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Hydrogen Bonding and Catalysis of Solvolysis of 4-Methoxybenzyl Fluoride

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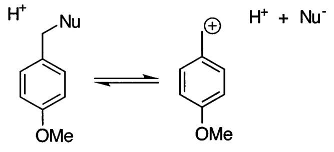
Abstract: Values of $k_o = 8.0 \times 10^{-3}$ s^{-1} and $k_H = 2.5 \times 10^{-2}$ M^{-1} s^{-1}, respectively, were determined for the spontaneous and the acid-catalyzed cleavage of 4-methoxybenzyl fluoride (**1-F**) to form the 4-methoxybenzyl carbocation (**1**$^+$). Values of $k_F = 1.8 \times 10^7$ M^{-1} s^{-1} and $k_{HF} = 7.2 \times 10^4$ M^{-1} s^{-1} were determined for addition of F$^-$ and HF to **1**$^+$ for reaction in the microscopic reverse direction. Evidence is presented that the reversible addition of HF to **1**$^+$ to give **1-F** + H$^+$ proceeds by a concerted reaction mechanism. The relatively small 250-fold difference between the reactivities of fluoride ion and neutral HF toward **1**$^+$ is attributed to the tendency of the strong aqueous solvation of F$^-$ to decrease its nucleophilic reactivity and to the advantage for the concerted compared with the usual stepwise pathway for addition of HF. There is no significant stabilization of the transition state for cleavage of **1-F** from general acid catalysis by 0.80 M cyanoacetate buffer at pH 1.7. The estimated 3 kcal/mol larger Marcus intrinsic barrier for heterolytic cleavage of **1-F** than for cleavage of **1-Cl** is attributed to a *lag* in the development at the transition state of the ca. 30 kcal/mol greater stabilizing solvation of the product ion F$^-$ compared with Cl$^-$. The decrease in the electronegativity of X along the series X = F, OH, Cl is accompanied by a ca. 10^{10}-fold increase in the carbon basicity compared with the proton basicity of X$^-$.

Introduction

There is much interest in the effects of hydrogen bonding on chemical reactivity[1,2] and speculation about the contribution of hydrogen bonding to the catalytic rate acceleration for enzyme catalysts.[3−5] These effects will be largest in reactions where strong hydrogen bonds are formed or cleaved, such as heterolytic C−F bond cleavage to form fluoride ion, a strong hydrogen bond acceptor.[2] The strong solvation of product fluoride ion[6] will result in an increase in the overall equilibrium constant for C−F bond cleavage, and this effect will be expressed in the rate constants for cleavage and synthesis of alkyl fluorides. Also, the transition state for the cleavage reaction can be stabilized by proton transfer from hydronium ion (specific acid catalysis) and possibly from general acids (general acid catalysis).

Scheme 1



1-Nu **1**$^+$

Nu = Cl, F, OH

Specific acid catalysis has been reported for the solvolysis in aqueous solution of simple alkyl fluorides,[7,8] benzyl fluoride,[9] triphenylmethyl fluoride,[10,11] and α-D-glucosyl fluoride.[12] However, the question of the effect of the strong solvation of fluoride ion on the chemical reactivity of alkyl fluorides has not been specifically addressed. A comparison of the reactivity toward solvolysis of alkyl fluorides and related compounds with leaving groups that form substantially weaker hydrogen bonds to solvent than does fluoride ion should provide interesting insight into the effects of hydrogen bonding on the rate of C−X bond cleavage. 4-Methoxybenzyl derivatives (**1-Nu**, Scheme 1) are an attractive candidate for this study because these compounds are sufficiently soluble and reactive for a room-temperature study in aqueous solution, where the solvation of fluoride ion is particularly strong.[6] Several 4-methoxybenzyl derivatives (**1-Nu**) have been shown to react by concurrent concerted (A_ND_N) and stepwise ($D_N + A_N$) reaction mechanisms[13] through the 4-methoxybenzyl carbocation intermediate (**1**$^+$) of known lifetime,[14−16] and the mechanism for reaction of 4-methoxy-

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benzyl chloride has been particularly well characterized.[14] It is also possible to determine the rate constant for reaction in the microscopic direction of the addition of halide ion to $\mathbf{1}^+$, the equilibrium constant for heterolytic bond cleavage,[17,18] and the corresponding rate and equilibrium constants for the acid-catalyzed cleavage of **1-Nu** (Scheme 1).[19,20]

We report here pL-rate profiles for heterolytic cleavage of **1-F** in H_2O and D_2O, the failure to observe general acid catalysis of this reaction, absolute rate constants for the addition of F^- and HF to the 4-methoxybenzyl carbocation ($\mathbf{1}^+$), and the effect of protonation of the fluoride leaving group on the mechanism for heterolytic C−F bond cleavage. A comparison with the corresponding data for cleavage of **1-Cl** allows an evaluation of certain aspects of the effect of hydrogen bonding on the rate and equilibrium constants and mechanism for heterolytic cleavage of the carbon−fluorine bond at **1-F** in water.

Experimental Section

4-Methoxybenzyl fluoride (**1-F**) was prepared by a literature procedure.[21] 4-Methoxybenzyl chloride (**1-Cl**) was purchased from Aldrich and was distilled before use. A 1 M solution of LiCl was prepared by neutralization of 1 M LiOH with HCl. All other organic and inorganic chemicals were reagent grade and were used without further purification. Deuterium oxide (99.9% D) was purchased from Cambridge Isotope Laboratories.

Product Studies. Product studies were carried out at 25 °C and $I = 1.0$ (KCl). The products of the reactions of **1-Cl** and **1-F** were separated and quantified by HPLC as described previously,[14,22,23] except that peak detection was by a Waters 996 diode array detector. The products were detected by their UV absorbance at 273 nm, which is λ_{max} for the solvent adduct **1-OH**. The ratio of the rate constants for reaction of **1-F** ([S] = 0.1−0.2 mM) with solvent and azide ion in water was determined from the ratio of the yields of **1-OH** and $\mathbf{1\text{-}N_3}$ as described in an earlier study of the solvolysis of **1-Cl**.[14] The azide ion adduct $\mathbf{1\text{-}N_3}$ was characterized in earlier studies of nucleophilic substitution reactions at **1-X**.[14,15b] This compound is stable to HPLC analysis: the halftime for its solvolysis in 50/50 (v/v) trifluoroethanol/water is ca. 10^9-fold longer than that (1 s) for solvolysis of **1-Cl**.[24] A value of $\epsilon_{\mathbf{1-OH}}/\epsilon_{\mathbf{1-F}} = 1.14$ for the ratio of the extinction coefficients of **1-OH** and **1-F** at 273 nm was determined from the ratio of the observed peak areas from HPLC analyses of solutions that contained known concentrations of **1-OH** and **1-F**.

