Lifetimes of Iminium Ions in Aqueous Solution[1]

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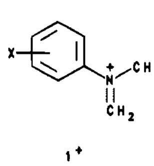
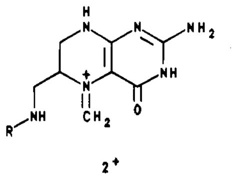
Abstract: Iminium cations have been generated in aqueous solution from the solvolysis of anilinothioethers ArN(CH$_3$)CH$_2$SR at 25 °C. Common ion inhibition of the solvolysis of anilinothioethers was observed when the thiolate anion leaving group was added to the reaction mixture. This inhibition results from trapping of the iminium ion by RS$^-$ to regenerate the anilinothioether. Rate constants, $k_{\mathrm{H_2O}}$, for hydration of the iminium ions were determined from common ion inhibition of the solvolysis of anilinothioethers in the presence of added thiolate ions and a rate constant of 5×10^9 M^{-1} s^{-1} for diffusion-controlled trapping of the iminium ions by RS$^-$, which regenerates the starting material. The values of $k_{\mathrm{H_2O}}$ for H$_2$C=N$^+$(CH$_3$)C$_6$H$_4$X are 1.0×10^8, 3.1×10^7, 3.0×10^7, 5.5×10^6, 4.5×10^6, and 3.1×10^6 s^{-1} for X = 4-NO$_2$, 4-CN, 3-NO$_2$, 3-Cl, 4-COO$^-$, and 4-Cl, respectively. Rate constants for the solvolysis of anilinothioethers, k_{solv}, depend on the pK_a of the thiolate leaving group with $\beta_{\mathrm{lg}} = -0.93 \pm 0.09$, which shows that the dissociation reaction has a very late transition state. This result is consistent with rate-limiting diffusion-controlled encounter of RS$^-$ with H$_2$C=N$^+$(CH$_3$)Ar in the reverse direction. The value of $\beta_{\mathrm{nuc}} = 1.00 - 0.93 = 0.07 \pm 0.09 \approx 0$ is expected for a diffusion-controlled addition reaction. The solvolysis reaction is sensitive to the basicity of the electron-donating nitrogen atom of the aniline with a value of $\beta_{\mathrm{dg}} = 0.79 \pm 0.06$; i.e., there is a large amount of electron donation from the nitrogen atom that provides the driving force for cleavage of the CH$_2$—S bond in the late transition state. Hammett correlations of the rate constants for the solvolysis reaction, k_{solv}, show a better correlation with σ^- than with σ for substituents on the aniline and follow $\rho^- = -3.3 \pm 0.3$. This also indicates a large amount of electron donation and an important contribution of resonance in the transition state of the solvolysis reaction. Reaction of the iminium ions with water is accelerated by electron-withdrawing substituents on the aniline ring and follows $\rho^- = 1.5 \pm 0.2$ and $\beta_{\mathrm{dg}} = -0.35 \pm 0.03$; i.e., the rate of reaction of the iminium cation with water is approximately half as sensitive to polar substituents as the solvolysis reaction.

Introduction

Although iminium ions, >C=N$^+$<, are intermediates in many chemical and enzyme-catalyzed reactions,[2] there is little quantitative information about the reactivity and lifetimes of iminium ions in aqueous solution. For example, it is not clear whether the reaction of dUMP with N^5,N^{10}-methylenetetrahydrofolate to give dTMP, catalyzed by thymidylate synthase, proceeds through an iminium cation with a significant lifetime[3] or through a concerted mechanism.[4] We report here an examination of the properties of an iminium ion, arylmethylmethyleneammonium ion, **1**$^+$, that gives some indication of the behavior that might be expected for the iminium ion that is formed from N^5,N^{10}-methylenetetrahydrofolate, **2**$^+$.



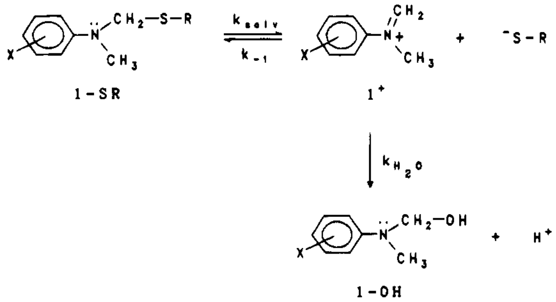
1$^+$



2$^+$

Since the reaction of an iminium ion with water is very rapid and difficult to follow directly by conventional methods, 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 oxocarbenium ions and nitrenium ions in aqueous solution.[5,6] We report here an extension of the use of this technique to the determination of the lifetimes of iminium ions.

The solvolysis of **1**—SR generates a short-lived cationic intermediate, **1**$^+$, and a nucleophilic leaving group, RS$^-$, with the rate constant k_{solv}. This is followed by rapid reaction of the intermediate with solvent. However, if RS$^-$ is present in the reaction mixture, it will trap the intermediate to regenerate **1**—SR with the rate constant k_{-1} [RS$^-$] and inhibit the solvolysis reaction, as shown in eq 1.



(1)

The rate law for solvolysis under these conditions is given by eqs 2 and 3. The ratio $k_{-1}/k_{\mathrm{H_2O}}$ can be determined from the

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dependence of k_{obs} on $[ArS^-]$; for example, when $k_{-1}\,[ArS^-]$

$$k_{obs} = \frac{k_{solv}k_{H_2O}}{k_{H_2O} + k_{-1}[ArS^-]} = \frac{k_{solv}}{1 + ((k_{-1}/k_{H_2O})[ArS^-])} \quad (2)$$

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

$= k_{H_2O}$, the observed rate constant for solvolysis will be decreased by 50%. The lifetime of the unstable intermediate in aqueous solution, $1/k_{H_2O}$, was calculated from the determined value of k_{-1}/k_{H_2O} and the value of k_{-1}. We assume that the strong nucleophile RS^- adds to the unstable iminium cation $\mathbf{1}^+$ in a diffusion-controlled reaction with a rate constant[5,7] of $k_{-1} = 5 \times 10^9\ M^{-1}\ s^{-1}$.

