Lifetime of an Aliphatic Iminium Ion in Aqueous Solution

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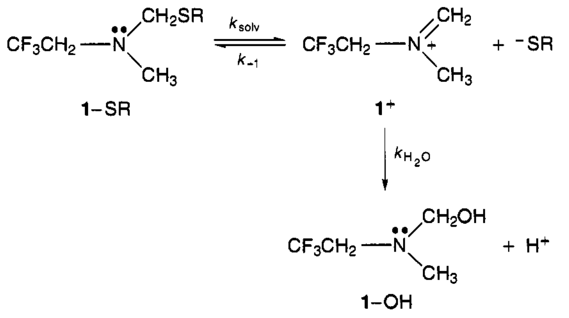
Iminium ions, $>C{=}N^+<$, are intermediates in many chemical and enzyme-catalyzed reactions,[1] and some iminium ion salts, such as Eschenmoser's salt, $H_2C{=}N^+(CH_3)_2\ I^-$, are commercially available and are used in synthetic applications.[2] However, there is little quantitative information about the reactivity of iminium ions in aqueous solution. There are reports[3] of the lifetime in aqueous solution of iminium ions in which the cationic carbon atom is stabilized by conjugation with a benzene ring, and we have recently determined the lifetimes of iminium ions derived from substituted anilines.[4] We report here the first determination of the lifetime in aqueous solution of a simple aliphatic iminium ion derived from formaldehyde, $H_2C{=}N^+(CH_3)CH_2CF_3$ (**1**$^+$).

The reaction of $H_2C{=}N^+(CH_3)CH_2CF_3$ with water is very rapid and difficult to follow directly by conventional methods. Therefore, we employed the indirect method of using the diffusion-controlled reaction of a strong nucleophile with the unstable cation as a "clock" for determining the lifetime of this unstable intermediate in water. This technique has been utilized previously for determination of the lifetimes of *N*-aryliminium ions,[4] oxocarbenium ions,[5] and nitrenium ions[6] in aqueous solution.



(1)

The solvolysis of **1**-SR[7] generates the short-lived iminium ion, **1**$^+$, and the nucleophilic leaving group, RS^-, with the rate constant k_{solv}. This is followed by rapid reaction of **1**$^+$ with solvent, with the rate constant k_{H_2O} (eq 1). The reaction of the nucleophilic leaving group, RS^-, with the iminium cation in the reverse direction is diffusion-controlled,[8] with a rate constant of $k_{-1} \simeq 5 \times 10^9\ M^{-1}\ s^{-1}$. The value of k_{H_2O} is given by the ratio k_{-1}/k_{H_2O}, which is obtained from common ion inhibition of the solvolysis of **1**-SR and the value of $k_{-1} = 5 \times 10^9\ M^{-1}\ s^{-1}$. The ratio k_{-1}/k_{H_2O} was obtained from a least-squares fit of k_{obs} and the values of $[RS^-]$ to eq 2 or the equivalent equation 3.