The product rate constant ratio k_F/k_s (M^{-1}) for reaction of fluoride ion and solvent water with **1-Cl** was determined from the ratio of peak areas $(A_{\mathbf{1-F}})_o/(A_{\mathbf{1-OH}})_o$ for the products **1-F** and **1-OH** formed from reaction of **1-Cl** in the presence of 1 M KF and the extinction coefficient ratio $\epsilon_{\mathbf{1-OH}}/\epsilon_{\mathbf{1-F}} = 1.14$.[23] The halftime for solvolysis of **1-Cl** in water is ca. 0.2 s.[24a] This reaction was initiated by making a 100-fold dilution of a solution of **1-Cl** in acetonitrile into water containing 1 M KF to give a final substrate concentration of 0.04 mM, with vigorous agitation on a vortex mixer. The product of nucleophilic substitution of fluoride ion, **1-F**, undergoes solvolysis to give **1-OH** with a halftime of 110 s during the ca. 30 s required to prepare the sample for HPLC analysis. The areas of the peaks for the products **1-F** [$(A_{\mathbf{1-F}})_t$] and **1-OH** [$(A_{\mathbf{1-OH}})_t$] were obtained by HPLC analysis, and the initial areas $(A_{\mathbf{1-F}})_o$ and $(A_{\mathbf{1-OH}})_o$ of these peaks before decay of **1-F** were estimated using eqs 1 and 2, where $k_{obsd} = 6.6 \times 10^{-3}$ s^{-1} is the first-order rate constant for solvolysis of **1-F** in water that contains 1 M KF, $t \approx 30$ s (±1 s) is the time between initiation of the reaction of **1-Cl** and HPLC product analysis, and 1.14 is the ratio of the extinction coefficients of **1-OH** and **1-F** at 273 nm. The difference between the observed [$(A_{\mathbf{1-F}})_t$ and $(A_{\mathbf{1-OH}})_t$] and corrected [$(A_{\mathbf{1-F}})_o$ and $(A_{\mathbf{1-OH}})_o$] peak areas was less than 20%.

$$\ln(A_{\mathbf{1-F}})_o = \ln(A_{\mathbf{1-F}})_t + k_{obsd}t \qquad (1)$$

$$(A_{\mathbf{1-OH}})_o = (A_{\mathbf{1-OH}})_t - 1.14\{(A_{\mathbf{1-F}})_o - (A_{\mathbf{1-F}})_t\} \qquad (2)$$

Kinetic Studies. The reactions of **1-F** were initiated by making a 100-fold dilution of a 0.01−0.02 M solution of substrate in acetonitrile into an aqueous solution at 25 °C and $I = 1.0$ (KCl). The reaction progress was monitored spectrophotometrically by following the change in absorbance at 235 or 282 nm. Pseudo-first-order rate constants (k_{obsd}, s^{-1}) were determined from the slope of semilogarithmic plots of reaction progress against time, which were linear for at least 3 halftimes. The rate constants were reproducible to ±5%.

Results

Values of $k_o = 8.0 \times 10^{-3}$ and 7.3×10^{-3} s^{-1} for the spontaneous solvolysis of **1-F** in H_2O and D_2O, respectively, at 25 °C and $I = 1.0$ (KCl) were determined as the observed first-order rate constants for reaction in the presence of 0.1 M acetate buffer ([B]/[BL$^+$] = 1.0). The value of k_o in H_2O at $I = 1.0$ (KCl) determined here is identical with that determined earlier in the presence of 0.1 M NaOH at $I = 0.2$ ($NaClO_4$).[24a]

Specific salt effects on the solvolysis of **1-F** causes k_o to vary from 8.0×10^{-3} s^{-1} at $I = 1.0$ (KCl) to 9.3×10^{-3} and 1.3×10^{-2} s^{-1}, respectively, for reactions in the presence of 1.0 M NaCl and LiCl at neutral pH. We attribute the larger 4-fold increase to $k_{obsd} = 3.3 \times 10^{-2}$ s^{-1} observed for reaction in the presence of 1.0 HCl largely or entirely to specific acid catalysis of the solvolysis of **1-F**. Values of $k_H = 0.025$ M^{-1} s^{-1} and $k_D = 0.023$ M^{-1} s^{-1} for acid-catalyzed cleavage of **1-F** in H_2O and D_2O, respectively, at 25 °C and $I = 1.0$ (KCl) were determined as the slope of plots of k_{obsd} (s^{-1}) against [H$^+$] or [D$^+$] (0.01−1.0 M). The fit of the experimental data to the logarithmic form of eq 3, obtained using these kinetic parameters, is shown in Figure 1 (●, H_2O; ▲, D_2O).

$$k_{obsd} = k_o + k_L[L^+] \qquad (3)$$

The value of $k_{obsd} = 7.8 \times 10^{-3}$ s^{-1} determined for reaction of **1-F** in the presence of 0.80 M cyanoacetate buffer at pH 1.7 ([BH$^+$]/[B] = 4) and $I = 1.0$ (KCl) is 10% smaller than $k_{obsd} = 8.6 \times 10^{-3}$ s^{-1}, which can be calculated for reaction in the absence of buffer at pH 1.7 using eq 3 and the experimental values of k_o and k_H. There is a 20% decrease in k_{obsd} for solvolysis of **1-F** as the concentration of added fluoride ion is increased from zero to 1.0 M at a constant ionic strength of 1.0 (KCl). The product rate constant ratio for reaction of **1-Cl** with fluoride ion and solvent water, determined from the ratio of the yields of **1-F** and **1-OH** from reaction of **1-Cl** in the presence of 1.0 M KF, is $k_F/k_s = 0.070$ M^{-1}. The value of k_{obsd} (s^{-1}) for the spontaneous solvolysis of **1-F** in water at $I = 1.0$ (KCl) remains constant as the concentration of azide ion is increased

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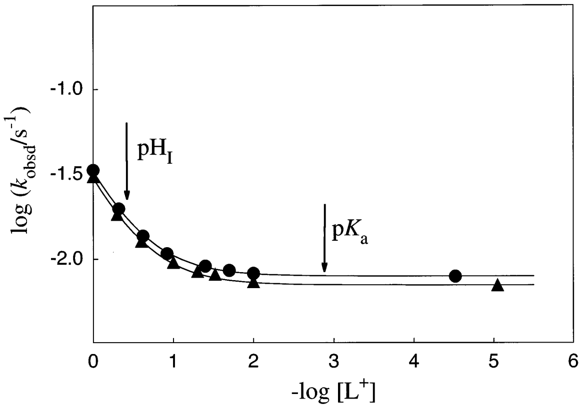


Figure 1. Dependence of log k_{obsd} (s^{-1}) for the solvolysis of **1-F** in H_2O (●) and D_2O (▲) at 25 °C and $I = 1.0$ (KCl) on $-\log$ [L$^+$]. The values of $-\log [H^+] = 4.52$ and $-\log [D^+] = 5.05$ were calculated from the measured values of pH = 4.58 and pD = 5.11 and the relationship $pL = -\log\{\gamma[L^+]\}$, where $\gamma = 0.87$ is the apparent activity coefficient of hydronium ion determined for the electrode under our experimental conditions ($I = 1.0$, KCl). The labels show (1) $-\log [H^+] = pK_a$ for HF (2.9) and (2) $-\log [H^+] = pH_I = 0.49$, where identical first-order rate constants are observed for the spontaneous and specific-acid-catalyzed reactions of **1-F**.

from zero to 0.10 M at a constant ionic strength of 1.0 (KCl). The product rate constant ratio $k_{az}/k_s = 20$ M^{-1} (±10%) for reaction of **1-F** with azide ion and solvent water is the average of the rate constant ratios determined at five different concentrations of azide ion between zero and 0.1 M.