Experimental Section

Materials. All chemicals were reagent grade: anhydrous DMSO, 2-mercaptoethanol (>99%), and ethylenediaminetetraacetic acid disodium salt from Fluka, 3-mercaptobenzoic acid and 4-mercaptobenzoic acid from Toronto Research Chemicals, 3-chloro-*N*-methylaniline (>95%) from Maybridge Chemical Co., U.K., 4-nitro-*N*-methylaniline from Eastman Kodak, 4-(*N*-methylamino)benzonitrile from Apin Chemicals, U.K., 4-mercaptotoluene (98%) from Lancaster Synthesis, 4-chloro-*N*-methylaniline (94%), thiosalicylic acid (97%), sodium hydride (95%), 4-nitroaniline (98%), thiophenol (>99%), 4-chlorothiophenol, mercaptoacetic acid (97%), methyl mercaptoacetate (95%, distilled before use), 4-(methylamino)benzoic acid (97%), 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) (99%), dimethyl sulfate (99+%), and *N*,*N*-dimethylaniline (99%) from Aldrich Chemical Co., benzaldehyde and sodium bicarbonate from Fisher Scientific, and materials for buffers (citric acid, ADA, MES, Tris, MOPS, CHES, and CAPS) from Sigma.

All solutions were prepared with double-distilled water and contained ~3% DMSO. The pH was measured with an Orion Model 701A pH meter and a 476541 Corning combination electrode. Kinetic measurements were followed spectrophotometrically with a Cary 13E or Perkin-Elmer λ6 spectrophotometer.

Methyl thiosalicylate was prepared from thiosalicylic acid by refluxing in 5% sulfuric acid–methanol under argon for 24 h[8] The ester was purified by distillation. ^1H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.69 (s, 1H), 7.1–8.1 (m, 4H).

4-Thiocyano-*N*,*N*-dimethylaniline, mp 73 °C, was prepared from *N*,*N*-dimethylaniline with 2 equiv of ammonium thiocyanate and 1 equiv of bromine in glacial acetic acid.[9]

4-(*N*,*N*-Dimethylamino)thiophenol was prepared from 4-thiocyano-*N*,*N*-dimethylaniline according to the procedure of J. E. Banfield.[10] ^1H NMR (300 MHz, $CDCl_3$): δ 2.88 (d, 6H), 6.5–6.7 (m, 2H), 7.2–7.4 (m, 2H).

Disodium Thiosalicylate. Thiosalicylic acid (3.06 g, 19.2 mmol) was dissolved in 250 mL of dry THF in a round-bottomed flask. NaH (0.92 g, 36.2 mmol) was then added to the flask and the mixture was stirred overnight. The disodium thiosalicylate was collected on a sintered glass filter, and washed with dry diethyl ether. The solvent was removed under vacuum to yield 4 g of disodium thiosalicylate, mp > 310 °C.

3-Nitro-*N*-methylaniline, mp 62 °C, was prepared in 76% yield from 3-nitroaniline according to the procedure of J. J. Lucier and co-workers.[11] ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (d, 3H), 4.1 (brs), 6.8–7.6 (m, 4H).

Anilinothioethers *N*-methyl-*N*-[(arylthio)methyl]anilines and *N*-methyl-*N*-[(alkylthio)methyl]anilines, $ArN(CH_3)CH_2SR$, were synthesized according to the procedure of Grillot and Schaffrath,[12] in which thiols are condensed with substituted *N*-methylanilines and formaldehyde in the molar ratio 1:1:1.[13] Yields ranged from 75% to 95%. The parent compound *N*-methyl-*N*-[(phenylthio)methyl]aniline was purified by vacuum distillation and melted at 36 °C, as reported by Grillot and Schaffrath. The IR spectrum matched the reported spectrum.[14]

$C_6H_5N(CH_3)CH_2SC_6H_5$. White solid. mp: 36 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.89 (s, 3H), 4.95 (s, 2H), 6.75–6.85 (m, 3H), 7.15–7.30 (m, 5H), 7.40–7.50 (m, 2H).

$C_6H_5N(CH_3)CH_2SC_6H_4$-4-NO_2. Yellow solid. mp: 61–64 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (s, 3H), 5.15 (s, 2H), 6.8–8.2 (m, 9H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_5$. Yellow liquid at room temperature. ^1H NMR (300 MHz, DMSO-d_6): δ 2.91 (s, 3H), 5.22 (s, 2H), 7.25–7.52 (m, 9H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-4-Cl. Yellow liquid at room temperature; ^1H NMR (300 MHz, DMSO-d_6): δ 2.92 (s, 3H), 5.25 (s, 2H), 7.25–7.55 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-4-$CH_3$. Yellow liquid at room temperature. ^1H NMR (300 MHz, DMSO-d_6): δ 2.26 (s, 3 H), 2.88 (s, 3H), 5.15 (s, 2H), 7.1–7.6 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-COOH. Yellow solid. mp: 170 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 3.03 (s, 3H), 5.23 (s, 2H), 7.2–7.8 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-3-COOH. Yellow solid. mp: 120 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 2.91 (s, 3H), 5.26 (s, 2H), 7.2–7.9 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-4-COOH. Yellow solid. mp: 170 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 2.95 (s, 3H), 5.35 (s, 2H), 7.2–7.9 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-$COOCH_3$. Yellow solid. mp: 85 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.02 (s, 3H), 3.88 (s, 3H), 5.05 (s, 2H), 7.0–7.8 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-3-$COOCH_3$. Yellow liquid at room temperature; ^1H NMR (300 MHz, $CDCl_3$): δ 2.97 (s, 3H), 3.91 (s, 3H), 5.02 (s, 2H), 7.0–8.2 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-4-N-$(CH_3)_2$. Yellow liquid at room temperature; ^1H NMR (300 MHz, DMSO-d_6): δ 2.87 (d, 6H), 3.33 (s, 3H), 4.95 (s, 2H), 6.6–7.6 (m, 8H).

