characteristics that are expected for classical general base catalysis of the reactions of hydroxylic nucleophiles. The Brønsted plot shown in Figure 3 is consistent with a slope of $\beta = 0.26$ for anionic catalysts, which is similar to the Brøsted slopes reported previously for base catalysis of intramolecular substitution reactions with less acidic hydroxyl groups.[11,14,25]

Trifluoroethylamine, an uncharged base, falls significantly above the line. The rate constant for water is below the line, but this may not be significant in view of the uncertainty of the rate constant for weakly basic catalysts.

The absence of significant general base catalysis of the reactions with ethanol reflects the characteristic decrease in the Brønsted β value and the amount of catalysis that is observed with decreasing acidity of the nucleophilic reagent in reactions of hydroxylic nucleophiles.[7,8,17] This decrease may be described by a positive value of the interaction coefficient, $p_{xy'} = \partial\beta/-\partial \mathrm{p}K_{\mathrm{nuc}} = \partial\beta_{\mathrm{nuc}}/-\partial \mathrm{p}K_{\mathrm{BH}}$.[17] The Brønsted slope for catalysis of the reaction with trifluoroethanol and an estimated upper limit of $\beta \leq 0.14$ for ethanol give a value of $p_{xy'} \geq 0.05$.[26]

There is no detectable solvent deuterium isotope effect on the reaction; the rate constants for catalysis by acetate ion in H_2O and D_2O correspond to a value of $k_{\mathrm{HOH}}/k_{\mathrm{DOD}} = 1.0 \pm 0.2$. Similar small or insignificant solvent isotope effects have been observed previously for general base catalysis of the ring closure of 4-chlorobutanol[10] and other intramolecular nucleophilic reactions.[14,15] These small isotope effects suggest that the proton has not lost a significant amount of zero-point energy as a consequence of being "in flight" in the transition state; it appears that the catalysis involves a modest stabilization of the transition state by hydrogen bonding to the buffer base. This is consistent with the suggestion of Swain, Kuhn, and Schowen that the proton is in a potential well in the transition state and that catalysis arises by hydrogen bonding, or "solvation", with a base catalyst.[11] There is evidence from Brønsted coefficients and interaction coefficients for similar catalysis by hydrogen bonding for the attack of alcohols on substituted 1-phenylethyl carbocations.[7]

However, hydrogen bonding alone does not account for the observed catalysis. The amount of stabilization of the transition state by acetate anion compared with water is given by the equilibrium constant K_{AB} for formation of the hydrogen-bonded complex of the transition state with acetate (eq 2). This equilibrium constant is related to the pK_a of the transition state, pK_{AH}, and the base catalyst, pK_{BH}, by eq 3,



(2)

$$\log K_{\mathrm{AB}} = 0.013\,(\mathrm{p}K_{\mathrm{AH}} - \mathrm{p}K_{\mathrm{HOH}})(\mathrm{p}K_{\mathrm{H_3O^+}} - \mathrm{p}K_{\mathrm{BH}}) - 1.74 \quad (3)$$

as described by Hine.[27] The observed catalysis by acetate compared with water corresponds to $K_{\mathrm{AB}} = 4.6\ \mathrm{M}^{-1}$, which would require that the pK_a of the transition state be −13 if the catalysis arose only from hydrogen bonding. This pK_a value is far below any reasonable estimate of the acidity of the transition state.

We conclude that the catalysis must involve more than simple hydrogen bonding and "solvation". Partial removal of the proton by hydrogen bonding to the catalyst may increase the charge density on the attacking alcohol and give rise to stronger O··C bonding that stabilizes the transition state. The observation that the α-secondary deuterium isotope effects for intramolecular displacement reactions decrease and, presumably, the amount of bond formation to carbon increases with an increase in the pK of the base catalyst[5,28] is consistent with this hypothesis. It is also possible that the catalyst plays a more active role in facilitating the proton transfer process than is expected from simple hydrogen bonding. There is evidence from several criteria that in addition reactions of hydroxylic nucleophiles to sp^2 carbon the reaction becomes concerted, with an active role for proton transfer to the catalyst in the transition state, as the base catalyst becomes stronger and the electrophile becomes less reactive.[9,17,29] A concerted, coupled mechanism is not excluded for the reaction of **1** because isotope effects may also be decreased by coupling of the motions of the proton and heavy atoms in the transition state.[30]

General-base catalysis was observed only for the sulfonium compound, with a sulfur leaving group; there is no significant catalysis of the reaction of trifluoroethanol with 4-(trifluoromethyl)benzyl bromide. This may be attributed to a larger amount of bond formation to the nucleophilic reagent in the transition state with the sulfur leaving group, which results in a larger development of positive charge on the attacking hydroxyl group

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[26] The calculation was made assuming a 10% increase in the reaction with ethanol with 0.4 M acetate. A value of $\beta = 0.34$ for catalysis by water and acetate of the reactions with trifluoroethanol was used for the comparison.