Discussion

Reaction Mechanism. The observed first-order rate constant for reaction of **1-F** in unbuffered solution remains constant as the concentration of azide ion is increased from zero to 0.1 M at 25 °C ($I = 1.0$, KCl): these reactions give up to a 67% yield of the azide ion adduct **1-N$_3$**. This result shows that, in water, **1-F** reacts with nucleophiles by the same stepwise $D_N + A_N$ (S_N1)[13] mechanism through the 4-methoxybenzyl carbocation **1**$^+$ that is observed for other 4-methoxybenzyl derivatives (Scheme 2).[14] Competing stepwise and concerted nucleophilic substitution by azide ion has been reported for **1-Cl**[14] and **1-SR$_2$**$^{+}$ [15,16] under some reaction conditions. However, we observe no significant bimolecular substitution reaction of **1-F** with azide ion in water.

The value of $k_{az}/k_s = 20$ M^{-1} for partitioning of **1**$^+$ between addition of azide ion and solvent in water ($I = 1.0$, KCl) (Scheme 2) is similar to the value of $k_{az}/k_s = 25$ M^{-1} for partitioning of **1**$^+$ in 50/50 (v/v) water/trifluoroethanol ($I = 0.50$, $NaClO_4$) determined in earlier work.[14]

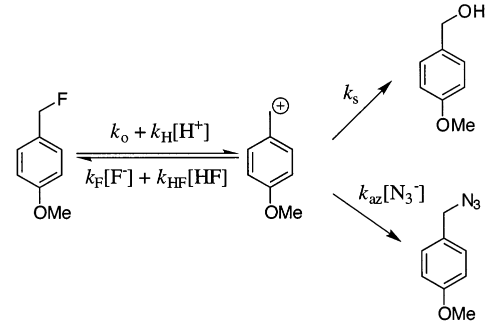
$$\frac{k_F}{k_{HF}} = \frac{k_o}{k_H K_a} \tag{4}$$

$$pH_I = pK_a - \log\left(\frac{k_F}{k_{HF}}\right) \tag{5}$$

It has been reported in earlier work that the effect of similar changes in solvent and salt on k_{az}/k_s (M^{-1}) for partitioning of the 1-(4-methoxyphenyl)ethyl carbocation is ~2-fold.[23]

The 20% decrease in k_{obsd} for solvolysis of **1-F** in water as the concentration of added fluoride ion is increased from zero to 1.0 M at $I = 1.0$ (KCl) shows that there is little common ion inhibition of the solvolysis of **1-F** in water. Therefore, there can be little trapping of the 4-methoxybenzyl carbocation intermediate **1**$^+$ by fluoride ion in water. The product rate constant ratio $k_F/k_s = 0.070$ M^{-1} for reaction of **1**$^+$ with fluoride ion and solvent water, determined from the low yield of **1-F** from the reaction of **1-Cl** in the presence of 1.0 M fluoride ion, shows that about 35% of the small observed effect of fluoride ion on k_{obsd} for **1-F** is due to common ion inhibition; we attribute the remainder of this effect to a specific fluoride ion salt effect on k_{obsd}.

Scheme 2



The reaction of azide ion with **1**$^+$ is diffusion-limited with $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}, so that this reaction can be used as a "clock" to determine absolute rate constants for addition of other nucleophiles to **1**$^+$.[18,25−27] Combining the values of $k_{az}/k_s = 20$ M^{-1} and $k_F/k_s = 0.070$ M^{-1} with $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} gives absolute rate constants $k_s = 2.5 \times 10^8$ s^{-1} and $k_F = 1.8 \times 10^7$ M^{-1} s^{-1} (Table 1) for addition of water and fluoride ion, respectively, to **1**$^+$.

pL-Rate Profiles for Cleavage of 1-F. The pL-rate profiles for cleavage of **1-F** in Figure 1 show the relative rates of the spontaneous (k_o) and specific-acid-catalyzed (k_H) cleavage reactions of **1-F** to form the carbocation intermediate **1**$^+$. It is less well recognized that such pH-rate profiles also define the relative rates of the "uncatalyzed" and "hydrogen-ion-catalyzed" reactions in the microscopic reaction, which in this case correspond to the addition of F$^-$ (k_F) and HF (k_{HF}) to the 4-methoxybenzyl carbocation (Scheme 3).

The *shape* of the pL-rate profiles in Figure 1 is defined by the value of $-\log[L^+]$, at which identical first-order rate constants are observed for the uncatalyzed and acid-catalyzed reactions of **1-F**, $-\log[H^+]_I = pH_I$.[19] Equation 5 gives the relationship between pH$_I$, the pK_a of the conjugate acid of the leaving group anion, and the rate constant ratio $\log(k_F/k_{HF})$ for the reaction of the carbocation intermediate **1**$^+$ with F$^-$ and HF. Equation 5 follows from eq 4, derived for Scheme 3, and the relationship $k_H[H^+]_I = k_o$, which holds when the reaction is conducted at pH$_I$.[19] Equation 5 shows that the shape of the pL-rate profiles for the stepwise solvolysis of **1-F** is *controlled* by the rate constant ratio for partitioning of the reaction intermediate, $\log(k_F/k_{HF})$, and the pK_a of the conjugate acid of the fluoride leaving group (HF). The maximum possible pH$_I$ when the leaving group is fluoride ion is the pK_a of 2.9 for HF:[28a] at this maximum, $\log(k_F/k_{HF}) = 0$ (eq 5), and there is no selectivity for the addition of fluoride ion and neutral HF to **1**$^+$. Values of

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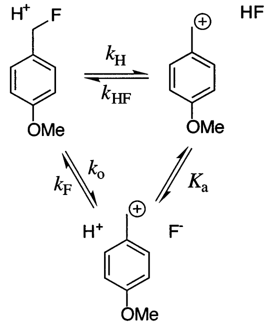
Table 1. Rate and Equilibrium Constants for Reactions of 4-Methoxybenzyl Derivatives in Water at 25 °C

Nu^- (pK_a)	k_{Nu}[a] ($M^{-1} s^{-1}$)	k_o[b] (s^{-1})	K_{Nu} (M^{-1})[c] ($\log K_{Nu}$)	k_{HNu}[d] ($M^{-1} s^{-1}$)	k_H[e] ($M^{-1} s^{-1}$)	$\log K_T$[f]	$\log K_X$[g]
F^- (2.9)	1.8×10^{7}[h]	8.0×10^{-3}[h]	2.3×10^{9} (9.4)	7.2×10^{4}[h]	2.5×10^{-2}[h]	6.5	0
Cl^- (−8)	2×10^{9}[i]	4[j]	5.0×10^{8} (8.7)			16.7[k]	10.2
HO^- (15.7)			2×10^{26}[k] (26.3)	4.5×10^{6}[h]	1.1×10^{-4}[l]	10.6	4.1