3-$NO_2C_6H_4N(CH_3)CH_2SCH_2COOH$. Yellow liquid at room temperature; ^1H NMR (300 MHz, DMSO-d_6): δ 2.97 (s, 3H), 3.36 (s, 2H), 5.19 (s, 2H), 7.2–7.7 (m, 4H).

3-$NO_2C_6H_4N(CH_3)CH_2SCH_2COOCH_3$. Yellow liquid at room temperature; ^1H NMR (300 MHz, $CDCl_3$): δ 3.13 (s, 3H), 3.24 (s, 2H), 3.75 (s, 3H), 4.82 (s, 2H), 6.8–7.8 (m, 4H).

3-$NO_2C_6H_4N(CH_3)CH_2SCH_2CH_2OH$. Yellow liquid at room temperature; ^1H NMR (300 MHz, DMSO-d_6): δ 2.66 (t, 3H), 3.07 (s, 3H), 3.54 (t, 2H), 4.84 (s, 2H), 7.2–7.8 (m, 4H).

4-$NO_2C_6H_4N(CH_3)CH_2SC_6H_5$. Yellow solid. mp: 57 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.97 (s, 3H), 4.92 (s, 2H), 6.65 (d, 2H), 7.26–7.30 (m, 3H), 7.45–7.50 (m, 2H), 8.10 (d, 2H).

4-$NO_2C_6H_4N(CH_3)CH_2SCH_2COOCH_3$. Yellow solid. mp: 123 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.19 (s, 3H), 3.25 (s, 2H), 3.74 (s, 3H), 4.83 (s, 2H), 6.81–6.85 (m, 2H), 8.1–8.2 (m, 2H).

4-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-COOH. Yellow solid. mp: 168–171 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 3.09 (s, 3H), 5.22 (s, 2H), 6.9 (d, 2H), 7.2–7.3 (m, 1H), 7.4–7.5 (m, 2H), 7.8 (d, 1H), 8.1 (d, 2H).

4-$COOHC_6H_4N(CH_3)CH_2SC_6H_4$-2-COOH: White solid. mp: 220 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 3.02 (s, 3H), 5.17 (s, 2H), 6.9 (d, 2H), 7.2–7.4 (m, 1H), 7.47–7.49 (m, 2H), 7.76–7.81 (m, 3H).

3-$ClC_6H_4N(CH_3)CH_2SC_6H_4$-2-COOH. White solid. mp: 138 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 2.94 (s, 3H), 5.13 (s, 2H), 6.7–6.9 (m, 3H), 7.2–7.39 (m, 2H), 7.45 (d, 2H), 7.8 (d, 1H).

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(13) The reaction mixture was heated at 80 °C for 2 h. However, the synthesis of *N*-methyl-*N*-[[(2-carboxyphenyl)thio]methyl]-3-chloroaniline was completed within a minute of stirring at ~40 °C.

(14) Sadtler Research Laboratories, Philadelphia, PA, 1956; Standard Infrared Vol. 11, Prism *No.* 10482.

Table 1. First-Order Rate Constants for the Solvolysis of $3\text{-}NO_2C_6H_4N(CH_3)CH_2SR$ in 0.05 M Buffers, with 3% DMSO, μ = 1 (NaCl), at 25 °C

R	pK_a(RSH)	λ, nm[a]	pH	k_{solv}, s^{-1}
$-C_6H_4\text{-}2\text{-}COO^-$	7.60	380	9.0−10.5	9.8×10^{-4}
$-C_6H_4\text{-}2\text{-}COOCH_3$	6.30	412	3.9−9.1	1.5×10^{-2}
$-C_6H_4\text{-}4\text{-}CH_3$	6.19	412	6.9, 10.5	9.1×10^{-3}
$-C_6H_5$	5.98	380	6.9, 10.5	2.2×10^{-2}
$-C_6H_4\text{-}3\text{-}COO^-$	5.78	360, 267	10.5	9.5×10^{-3}
$-C_6H_4\text{-}4\text{-}Cl$	5.49	412, 380	6.9, 10.5	2.0×10^{-2}
$-C_6H_4\text{-}4\text{-}COO^-$	5.48	380	10.3	3.0×10^{-2}
$-CH_2COOCH_3$	7.57	270	7.4	1.5×10^{-4}
$-CH_2CH_2OH$	9.17	270	7.4	1.1×10^{-5}
$-C_6H_4\text{-}4\text{-}N(CH_3)_2$	6.7[b]	270	6.3, 10.4	1.6×10^{-3}
$-C_6H_4\text{-}2\text{-}COOH$	NA	380	4.5	13.5

[a] Wavelength at which the reaction was followed. [b] The pK_a of the thiol group of $4\text{-}N(Me)_2C_6H_4SH$ was not determined, because of interference from the N atom of the *para* substituent; instead, the pK_a value was estimated from pK_a(thiol) = pK_a(thiophenol) − $2.2\sigma^-$ (Perrin, D. D.; Dempsey, B., Serjeant, E. P. In *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: New York, 1981; p 132).

$4\text{-}ClC_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COOH$. White solid. mp: 148−150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (s, 3H), 5.01 (s, 2H), 6.7 (d, 2H), 7.2−7.4 (m, 4H), 8.1 (d, 2H).