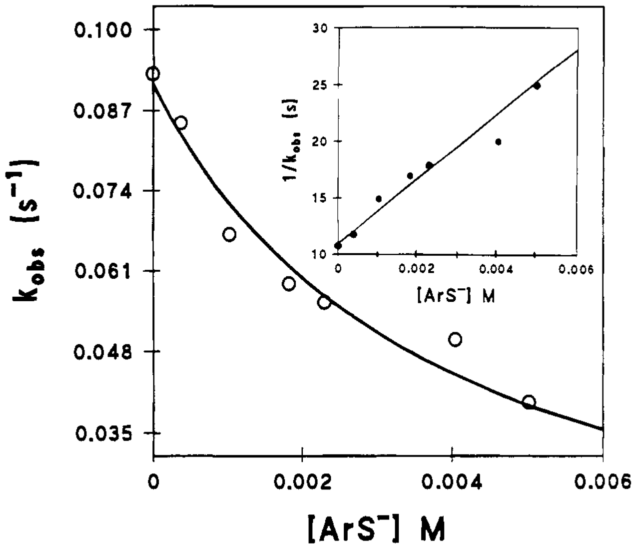


Figure 1. Inhibition of the solvolysis of $CF_3CH_2N(CH_3)CH_2SC_6H_4$-2-$COO^-$ in 0.05 M carbonate buffer, pH 10.5, μ = 0.5 (NaCl) at 25 °C, as a function of $[^-SC_6H_4$-2-$COO^-]$. The solid line shows the nonlinear least-squares fit of the data to eq 2, and the inset is a plot of $1/k_{obs}$ as a function of $[^-SC_6H_4$-2-$COO^-]$ that shows the linear least-squares fit of the data to eq 3.

$$k_{obs} = \frac{k_{solv}k_{H_2O}}{k_{H_2O} + k_{-1}[RS^-]} = \frac{k_{solv}}{1 + \left(\frac{k_{-1}}{k_{H_2O}}[RS^-]\right)} \qquad (2)$$

$$\frac{1}{k_{obs}} = \left(\frac{k_{-1}}{k_{H_2O}}\right)\left(\frac{1}{k_{solv}}\right)[RS^-] + \frac{1}{k_{solv}} \qquad (3)$$

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(7) Amino thioethers; *N*-methyl-*N*-((arylthio)methyl)-*N*-(2,2,2-trifluoroethyl)amine and *N*-methyl-*N*-((alkylthio)methyl)anilines, $CF_3CH_2N(CH_3)$-CH_2SR, were synthesized according to the procedure of Grillot and Schaffrath (*J. Org. Chem.* **1959**, *24*, 1035), in which thiols are condensed with *N*-methyl-*N*-(2,2,2-trifluoroethyl)amine and formaldehyde in the molar ratio 1:1:1. *N*-Methyl-*N*-(2,2,2-trifluoroethyl)amine hydrochloride, mp 210 °C ($CF_3CH_2NHCH_3{\cdot}HCl$), was prepared from *N*-methyl-*N*-(2,2,2−trifluoroethyl)acetamide (Aldrich) by $LiAlH_4$ reduction followed by HCl gas bubbling according to the procedure of Bissell and Finger (*J. Org. Chem.* **1959**, *24*, 1256). $CF_3CH_2N(CH_3)CH_2SC_6H_4$-2-COOH: white solid; mp 93−95 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.45 (s, 3H), 3.35 (q, 2H), 4.48 (s, 2H), 7.26 (t, 1H), 7.45 (t, 1H), 7.59 (d, 1H), 7.70 (d, 1H). $CF_3CH_2N(CH_3)CH_2SCH_2CH_2OH$: clear liquid at room temperature; ^1H NMR (300 MHz, DMSO-d_6) δ 2.42 (s, 3H), 2.65 (t, 2H), 3.26 (t, 2H), 3.52 (q, 2H), 4.06 (s, 2H). $CF_3CH_2N(CH_3)CH_2SCH_2COOCH_3$: clear liquid at room temperature; ^1H NMR (300 MHz, DMSO-d_6) δ 2.43 (s, 3H), 3.30 (q, 2H), 3.43 (s, 2H), 3.64 (s, 3H), 4.13 (s, 2H). $CF_3CH_2N(CH_3)$-$CH_2SCH_2CH_2NHCOCH_3$: clear liquid at room temperature; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (s, 3H), 2.43 (s, 3H), 2.65 (t, 2H), 3.20 (q, 2H), 3.30 (q, 2H), 3.40 (bs, 1H), 4.05 (s, 2H).