[a] Second-order rate constant for addition of the anionic nucleophile Nu^- to $\mathbf{1}^+$. [b] First-order rate constant for heterolytic cleavage of **1-Nu** to give $\mathbf{1}^+$ and $\mathbf{Nu}^-$. [c] Equilibrium constant for addition of the anionic nucleophile Nu^- to $\mathbf{1}^+$, calculated as $K_{Nu} = k_{Nu}/k_o$, unless noted otherwise (Scheme 7). [d] Second-order rate constant for addition of the protonated nucleophile HNu to $\mathbf{1}^+$. [e] Second-order rate constant for acid-catalyzed cleavage of **1-Nu** to give $\mathbf{1}^+$ and **HNu**. [f] Equilibrium constant for transfer of Nu^- from the proton to $\mathbf{1}^+$, calculated as $K_T = k_{HNu}/k_H$, unless noted otherwise (Scheme 7). [g] Equilibrium constant for the isodesmic exchange of Nu^- and F^- between the proton and $\mathbf{1}^+$ (Scheme 8). [h] Data from this work at $I = 1.0$ (KCl). [i] In 50/50 (v/v) water/trifluoroethanol at $I = 0.50$ ($NaClO_4$) [ref 31a]. [j] Data from ref 24a. [k] Calculated using the relationship $pK_a = \log K_{Nu} - \log K_T$ (Scheme 7). [l] Ref 59.

Scheme 3



$pH_I > pK_a$ are not expected, because this would require $\log(k_F/k_{HF}) < 0$ and a greater nucleophilic reactivity of HF than of the more basic fluoride ion toward $\mathbf{1}^+$.

Identical first-order rate constants are observed for the uncatalyzed and the specific-acid-catalyzed cleavage of **1-F** in H_2O at $pH_I = 0.49$ (Figure 1). A value of $k_F/k_{HF} = 250$ was calculated from eq 4 derived for Scheme 3, using $k_o/k_H = (0.0080\ s^{-1}/0.025\ M^{-1}\ s^{-1})$ and $K_a = 1.26 \times 10^{-3}$ M for ionization of HF.[28a] Combining this ratio with $k_F = 1.8 \times 10^7$ M^{-1} s^{-1} (Table 1) gives $k_{HF} = 7.2 \times 10^4$ M^{-1} s^{-1} for nucleophilic addition of HF to $\mathbf{1}^+$ (Table 1). Values of $pH_I = 1.8$ and 2.4, respectively, can be calculated from earlier data for the spontaneous and acid-catalyzed cleavage of benzyl fluoride in 90/10 water/acetone at 50 °C[9] and for the cleavage of triphenylmethyl fluoride in 70/30 water/acetone at 40 °C.[11] A quantitative analysis of these data using eq 5 is not possible, because of uncertainties about the effect of mixed aqueous organic solvents and the change in reaction temperature on the pK_a of HF.

Nucleophilic Reactivity of F^- and HF. There is a 3.3 kcal/mol difference in the apparent barriers for addition of anionic F^- and neutral HF to $\mathbf{1}^+$ ($k_F/k_{HF} = 250$, Table 1) for reactions at $pH = pK_a = 2.9$ for HF (Figure 2A). These apparent barriers will be equal in the limiting case where $k_{Nu} = k_{HNu}$ for reaction of anionic Nu^- and neutral HNu with $\mathbf{1}^+$, so that $\{pK_a - pH_I\} = \log(k_{Nu}/k_{HNu}) = 0$. This limit is approached for stepwise solvolysis reactions when the carbocation intermediate is very unstable and the leaving group/nucleophile anion is very reactive. For example, the value of $pK_a - pH_I = \log(k_{RS}/k_{RSH}) = 1.6$ determined for C−S bond cleavage at benzaldehyde *O*-ethyl,*S*-phenyl acetal (Scheme 4) is consistent with solvolysis through an oxocarbenium ion intermediate that shows a small selectivity between the diffusion-limited addition of thiophenoxide ion ($k_{PhS} = 5 \times 10^9$ M^{-1} s^{-1}) and the addition of neutral thiophenol ($k_{PhSH} \approx 1 \times 10^8$ M^{-1} s^{-1}).[19] At the other extreme, the rate constant ratio $k_{RS}/k_{RSH} = 2 \times 10^7$ determined for the addition of $HOCH_2CH_2S^-$ and $HOCH_2CH_2SH$ to the tris(4-methoxyphenyl)methyl carbocation corresponds to a 10.0 kcal/mol difference in the barriers to the reaction of these nucleophiles at $pH = pK_a$ for mercaptoethanol.[29]

The difference in the selectivities for addition of fluorine nucleophiles to $\mathbf{1}^+$ ($k_F/k_{HF} = 250$) and sulfur nucleophiles to the tris(4-methoxyphenyl)methyl carbocation ($k_{RS}/k_{RSH} = 2 \times 10^7$) may simply reflect a smaller nucleophilic selectivity for nucleophile addition to the more reactive carbocation $\mathbf{1}^+$. However, the magnitude of k_{Nu}/k_{HNu} for reaction of an anion and its conjugate acid in water depends on both the relative intrinsic reactivity of these nucleophiles and the attenuation of this reactivity by aqueous solvation. The strong solvation of the fluorine nucleophiles F^- and HF probably reduces the value of k_F/k_{HF} relative to k_{RS}/k_{RSH}, because of the tendency of solvation either to decrease the reactivity of fluoride ion or increase the reactivity of its conjugate acid (Figure 2A).

The strong solvation of fluoride ion in water[6] and the effect of this solvation on the nucleophilic reactivity of fluoride ion in concerted bimolecular substitution at aliphatic carbon has been extensively documented.[30] The data reported here provide evidence for a large effect of the strong aqueous solvation of fluoride ion on the reactivity of this nucleophile in carbocation addition (Figure 2A). For example, the value of $k_F = 1.8 \times 10^7$ M^{-1} s^{-1} for addition of F^- to $\mathbf{1}^+$ is ca. 100-fold *smaller* than $k_{Cl} = 2 \times 10^9$ M^{-1} s^{-1} for addition of the much more weakly basic chloride ion,[31a] and only 3-fold *larger* than $k_{HOH} = 4.5 \times 10^6$ M^{-1} s^{-1} for addition of water (Table 1).[31b] The low 7% yield of **1-F** from partitioning of $\mathbf{1}^+$ generated from reaction of

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(28) (a) The dissociation constant of HF at $I = 1.0$ (KCl) has not been reported. Values of the pK_a of HF at $I = 1.0$ ($NaClO_4$) ranging from 2.90 to 2.95 have been reported [*Stability Constants of Metal-Ion Complexes. Special Publication No. 17.*; Chemical Society: London, 1964]. A value of $pK_a = 2.82$ for ionization of HF in the presence of an unspecified electrolyte ($I = 1.0$) has been reported [Mosha, D.; Qulwi, Q.; Mhinzi, G. *J. Chem. Soc. Pak.* **1996**, 18, 96−100]. (b) Perrin, D. D. *Dissociation Constants of Inorganic Acids and Bases in Aqueous Solution*; Butterworth: London, 1969.