$4\text{-}CNC_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COOH$. White solid. mp: 163 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.01 (s, 3H), 5.17 (s, 2H), 6.9 (d, 2H), 7.35 (m, 1H), 7.47−7.61 (m, 4H), 7.78 (d, 1H).

Measurements of pK_a. The pK_a values of thiols under the conditions of the kinetic measurements (Table 1) were determined spectrophotometrically in the range 253−303 nm in buffers of known pH. The values of K_a for the thiols (Table 1) were obtained by least-squares fitting of the hydroxide ion concentrations and corresponding absorbances to eq 4, in which A is the absorbance at a given pH, A_∞ is the

$$A = \frac{(A_\infty - A_o)(K_a/K_w)[OH^-]}{1 + (K_a/K_w)[OH^-]} + A_o \qquad (4)$$

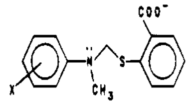
absorbance at a pH that is at least 3 units above the pK_a of the thiol, and A_o is the absorbance at a pH that is at least 3 units below the pK_a of the thiol.

The pK_a values of the protonated nitrogen atom of 3-chloro-*N,N*-dimethylaniline and 4-(*N,N*-dimethylamino)benzonitrile were determined spectrophotometrically at 250 and 300 nm, respectively, by titration in 3% DMSO, 0.05 M buffer, μ = 1.0 (NaCl), and 1 mM EDTA.

Kinetics. Iminium ions $\mathbf{1}^+$ were generated in aqueous buffer solutions at 25 °C from the dissociation of *N*-methyl-*N*-[(arylthio)methyl]anilines and *N*-methyl-*N*-[(alkylthio)methyl]anilines, **1**−SR (eq 1). An aliquot from a stock solution of **1**−SR in DMSO was added to a cuvette containing buffer. The final conditions in the cuvettes were 3% DMSO, 0.05 M buffer, μ = 1.0 (NaCl), and 1 mM EDTA. The solvolysis reaction was followed by monitoring the formation of released thiolate with Ellman's reagent (DTNB) at 412 nm, the release of thiolate anion directly in the range 250−270 nm, or the change in the absorbance when **1**−SR is cleaved to give an *N*-methylaniline, at the wavelengths shown in Table 2. Individual runs followed first-order kinetics accurately for at least four half-times.

Inhibition of the solvolysis of *N*-methyl-*N*-[(arylthio)methyl]anilines in water, water/glycerol mixtures, and water/methanol mixtures was measured by following the solvolysis in the presence of a range of concentrations of the corresponding thiolate ion leaving group. The concentrations of the thiolate ions were determined spectrophotometrically before the addition of the *N*-methyl-*N*-[(arylthio)methyl]aniline; $\epsilon_{350} = 70.5$ M^{-1} cm^{-1} for $^-SC_6H_4\text{-}2\text{-}COO^-$, and $\epsilon_{360} = 52$ M^{-1} cm^{-1} for $^-SC_6H_4\text{-}3\text{-}COO^-$. The final conditions in the cuvettes were 3% DMSO, 0.05 M carbonate or CHES buffer, pH 10.0−10.5, μ = 0.5 (NaCl), and 1 mM EDTA. The accuracy of the data is indicated by the fit of the experimental data to the calculated lines in the figures, with standard errors of <10%.

Table 2. First-Order Rate Constants for the Solvolysis of $ArN(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$, in 0.05 M Carbonate/Bicarbonate Buffers, pH 10.0−10.5, μ = 0.5 (NaCl), at 25 °C, and the Calculated[a] First-Order Rate Constant, k_{H_2O}, for Reaction of the Corresponding Iminium Ion with Water



X	λ, nm[b]	k_{solv}, s^{-1}	k_{-1}/k_{H_2O} M^{-1}	k_{H_2O}, s^{-1}
$4\text{-}NO_2$	412	1.6×10^{-5}	50	1.0×10^{8}
4-CN	320	1.5×10^{-3}	164	3.1×10^{7}
$3\text{-}NO_2$	380	8.3×10^{-4}	165	3.0×10^{7}
3-Cl	300	1.6×10^{-2}	905	5.5×10^{6}
$4\text{-}COO^-$	310	2.3×10^{-2}	1110	4.5×10^{6}
4-Cl	300	3.8×10^{-2}	1600	3.1×10^{6}

[a] Calculated from a value of $k_{-1} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-controlled recombination of the thiolate leaving group with the iminium ion. [b] Wavelength at which the reaction was followed.

The viscosity of water/glycerol mixtures and water/methanol mixtures was measured at 25 °C with a Cannon-Fenske routine viscometer according to the ASTM D 445 procedure.[15]

Results

Solvolysis Reactions. Iminium ions,$\mathbf{1}^+$ were generated in aqueous buffer solutions at 25 °C from the dissociation of *N*-methyl-*N*-[(arylthio)methyl]anilines and *N*-methyl-*N*-[(alkylthio)methyl]anilines, **1**−SR (eq 1), as described in the Experimental Section. An aliquot from a stock solution of **1**−SR in DMSO was added to a cuvette containing the reaction mixture. The final conditions were 3% DMSO, 0.05 M buffer, μ = 1.0 (NaCl), and 1 mM EDTA. The solvolysis reaction (eq 1) was followed by one or more of the following methods: (1) Monitoring the formation of 5-mercapto-2-nitrobenzoate released from Ellman's reagent (DTNB) upon dissociation of **1**−SR. This method is not applicable at pH > 8 because of the reaction of hydroxide ion with DTNB, nor is it applicable for experiments in which thiols are present in the reaction mixture in order to trap the iminium ion. (2) Monitoring the release of thiolate by following the increase in thiolate absorbance in the range 250−270 nm. (3) Following the change in absorbance of the aniline moiety when **1**−SR is cleaved to give an *N*-methylaniline, at the wavelengths shown in Table 2. Rate constants for a given compound that were obtained with these three methods showed excellent agreement.