(8) We have shown previously[4] that the recombination reaction of RS^- with substituted *N*-aryliminium ions is diffusion-controlled, based on the observed inverse dependence of k_{-1}/k_{H_2O} on viscosity, a value of $\beta_{lg} = -0.93 \pm 0.09$ that corresponds to $\beta_{nuc} \approx 0$ in the reverse direction, and the fact that the rate constants for the reaction of stable carbocations with thiolate ions approach the diffusion-controlled limit.[10] In this study we obtained $\beta_{lg} = -0.8 \pm 0.2$ from a four-point Brønsted plot (R = C_6H_4-2-COO^-, CH_2COOCH_3, CH_2CH_2OH, and $CH_2CH_2NHCOCH_3$), which is consistent with complete bond breaking in the transition state of the dissociation reaction and diffusion-controlled association of RS^- with the iminium ion in the association reaction with $\beta_{nuc} \approx 0$.

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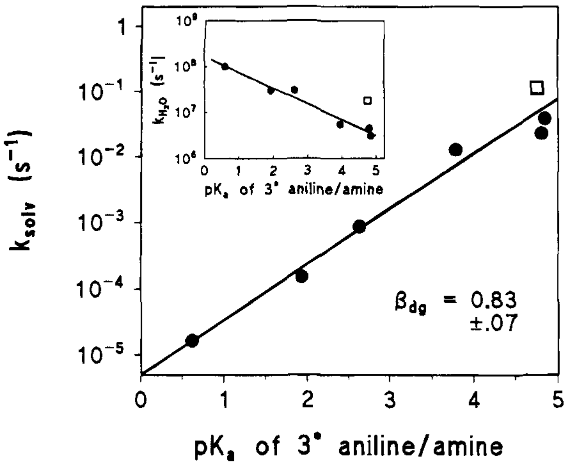

Figure 2. A Brønsted correlation of the rate constants for the solvolysis of $XC_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$ (●) and $CF_3CH_2N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$ (□) in 0.05 M CHES or carbonate buffer of pH 10.5, at 25 °C, with $\beta_{dg} = 0.83 \pm 0.07$. The inset shows a Brønsted correlation of the rate constants for the hydration of $H_2C{=}N^+(CH_3)C_6H_4X$ (●) and $H_2C{=}N^+(CH_3)CH_2CF_3$ (□), with $\beta_{dg} = -0.35 \pm 0.03$. Log k_{solv} and log k_{H_2O} are plotted against the pK_a of the corresponding amine or *N,N*-dimethylaniline; X = 4-NO_2, 4-CN, 3-NO_2, 4-NO_2, 3-Cl, and 4-COO^-.

The solvolysis of **1**-SR (R = $C_6H_4\text{-}2\text{-}COO^-$) was followed spectrophotometrically by monitoring the release of RS^- at 300 nm. Figure 1 shows the inhibition of solvolysis by RS^- in the reaction mixture.[9] The average value of the ratio k_{-1}/k_{H_2O}, obtained from four experiments, is 280 ± 20 M^{-1}, and that for k_{solv} is 0.11 ± 0.02 s^{-1}. This corresponds to $k_{H_2O} = (1.8 \pm 0.1) \times 10^7$ s^{-1} and a lifetime of $(5.5 \pm 0.3) \times 10^{-8}$ s for $H_2C{=}N^+(CH_3)CH_2CF_3$ in aqueous solution.

The rate constant, k_{solv}, for the solvolysis of **1**-SR, R = $C_6H_4\text{-}2\text{-}COO^-$, is consistent with the value predicted from the Brønsted correlation for the solvolysis of ring-substituted anilino thioethers with the same leaving group, which follows $\beta_{dg} = 0.83 \pm 0.07$ (□, Figure 2).[4] However, k_{H_2O} for the hydration of $\mathbf{1}^+$ falls significantly above the Brønsted correlation for the hydration of *N*-aryliminium ions,[4] which follows $\beta_{dg} = -0.35 \pm 0.03$ (inset in Figure 2). This deviation may reflect the absence of resonance stabilization in the aliphatic iminium ion. Loss of resonance stabilization in the transition state for hydration of the aromatic iminium ions may involve structural rearrangement that provides an additional barrier to hydration of the ions.

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(9) Cuvette-spacers were employed in the inhibition experiments to reduce the path length of the cuvettes to 0.2 cm. This permits the use of concentrations of RS^- up to 5 mM in the reaction mixture.

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