(29) Ritchie, C. D.; VanVerth, J. E.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1982**, *104*, 3491−3497.

(30) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1−32.

(31) (a) A value of $k_{Cl} = 2 \times 10^9$ M^{-1} s^{-1} has been reported for addition of chloride ion to $\mathbf{1}^+$ in 50/50 (v/v) trifluoroethanol/water [ref 14]. It has been shown that there is no effect of the change from this solvent to water on the rate constant $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion [refs 26 and 27]. (b) The value of $k_{HOH} = 4.5 \times 10^6$ M^{-1} s^{-1} for the second-order rate constant for addition of water to $\mathbf{1}^+$ was calculated from $k_{az}/k_s = 20$ M^{-1} for partitioning of $\mathbf{1}^+$ between addition of azide ion and water, $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion [refs 26 and 27], and the 55 M concentration of solvent water.

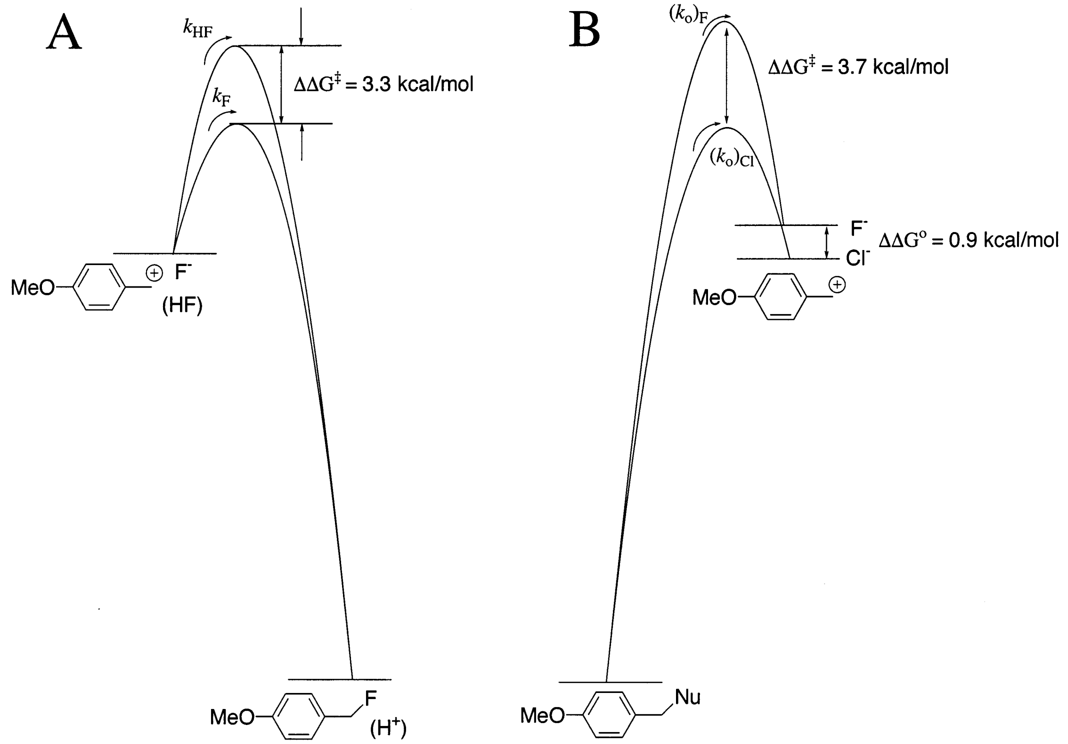
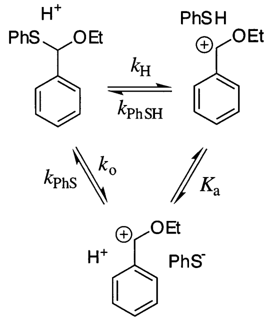


Figure 2. Free energy profiles that compare the activation barriers and changes in Gibbs free energy for the following reactions in water at 25 °C. (A) The addition of F^- and HF to the 4-methoxybenzyl carbocation $\mathbf{1}^+$ at pH = pK_a = 2.9 for HF. The arrows indicate the tendency of the strong solvation of fluoride ion and hydrofluoric acid to decrease and increase, respectively, the rate constant for their reaction with $\mathbf{1}^+$. (B) The heterolytic cleavage of **1-F** and **1-Cl** to form $\mathbf{1}^+$ and the corresponding halide ion.

Scheme 4



1-Cl in water in the presence of 1 M fluoride ion shows that the barrier to cleavage of a single hydrogen bond between F^- and water, which is required to free an electron pair at F^- in order for it to react with $\mathbf{1}^+$, is comparable to the barrier for the direct addition of 1 M water, so that the reaction of solvent dominates because of its large (55 M) concentration. It is as though the strong network of hydrogen bonds to fluoride ion has inhibited its nucleophilic addition to $\mathbf{1}^+$ by *entrapping* this anion in the surrounding solvent. The relatively large nucleophilic selectivity observed for reaction of fluoride ion with the covalent α-mannosyl intermediate of the reaction catalyzed by mutant forms of a *β*-mannosidase provides evidence that there is a large increase in the nucleophilic reactivity of fluoride ion upon its transfer from water to this enzyme catalyst.[32]

In addition, the relatively small rate constant ratio k_F/k_{HF} may reflect stabilization of the transition state for addition of neutral HF to $\mathbf{1}^+$ by partial proton transfer to a hydrogen-bonded water in a concerted pathway, which has the effect of increasing k_{HF} (see below).

By comparison, thiol anions are relatively weakly solvated in water[6] and thiols form weak hydrogen bonds to this solvent.[33] This should result in a smaller attenuation by solvation, compared with the strongly solvated fluoride ion, of the large difference in the intrinsic nucleophilic reactivity of these neutral and anionic nucleophiles.

Intrinsic Reaction Barriers. Figure 2B shows the 3.7 kcal/mol difference in the barriers to heterolytic cleavage of **1-F** ($k_o = 8.0 \times 10^{-3}$ s^{-1}) and **1-Cl** ($k_o = 4$ s^{-1})[24a] to give the common carbocation intermediate $\mathbf{1}^+$ in water. This difference in k_o is due primarily to the larger Marcus intrinsic barrier to the reaction of **1-F**,[34] since the heterolytic cleavage of **1-F** and **1-Cl** are each unfavorable by ca. 12 kcal/mol (Table 1).