The rate of solvolysis of $3\text{-}NO_2C_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$ in aqueous solutions at 25 °C (0.05 M buffer, μ = 0.5 (NaCl), 3% DMSO, and 1 mM EDTA) was found to be dependent on pH near the pK_a of the carboxylic acid functionality of the leaving group. Rates of solvolysis were measured for $3\text{-}NO_2C_6H_4N(CH_3)CH_2R$ (R = thiosalicylate and methyl thiosalicylate) under the same conditions over a wide pH range. The pH−rate profile for the solvolysis of $3\text{-}NO_2C_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$ in Figure 2 shows that the slope of log k_{obs} against pH is −0.9 in the region of pH 5.8−7.8 and the pK_a of the carboxylic acid moiety is 5.7. The rate of solvolysis of $3\text{-}NO_2C_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COOCH_3$ is independent of pH and is faster than that of $3\text{-}NO_2C_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$ by a factor of 20, which is consistent with the 1.3 unit difference in the pK_a of the thiolate ion leaving group and a value of β_{lg} = −1. However, Figure 2 shows that the rate constant for the solvolysis of $3\text{-}NO_2C_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COOH$ is an order of magnitude larger than that of $3\text{-}NO_2C_6H_4N(CH_3)CH_2SC_6H_4\text{-}$

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[15] *IP Standards for Petroleum and its Products; Part I, Methods for Analysis and Testing*; Applied Science: Essex, England, 1976; p 71.1.

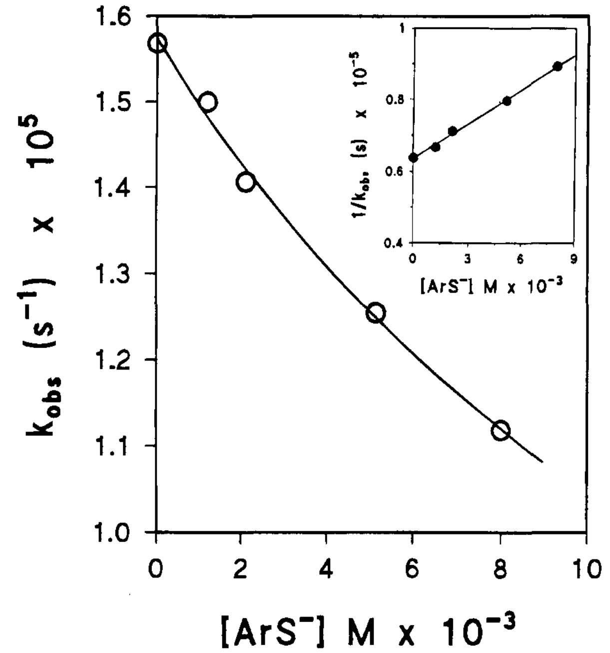

Figure 1. Inhibition of the solvolysis of 4-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-$COO^-$ in 0.05 M carbonate buffer, pH 10.5, μ = 0.5 (NaCl), at 25 °C, as a function of [ArS^-] (open circles). The solid line shows the nonlinear least-squares fit of the data to eq 2, and the inset is a plot of $1/k_{obs}$ as a function of [ArS^-] (closed circles). The solid line shows the linear least-squares fit of the data to eq 3.

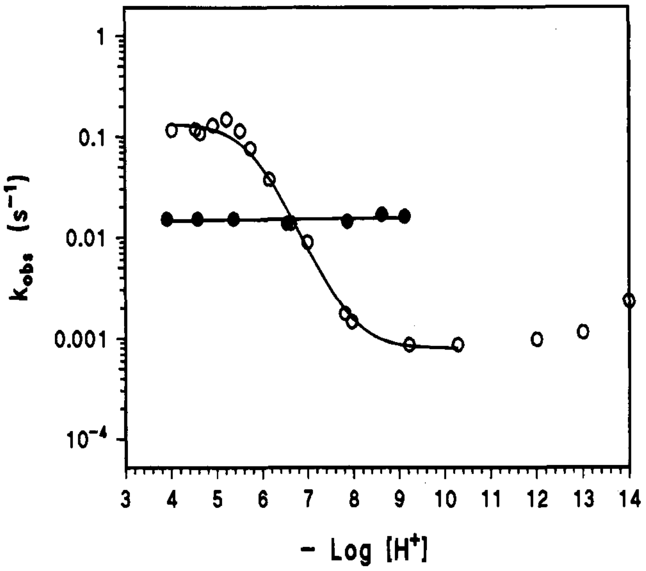

Figure 2. pH-rate profile for the solvolysis of 3-$NO_2C_6H_4N(CH_3)CH_2$-SAr in aqueous solution, μ = 0.5 (NaCl), at 25 °C. Ar = $-C_6H_4$-2-COO(H) (open circles) and Ar = $-C_6H_4$-2-$COOCH_3$ (closed circles).

2-$COOCH_3$. A carboxylic acid group and its methyl ester have the same *meta* and the same *para* substituent constants,[16] and would be expected to have a similar substituent effect in the *ortho* position. The observed increase in rate for the acid suggests that the $-COOH$ group provides intramolecular general acid catalysis for cleavage of the CH_2-S bond. Molecular models show that the $-COOH$ group and the S atom are within a distance range that may allow such catalysis.

Measurements of inhibition of the solvolysis of *N*-methyl-*N*-[(arylthio)methyl]anilines were carried out in CHES or carbonate buffer (pH 10.0–10.5) where the solvolysis is independent of pH.