[27] Hine, J. *J. Am. Chem. Soc.* **1972**, *94*, 5766–5771. Stahl, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4196–4205. In eq 3, log 55 = 1.74 is the concentration of H_2O protons in 50% trifluoroethanol–water (v/v). No account is taken of the low pK_a of trifluoroethanol, which will favor hydrogen bonding of acetate ion to the solvent and make hydrogen bonding to the transition state even less favorable.

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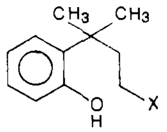
and a larger advantage from partial proton transfer to the catalyzing base. Similar behavior has been observed for the intramolecular ring closure of **2**, which shows general base catalysis



2

when the leaving group is methyl 4-nitrophenyl sulfide[16] but not with $^-OSO_2CH_3$, $^-OPO(OEt)_2$, or $^-OOCCCl_3$ as leaving groups.[16,31] There is precedent for a relatively large amount of nucleophilic participation in the transition state for reactions of sulfonium compounds in the observed second-order reaction of azide with [1-(4-methylphenyl)ethyl]dimethylsulfonium ion; there is no detectable reaction of this compound with azide when chloride or pentafluorobenzoate is the leaving group.[19]

Catalysis of Bimolecular and Intramolecular Reactions. General-base catalysis of intramolecular substitution reactions has been observed for the attack of weakly acidic aliphatic alcohols, as well as phenolic hydroxyl groups,[11-15,25] but is observed only with an acidic alcohol, trifluoroethanol, in bimolecular substitution. It is not immediately obvious what structural features are responsible for the enhanced catalysis of the intramolecular reactions; there is no significant catalysis of the bimolecular reaction with ethanol. The product of an intramolecular reaction that gives a five-membered ring is a tetrahydrofuran derivative, and tetrahydrofuran is more basic than aliphatic ethers.[32] This suggests that intramolecularity is not likely to increase the acidity of the transition state simply as a consequence of ring formation. However, the fact that catalysis is observed in the intramolecular reaction suggests that the transition state is, in fact, more acidic than that of the bimolecular substitution reactions. It appears that the geometric constraints of the intramolecular reaction give a transition state that has a relatively large amount of bond formation and development of positive charge on the oxygen atom, so that it is sufficiently acidic to be stabilized by interaction with a catalyzing base.

The maximum advantage for an intramolecular reaction occurs when the corresponding bimolecular reaction has a large negative $\Delta S^{\ddagger}$ that reflects a high degree of order in the transition-state structure.[3,33,34] A large negative $\Delta S^{\ddagger}$ is found for transition states that have a large amount of bond formation and, therefore, low entropy in the transition state; loose bonds have low-frequency vibrations and a correspondingly larger entropy. Consequently, there is a tendency for favorable intramolecular reactions to have a relatively large amount of bond formation in the transition state. In particular, intramolecular reactions of hydroxylic nucleophiles are likely to have late transition states with a large amount of charge development and acidity of the OH group, which will be stabilized by interaction of a buffer base with the acidic proton.

The amount of variation in the structure of the transition state for a bimolecular reaction is reflected in the entropy of activation; a negative $\Delta S^{\ddagger}$ represents a reaction coordinate that passes through a narrow col on the reaction surface, while a less negative or positive $\Delta S^{\ddagger}$ represents a broad barrier that can be crossed with many slightly different geometries. Since a favorable intramolecular reaction has a restricted geometry, with a low entropy, a low $\Delta H^{\ddagger}$, and a relatively large amount of bond formation and acidity of the OH group in the transition state, it is likely to have a larger advantage from buffer catalysis than the comparable bimolecular reaction.

The same situation may apply to enzyme catalysis. Catalysis will be favored when the transition state is sufficiently acidic to provide stabilization by a base in the active site, so that natural selection will favor enzyme catalysis that occurs through transition states with a large amount of bond formation. The very small secondary α-deuterium isotope effect for the displacement reaction catalyzed by catechol *O*-methyltransferase is consistent with a large amount of bond formation to the hydroxyl group in the transition state.[5,6] This has been interpreted as evidence for catalysis by physical compression of the transition state at the active site;[6] however, base catalysis may favor a tight transition state and provide an additional, or alternative, reason for this result.

When the basicity of the catalyst is increased there will also be a greater advantage from interaction with transition states that have more bond formation and acidity of the OH group, so that such transition states will be favored. This is consistent with the observed increased tightness of the transition state with increasing basicity of the catalyzing base in intramolecular displacement reactions, as indicated by a decrease in the α-secondary deuterium isotope effect.[5,28] These changes in transition-state structure can also be described as movements of the transition state perpendicular to the reaction coordinate in such a way as to take advantage of a structural change that stabilizes the transition state.[35]

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