The free energy of solvation of fluoride ion in water (ca. 105 kcal/mol) is much larger than that of chloride ion (ca. 75 kcal/mol)[6] and strongly favors processes such as heterolytic cleavage that generate fluoride ion as a product. By contrast, the very similar thermodynamic barrier observed for heterolytic cleavage of **1-F** and **1-Cl** in water (Figure 2B and Table 1) shows that the stronger solvation of F^- is offset by the larger carbon basicity of F^- than of Cl^-, which stabilizes the reactant **1-F** compared with **1-Cl**. The estimated Marcus intrinsic barrier to heterolytic cleavage of **1-F** is 3 kcal/mol larger than that for cleavage of **1-Cl**.[35] Similar intrinsic barriers for these cleavage reactions would be observed if the *progress* in the transition state toward heterolytic cleavage of the carbon−halogen bond, which is stronger for **1-F** than **1-Cl** (see above), were balanced by the

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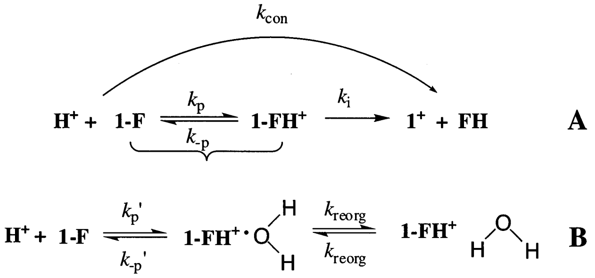
[32] Zechel, D. L.; Reid, S. P.; Nashiru, O.; Mayer, C.; Stoll, D.; Jakeman, D. L.; Warren, R. A. J.; Withers, S. G. *J. Am. Chem. Soc.* **2001**, *123*, 4350−4351.

[33] Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 4433−4436.

[34] Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966−978. Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891−899.

Scheme 5



progress toward development of the stabilizing aqueous solvation of the developing product anion, which is more stabilizing for fluoride than for chloride ion. The estimated 3 kcal/mol larger intrinsic barrier to heterolytic cleavage of **1-F** compared with **1-Cl** in water is consistent with an *imbalance* between the fraction of cleavage of the carbon−halogen bond (large) and the fractional development of the total anion stabilization by solvation in the transition state for heterolytic C−X bond cleavage (relatively smaller). This results in a larger barrier to formation of the transition state, where the requirement for stabilization by solvation is large.[36−38]

The data reported here are consistent with the notion that there is little or no solvation of the electron pair used in formation of the C−Cl and C−F bonds at the transition state for heterolytic C−X bond cleavage to form the intimate ion pair reaction intermediate, so that this solvation develops only *after* the transition state for cleavage of **1-Nu**, when the intimate ion pair undergoes separation to the solvent-separated ion pair.[39−41]

Catalysis by the Proton. The large reactivity of HF ($pK_a \approx -12$ for H_2F^+)[42a] compared to much more basic F^- ($pK_a = 2.9$ for HF)[28a] toward 1^+ in water may reflect the advantage of a concerted compared with a stepwise mechanism for the acid-catalyzed cleavage and synthesis of the C−F bond (k_{con}, Scheme 5A). A concerted mechanism would result in an increase in the nucleophilicity of HF due to partial proton transfer to the hydrogen bond acceptor water in the transition state for nucleophilic addition of HF. The solvent deuterium isotope effect $k_H/k_D = 1.09$ (Results section) for acid-catalyzed cleavage of **1-F** determined here is larger than the inverse solvent deuterium isotope effects $k_H/k_D = 0.33{-}0.50$ observed for stepwise acid-catalyzed solvolysis reactions.[43] Such inverse solvent deuterium isotope effects are a consequence of the larger concentration of the protonated substrate in D_2O, which arises from the greater tendency of D_3O^+ than of H_3O^+ to undergo proton transfer to form a monoprotic acid and a molecule of L_2O.[43] The solvent deuterium isotope effect for acid-catalyzed cleavage of **1-F** of near unity observed here is consistent with a concerted reaction mechanism (k_{con}, Scheme 5A) in which there is movement of the proton from L_3O^+ to the leaving group in the rate-determining transition state, so that the 3-fold greater acidity of D_3O^+ compared with H_3O^+ is balanced by a normal primary isotope effect.

There is good evidence that a concerted mechanism for acid-catalyzed heterolytic bond cleavage at carbon is favored when the leaving group is weakly basic,[44−49] because a decrease in leaving group basicity is accompanied by a decrease in the stability of the protonated intermediate of the stepwise reaction (e.g., $\mathbf{1\text{-}FH^+}$), and this will favor the concerted mechanism that avoids its formation. For example, the increase in the solvent deuterium isotope effect from $k_H/k_D = 0.33$ to $k_H/k_D = 1.09$ for acid-catalyzed cleavage of benzaldehyde mixed acetals PhCH(OMe)OR that is observed as the leaving group ROH is changed from methanol ($pK_a = 15.5$) to *m*-nitrophenol ($pK_a = 8.4$) is consistent with a change from a stepwise to a concerted reaction mechanism.[47] This change in mechanism has been thoroughly documented for *general* acid catalysis of the cleavage of acetals[45−47] and, in the microscopic direction, for *general* base catalysis of the addition of alcohols to ring-substituted 1-phenylethyl carbocations.[48,49] By contrast, it is less commonly observed for *specific* acid catalysis of heterolytic bond cleavage.[46]

The substrate **1-F** is so weakly basic that its protonation by H_3O^+ to form solvent-equilibrated $\mathbf{1\text{-}FH^+}$ (Scheme 5A) is not expected to be much faster than the overall rate of its acid-catalyzed cleavage to give $\mathbf{1}^+$ and HF ($k_H = 0.025\ M^{-1}\ s^{-1}$, Table 1). For example, a value of $k_p = 0.1\ M^{-1}\ s^{-1}$ for formation of solvent-equilibrated $\mathbf{1\text{-}FH^+}$ can be calculated with the limiting value of $k_{-p} = k_{reorg} \approx 10^{11}\ s^{-1}$ for deprotonation of $\mathbf{1\text{-}FH^+}$ (Scheme 5B, reverse reaction),[50] and $1/K_a = k_p/k_{-p} = 10^{-12}$ for this protonated alkyl fluoride.[42b] This calculation is approximate, because the acidity of protonated alkyl fluorides is poorly documented, but it does suggest that solvent-equilibrated $\mathbf{1\text{-}FH^+}$ forms only barely fast enough for it to be an intermediate in the acid-catalyzed cleavage of **1-F**.

It is interesting to consider whether the concerted mechanism for acid-catalyzed cleavage of **1-F** is *enforced* because the putative intermediate $\mathbf{1\text{-}FH^+}$ of the stepwise reaction is too unstable to exist in a potential energy well for the time of a bond vibration (Scheme 5A).[51,52] There is in fact little or no

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(35) Intrinsic barriers of $\Lambda = 9.8$ and $\Lambda = 13.2$ kcal/mol for heterolytic cleavage of **1-Cl** and **1-F**, respectively, can be calculated using eq 6 (derived at 298 K) using $k_o = 4\ s^{-1}$ and $K = 1/K_{Nu} = 2 \times 10^{-9}$ M for the reaction of **1-Cl**, and $k_o = 0.0080\ s^{-1}$ and $K = 1/K_{Nu} = 4.3 \times 10^{-10}$ M for the reaction of **1-F**.

$$\log k_o = \frac{1}{1.36}\left\{17.44 - \Lambda\left(1 - \frac{1.36 \log K}{4\Lambda}\right)^2\right\} \qquad (6)$$