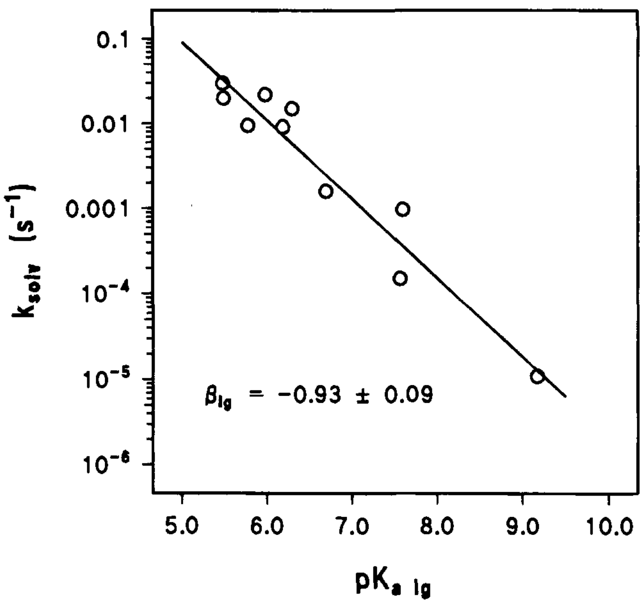

Figure 3. A Brønsted correlation of the rate constants for the solvolysis of 3-$NO_2C_6H_4N(CH_3)CH_2SR$ in aqueous solution, μ = 1.0 (NaCl), at 25 °C with β_{lg} = −0.93 ± 0.09.

There was no significant change in the rate constant for the solvolysis of 3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-$COO^-$ with a change in buffer concentration. The solvolysis was followed in 0.02, 0.05, and 0.5 M carbonate buffer of pH 10.5 at a constant ionic strength of 1.0 (NaCl), and the corresponding rate constants were 9.3 × 10^{-4}, 9.8 × 10^{-4}, and 9.7 × 10^{-4} s^{-1}, respectively.

Solvolysis of *N*-Methyl-*N*-[(arylthio)methyl]-3-nitroanilines and *N*-Methyl-*N*-[(alkylthio)methyl]-3-nitroanilines with Different Leaving Groups. The rate constants shown in Table 1 for the solvolysis of 3-$O_2NC_6H_4N(CH_3)CH_2SR$ with R = $-C_6H_4$-4-COO^-, $-C_6H_4$-4-Cl, $-C_6H_4$-3-COO^-, $-C_6H_5$, $-C_6H_4$-4-CH_3, $-C_6H_4$-4-$N(CH_3)_2$, $-C_6H_4$-2-COO^-, $-C_6H_4$-2-$COOCH_3$, $-CH_2COOCH_3$, and $-CH_2CH_2OH$ were determined at 25 °C in aqueous solutions containing 3% DMSO, 0.05 M CHES, or carbonate buffer (pH 10.0–10.5) and 1 mM EDTA at μ = 1.0 (NaCl). The Brønsted correlation in Figure 3 shows that the rate constants decrease with increasing pK_a of the leaving group with a slope of β_{lg} = −0.93 ± 0.09 over the range of pK_a = 5.5–9.2.

Solvolysis of *N*-Methyl-*N*-[[(2-carboxyphenyl)thio]methyl]-anilines with Different Substituted Anilines. Rate constants for the solvolysis of $XC_6H_4N(CH_3)CH_2SC_6H_4$-2-$COO^-$, with X = 4-$COO^-$, 4-$NO_2$, 3-$NO_2$, 4-Cl, 3-Cl and 4-CN (Table 2), were determined at 25 °C in aqueous solutions containing 3% DMSO, 0.05 M CHES or carbonate buffer, NaCl to give μ = 0.5, and 1 mM EDTA. Figure 4 shows a Brønsted correlation with a slope of β_{dg} = 0.79 ± 0.06 for log k_{solv} as a function of the pK_a of the protonated nitrogen atom of *N,N*-dimethylanilines, which ranges from 0.6 to 4.8. This pK_a should be close to the pK_a of the protonated nitrogen atom of the aniline moiety in the corresponding anilinothioether. The pK_a values of the protonated *N,N*-dimethylanilines $XC_6H_4N(CH_3)_2$ are 3.95, 1.94, 0.61, 2.63, 4.80, and 4.84 for X = 3-Cl, 4-CN, 4-NO_2,[17] 3-NO_2,[17] 4-COO^-,[18] and 4-Cl,[18] respectively.

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[16] (16) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[17] (17) Kumler; Eiler. *J. Am. Chem. Soc.* **1943**, *65*, 2355. Quoted in Jencks, W. P.; Regenstein, J. *CRC Handbook of Biochemistry, Physical and Chemical Data*; Chemical Rubber Co.: Cleveland, OH, 1968; p 171.

[18] (18) The pK_a value was estimated from pK_a = 5.06 − 3.46 σ^+ (Perrin, D. D.; Dempsey, B.: Serjeant, E. P. *pK$_a$ Prediction for Organic Acids and Bases*; Chapman and Hall: New York, 1981).

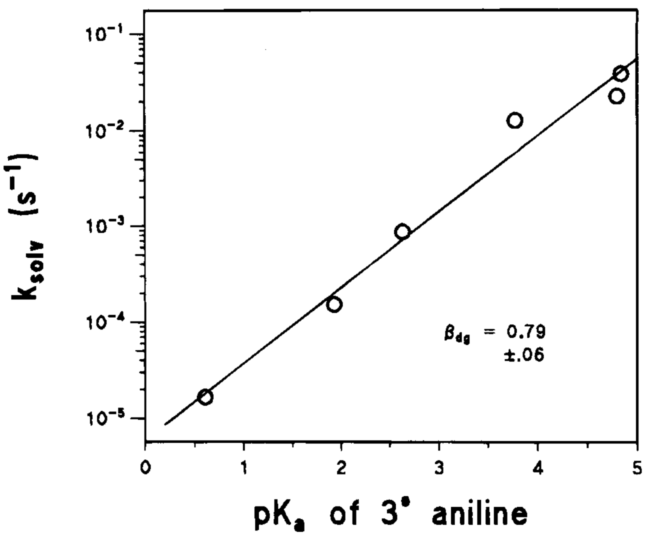

Figure 4. A Brønsted correlation of the rate constants for the solvolysis of $XC_6H_4N(CH_3)CH_2SC_6H_4$-2-$COO^-$ in 0.05 M CHES or carbonate buffer, μ = 1.0 (NaCl), at 25 °C with β_{dg} = 0.79 ± 0.06. log k_{solv} is plotted against the pK_a of the corresponding *N,N*-dimethylanilines $XC_6H_4N(CH_3)_2$, X = 4-NO_2, 4-CN, 3-NO_2, 4-NO_2, 3-Cl, and 4-COO^-.

Common Ion Inhibition of Solvolysis. The solvolysis of *N*-methyl-*N*-[(arylthio)methyl]anilines produces an iminium cation, $\mathbf{1}^+$, and a thiolate anion, ArS^-, as shown in eq 1. The rate of solvolysis is decreased in the presence of the leaving thiolate ion by common ion inhibition, as shown in Figure 1. The rates of solvolysis of *N*-methyl-*N*-[(arylthio)methyl]anilines and inhibition of solvolysis in the presence of the thiolate leaving group were examined in aqueous solutions, with μ = 0.5 (NaCl), pH 10.0–10.5, 3% DMSO, 0.05 M CHES or carbonate buffer, and 1 mM EDTA. The concentrations of the *N*-methyl-*N*-[(arylthio)methyl]anilines were in the range 2×10^{-5} to 2×10^{-4} M, and the concentrations of the thiolate anions were in the range 0–0.016 M. The presence of the carboxylate group on the thiophenol was necessary in order to obtain sufficient concentrations of the aromatic thiolates in solution. The concentrations of the thiolate anions were measured spectrophotometrically before the addition of the *N*-methyl-*N*-[(arylthio)methyl]aniline. Values of k_{-1}/k_{H_2O} and k_{solv} were obtained directly by least squares fitting of the values of k_{obs} and $[ArS^-]$ to eq 2 and from linear correlations of $1/k_{obs}$ with $[ArS^-]$, in which the intercept is $1/k_{solv}$ and the slope/intercept ratio is k_{-1}/k_{H_2O} (eq 3). The lifetimes, $1/k_{H_2O}$, for the iminium cations $H_2C{=}N^+(CH_3)C_6H_4$-X, are 1.0×10^{-8}, 3.2×10^{-8}, 3.3×10^{-8}, 1.8×10^{-7}, 2.2×10^{-7}, and 3.2×10^{-7} s for X = 4-NO_2, 4-CN, 3-NO_2, 3-Cl, 4-COO^-, and 4-Cl, respectively.[19]

Inhibition of Solvolysis in Solutions of Higher Viscosity. Solvolysis and inhibition of solvolysis for 3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-$COO^-$ were measured in aqueous solutions as described above in the presence of the viscogens glycerol and methanol. Initially, glycerol was chosen as the viscogen and methanol was chosen as a hydroxylic cosolvent that might not significantly alter the viscosity and would serve as a control. However, methanol also increases the viscosity and was also used as a viscogen. A slope of −1.0 ± 0.1 was obtained by linear least-squares fitting of η/η_o and the corresponding ratio $(k_{-1}/k_{solvent})/(k_{-1}/k_{solvent})_o$, with the fit forced through the origin. The results are summarized in Table 3.

Table 3. Effect of Viscosity on the Rate Constant for the Solvolysis of 3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-$COO^-$, k_{obs}, and on the Ratio $k_{-1}/k_{solvent}$ for the the Iminium Cation, $H_2C{=}N^+(CH_3)C_6H_4$-3-NO_2, in 0.05 M Carbonate/Bicarbonate Buffers, pH 10.5, 3% DMSO, μ = 0.5 (NaCl), at 25 °C

viscogen	concn, % (v/v)	η, cSt	10^4k_{obs}, s^{-1}	$k_{-1}/k_{solvent}$, M^{-1}	η/η_o	$(k_{-1}/k_{solvent})/(k_{-1}/k_{solvent})_o$
glycerol	0	1.05	8.5	165	1.00	1.00
	4	1.20	3.2	156	1.15	0.95
	8	1.31	8.5	104	1.25	0.63
	11	1.45	5.1	84	1.38	0.51
	13	1.56	4.0	108	1.49	0.65
	18	1.85	3.0	75	1.77	0.45
	19	1.93	3.1	34	1.84	0.21
methanol	4	1.15	5.6	118	1.10	0.72
	7	1.23	5.0	140	1.29	0.85
	10	1.31	3.8	103	1.25	0.62
	14	1.44	2.7	70	1.38	0.42
	16	1.45	2.2	56	1.38	0.34
	19	1.59	1.8	48	1.51	0.29

Discussion

Anilinothioethers $ArN(CH_3)CH_2SR$ undergo solvolysis in aqueous solution to generate an iminium cation, $\mathbf{1}^+$, and a thiolate anion, RS^-, as shown in eq 1. Common ion inhibition of the solvolysis is observed when the thiolate anion leaving group is present in the reaction mixture. This shows that the reaction generates a free, solvent-equilibrated iminium ion with a lifetime that is long enough to permit trapping by added RS^-, which regenerates the anilinothioether with the rate constant k_{-1}. The dependence of k_{obs} for solvolysis on $[ArS^-]$, shown in Figure 1, is described by eq 2, from which the ratio k_{-1}/k_{H_2O} was obtained (Table 2).