(36) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9−16.
(37) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119−238.
(38) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301−308.
(39) Richard, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 1768−1769.
(40) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373−1383.
(41) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1992**, *114*, 1816−1823.
(42) (a) The pK_a of the very strong acid H_2F^+ in water has not been determined. A pK_a of −12 can be estimated from $K_s = 10^{-12}\ M^2$ for the autoionization constant of pure (50 M) hydrofluoric acid [Gillespie, R. J.; Liang, J. *J. Am. Chem. Soc.* **1988**, *110*, 6053−6057] and the pK_a of 3.2 for the ionization of HF in water [ref 28b], with the assumption that the equilibrium constant for proton transfer between two HF molecules to form H_2F^+ and F^- in water is the same as that in pure HF. (b) This pK_a is estimated to be similar to the pK_a of −12 estimated for H_2F^+ [ref 42a] based on the similar pK_a's for NH_4^+ ($pK_a = 9.25$) and $PhCH_2NH_3^+$ ($pK_a = 9.34$) [Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology, Physical and Chemical Data*; 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, OH, 1976; Vol. 1, pp 305−351].
(43) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275−332.
(44) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425−432.
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(47) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4672−4677.
(48) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1396−1401.
(49) Ta-Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040−8050.
(50) A value of $k_{reorg} = 10^{11}\ s^{-1}$ is used for this limiting rate constant: this is the rate constant for reorganization of the solvent by dielectric relaxation [Giese, K.; Kaatze, U.; Pottel, R. *J. Phys. Chem.* **1970**, *74*, 3718−3725. Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371−374. Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys. Chem.* **1992**, *96*, 6017−6020].
(51) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161−169.
(52) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345−375.

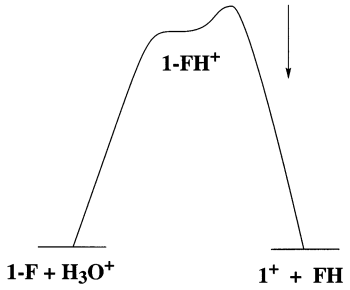


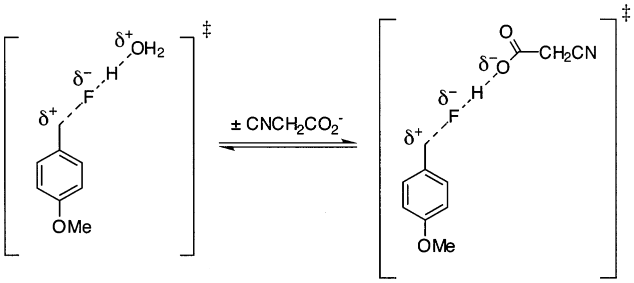
Figure 3. Free energy profile for the specific-acid-catalyzed cleavage of **1-F** by a hypothetical stepwise reaction mechanism (Scheme 5). The arrow is included to indicate that this reaction does in fact proceed by a concerted mechanism, which avoids formation of the highly unstable protonated alkyl fluoride **1-FH**$^+$.

barrier to proton transfer from **1-FH**$^+$ to water (reverse of reaction shown in Scheme 5B), because of the large thermodynamic driving force for this reaction (p$K_a \approx -12$ for **1-FH**$^+$)[42b] and the small intrinsic barrier to proton transfer between electronegative atoms.[53] Therefore, the rate-determining step for the deprotonation of **1-FH**$^+$ by water to form **1-F** (Scheme 5B, reverse reaction) and, by microscopic reversibility, for proton transfer from H_3O^+ to **1-F** should be the "rotation" of a molecule of solvent water into or out of a "reactive" position at **1-FH**$^+$ ($k_{reorg} \approx 10^{11}$ s^{-1}),[50] so that $k_{-p}' \gg k_{reorg}$ (Scheme 5B). There is, however, likely a small barrier for C−F bond cleavage at **1-FH**$^+$ to form **1**$^+$ (k_i, Scheme 5A). The alternative "barrierless" cleavage reaction would require that the change in leaving group from F^- to HF result in a ca. 10^{15}-fold increase in the rate constant for cleavage of the C−F bond, from $k_o = 8.0 \times 10^{-3}$ s^{-1} for cleavage of **1-F**, to $k_i \approx 10^{13}$ s^{-1} for cleavage of **1-FH**$^+$. This is approximately the same as the ca. 10^{15}-fold difference in the basicities of the F^- and HF leaving groups.[28,42a] It would correspond to values of $\beta_{lg} \approx -1.0$ and $\beta_{nuc} = 0$, and it would require that there be essentially no *chemical* selectivity for the addition of F^- and HF to **1**$^+$. However, there is good evidence for a small, but significant, selectivity for nucleophile addition to **1**$^+$.[14]

The available experimental data are consistent with the notion that there is a "flat" potential energy surface for the hypothetical stepwise specific-acid-catalyzed cleavage of **1-F** (Figure 3). It has been proposed that such a flat surface in the region of an unstable intermediate such as **1-FH**$^+$ will favor the observation of a concerted mechanism which avoids its formation.[54] This is because the barrier to a concerted reaction is related to the sum of the barriers for the two steps in the stepwise reaction (k_p and k_i, Scheme 5A), minus the advantage of the coupling of these two processes in a concerted process.[54] The favorable advantage of *coupling* will most likely reduce the barrier for a concerted reaction below that for the competing stepwise reaction when there is a shallow potential energy well (or no well at all) for the reaction intermediate (Figure 3).

General Acid Catalysis. Catalysis of the hydrolysis of α-D-glucopyranosyl fluoride by phosphate and phosphonate buffers has been reported and shown to be due mainly to the basic form of the buffer.[12] There should in fact be little or no general acid catalysis of this reaction, because of the absence of a significant thermodynamic driving force for proton transfer from these buffer acids (p$K_a \geq 4.3$) to the fluoride ion leaving group (pK_a = 3.2 for HF)[28b] ("libido" rule of Jencks).[55] Catalysis of the cleavage of alkyl fluorides by cyanoacetic acid (pK_a = 2.2) is allowed by this libido rule,[55] because proton transfer from cyanoacetic acid to fluoride ion is just favorable thermodynamically. However, there is no increase in the observed rate constant for solvolysis of **1-F** in the presence of 0.80 M cyanoacetic acid buffer at pH 1.7. We conclude that, under these reaction conditions, there is little or no stabilization of the transition state of the specific-acid-catalyzed reaction of **1-F** by replacement of the hydrogen bond to solvent water in the transition state with a hydrogen bond to cyanoacetate anion (Scheme 6).

Scheme 6



The failure to observe general acid catalysis of the cleavage of **1-F** in water by cyanoacetic acid is consistent with the conclusion that water (pK_a = −1.8 for H_3O^+) and cyanoacetate anion form hydrogen bonds of comparable stability in the transition state, but that the solvent reaction dominates because of the large (55 M) concentration of water.[44] The catalysis by chloroacetic acid that has been reported for the cleavage of benzaldehyde methyl phenyl acetal reflects the large negative deviation of the rate constant for the solvent (hydronium ion)-catalyzed reaction from the Brønsted plot for general acid catalysis.[44] By analogy, the absence of significant general acid catalysis of cleavage of **1-F** by cyanoacetic acid requires that the rate constant for hydronium ion show a smaller negative deviation from the corresponding Brønsted correlation for this reaction. We do not understand why the relative effectiveness of hydronium ion and carboxylic acids as catalysts should be different for different reactions. Finally, catalysis of the cleavage of trityl fluoride by HF has been reported for reaction in a mixed aqueous/organic solvent.[11] Such catalysis probably reflects the well-documented strength of the hydrogen bond between fluoride ion and HF in the complex $[F{\cdot}H{\cdot}F]^-$.[1]

Carbon and Proton Basicity. Table 1 summarizes the rate and equilibrium constants for the reactions in Schemes 7 and 8 for $Nu^- = F^-$ (this work), Cl^-, and HO^-. The equilibrium constants for ionization of HNu (K_a, M) and for addition of Nu^- to **1**$^+$ ($K_{Nu} = k_{Nu}/k_o$, M^{-1}) were combined to give values of the overall equilibrium constant K_T for transfer of anions from the proton to **1**$^+$ ($K_T = K_{Nu}K_a$, Scheme 7). The values of log K_T increase from 6.5 to 16.7 as the nucleophile/leaving group is changed from fluoride to chloride anion. Combining these values of K_T for reactions of different anions gives values of K_X for the isodesmic exchange of Nu^- and F^- between the proton and **1**$^+$ (log K_X = log $[(K_T)_X/(K_T)_F]$, Scheme 8). The values of K_X increase from 0 (by definition) for $Nu^- = F^-$ to 10.6 for $Nu^- = Cl^-$.

The data in Table 1 are consistent with the known preference of "soft" acids and bases (**1**$^+$ and Cl^-) and "hard" acids and

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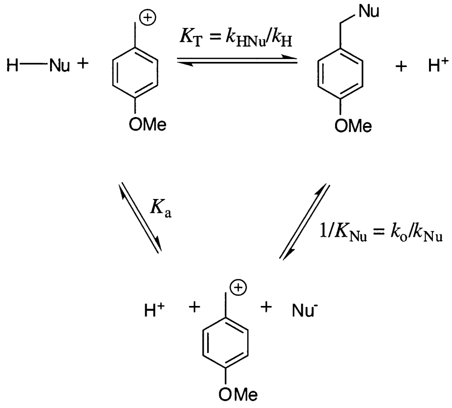
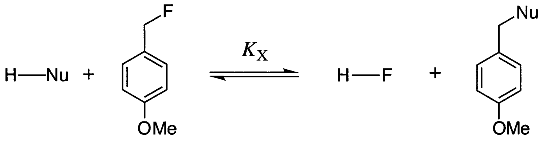
(53) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1−72.
(54) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209−219.
(55) Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731−4732.

Scheme 7



Scheme 8



bases (H^+ and F^-) to react with one another, and they can be rationalized within the framework developed to explain this general trend of organic and inorganic reactivity.[56] There is a good correlation for reaction of chorine, fluorine, and oxygen nucleophiles between the electronegativity of the electron donor atom at Nu and the equilibrium constant K_X for Scheme 8. This correlation results from (1) the large difference of 32.8 kcal/mol in the bond dissociation energies D_X for H−F (135.8 kcal/mol) and H−Cl (103.0 kcal/mol),[57] which reflects the optimal overlap between the 1s orbital of hydrogen and the corresponding sp^3-hybrid orbitals of chlorine and fluorine, and (2) the *attenuation* of this large difference on moving to the bond dissociation energies for **1-F** and **1-Cl**. We estimate the difference in the energies of the C−X bond at **1-F** and **1-Cl** to be similar to the 24.5 kcal/mol difference in the bond dissociation energies for CH_3CH_2-F (106 kcal/mol) and CH_3CH_2-Cl (81.5 kcal/mol).[57] This attenuation of bond dissociation energies reflects the less favorable overlap between the sp^3-hybrid orbitals of carbon compared to the 1s orbital of hydrogen with the corresponding sp^3-hybrid orbitals of chlorine and fluorine.

For reactions in water, the much larger range of the proton basicity compared with the carbon basicity of Nu^- leads directly to the large observed changes in K_T. For example, there is an 11 unit difference between the pK_a's of HF (p$K_a = 3.2$)[28b] and HCl (p$K_a \approx -8$),[6] but little difference in the observed carbon basicity of F^- and Cl^- toward $\mathbf{1}^+$ ($\Delta\log K_{Nu} = 0.7$, Table 1 and Figure 2B). This very large difference in the acidity of HF and HCl in water arises from the ca. 38 kcal/mol larger (less favorable) free energy change for heterolytic bond cleavage of HF than of HCl in the gas phase[58] and the 7 kcal/mol greater (more negative) free energy of solvation of HF than of HCl,[6] the sum of which is greater than the compensating ca. 30 kcal/mol larger (more negative) free energy of solvation of the product fluoride ion than of chloride ion.[6]

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(56) Pearson, R. G., Ed. *Hard and Soft Acids and Bases*; Dowden, Hutchinson and Ross: Stroudsberg, PA, 1973. Pearson, R. G. *Chemical Hardness*; John Wiley & Sons: New York, 1997.

(57) Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502−518.

(58) *NIST Standard Reference Database Number 69−July 2001 Release* (http://webbook.nist.gov/chemistry/).

(59) Calculated from $k_H = 3.7 \times 10^{-5}$ M^{-1} s^{-1} for acid-catalyzed cleavage of **1-OMe** in water at $I = 0.30$ (KCl)[24a] and a ratio of 0.11/0.038 = 2.9 for the rate constants for cleavage of 1-(4-methoxyphenyl)ethyl alcohol (**2-OH**) and 1-(4-methoxyphenyl)ethyl methyl ether (**2-OMe**) in 50/50 (v/v) trifluoroethanol at 25 °C and $I = 0.50$ ($NaClO_4$) (eq 7). An experimental value of $(k_H)^{HO} = 0.11$ M^{-1} s^{-1} (eq 7) is used [ref 23]. The value of $(k_H)^{MeO} = 0.038$ M^{-1} s^{-1} for cleavage of **2-OMe** was calculated from $(k_H)^{HO}$, $K_{eq} = 63$ for interconversion of 1-(4-methoxyphenyl)ethyl alcohol and 1-(4-methoxyphenyl)ethyl methyl ether [Rothenberg, M. E.; Richard, J. P.; Jencks W. P. *J. Am. Chem. Soc.* **1985**, *107*, 1340−1346], and $k_{MeOH}/k_{HOH} = 22$ for partitioning of the 1-(4-methoxyphenyl)ethyl carbocation $\mathbf{2}^+$ between addition of methanol and water [ref 40] (eq 7).

$$\mathrm{MeOH} + \mathbf{2\text{-}OH} \underset{k_{HOH}}{\overset{(k_H)^{HO}[H^+]}{\rightleftharpoons}} \mathbf{2}^+ \underset{(k_H)^{MeO}[H^+]}{\overset{k_{MeOH}}{\rightleftharpoons}} \mathrm{HOH} + \mathbf{2\text{-}OMe} \qquad (7)$$