This study was carried out in order to determine the lifetime of iminium ions in aqueous solution, i.e., the reciprocal of the rate constant for the reaction of the iminium ion with water, $1/k_{H_2O}$ (s). The value of k_{-1} is needed for the calculation of k_{H_2O} from the measured ratio k_{-1}/k_{H_2O}. The following strongly suggest that the rate constant for the reaction of the thiolate leaving group with the iminium ion is diffusion controlled; i.e., $k_{-1} = {\sim}5 \times 10^9$ M^{-1} s^{-1}.

(1) If k_{-1} is diffusion controlled, i.e., if the rate of the bimolecular reaction is limited by the frequency of encounter of the iminium ion with the thiolate anion, the value of k_{-1}, and consequently $k_{-1}/k_{solvent}$, will be reduced as the viscosity of the solution is increased.[20] Ideally, when the viscosity of a solution is increased from η_o to η in the presence of a viscogen, the value of $k_{-1}/k_{solvent}$ will be reduced by the factor η_o/η and a plot of $(k_{-1}/k_{solvent})/(k_{-1}/k_{solvent})_o$ against η_o/η will have a slope of unity. Rate constants for the solvolysis and inhibition of solvolysis of 3-$NO_2C_6H_4N(CH_3)CH_2SC_6H_4$-2-$COO^-$ in the presence of viscogens were determined in aqueous solutions (Table 3), and Figure 5 shows that the slope of the plot of $(k_{-1}/k_{solvent})/(k_{-1}/k_{solvent})_o$ against η/η_o is equal to −1.0 ± 0.1. This slope is expected for a diffusion-controlled reaction of the thiol anion with the iminium cation.

(2) The rate constants, k_{solv}, for solvolysis of the anilinothioether decrease with increasing pK_a of the thiolate leaving group, with β_{lg} = −0.93 ± 0.09 (Figure 3). This shows that the reaction has a very late transition state in which the bond to the leaving group is completely or almost completely broken.

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[19] Considerably longer lifetimes have been reported (Koehler, K; Sandstrom, W.; Cordes, E. H. *J. Am. Chem. Soc.* **1964**, *86*, 2413. Sollenberger, P. Y.; Martin, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4261) for iminium ions generated from aromatic enamines. The values for the lifetimes reported by Koehler et al. and Sollenberger et al. are not in conflict with the shorter lifetimes reported in this study. The iminium ions in the above reports are carbocations that are stabilized by a neighboring nitrogen atom and a phenyl ring, and therefore are expected to have relatively longer lifetimes.

[20] Kramers, H. A. *Physica (Amsterdam)*, **1940**, *7*, 284. Blacklow, S. C.; Raines, R. T.; Lim; W. A.; Zamore, P. D.; Knowles, J. R. *Biochemistry* **1988**, *27*, 1158.

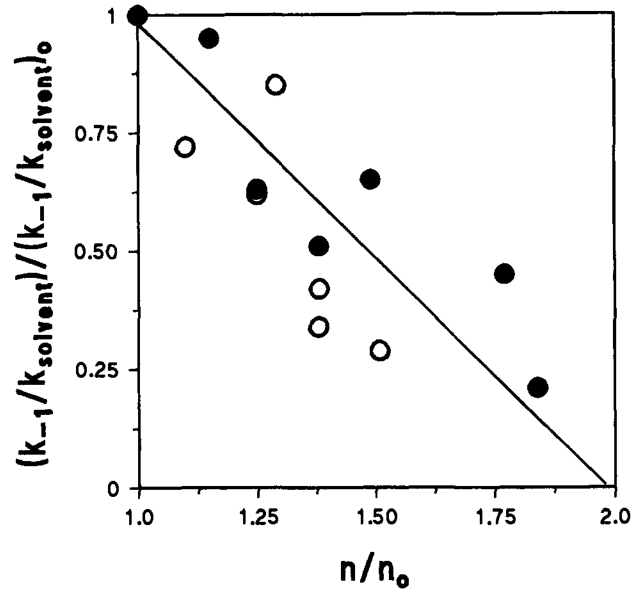

Figure 5. A plot of $(k_{-1}/k_{\text{solvent}})/(k_{-1}/k_{\text{solvent}})_o$ against η/η_o for the reaction of $H_2C{=}N^+(CH_3)C_6H_4\text{-}3\text{-}NO_2$ in the presence of viscogens in 0.05 M carbonate buffer of pH 10.0–10.5 and μ = 0.5 (NaCl) at 25 °C: glycerol (open circles) and methanol (closed circles). A slope of −1.0 ± 0.1 is obtained by linear least-squares fitting of η/η_o and the corresponding ratios $(k_{-1}/k_{\text{solvent}})/(k_{-1}/k_{\text{solvent}})_o$, where the fit is forced through the origin.

By microscopic reversibility, the combination reaction between the thiolate anion group and the iminium ion intermediate, in the reverse direction, must proceed through a transition state that is insensitive to the pK_a of the thiolate ion; i.e., there is little or no bond formation in the transition state. This is consistent with a diffusion-controlled recombination reaction of the iminium cation with RS^-.

(3) The second-order rate constants for the combination reaction of the following cations with thiolate anions have been shown to approach the diffusion-controlled limit: log k = 7.85 for tri-*p*-anisylmethyl cation and 2-hydroxyethanethiolate anion, log k = 8.26 for tri-*p*-anisylmethyl cation and thiophenoxide anion, and log k = 8.80 for [*p*-(dimethylamino)phenyl]tropolium cation and thiophenoxide anion.[21] These cations are considerably less reactive than the iminium cations examined in this study. Therefore, the rate constants for the reaction of the iminium ions $\mathbf{1}^+$ with thiolate ions are expected to be diffusion controlled, with k_{-1} = ~5 × 10^9 M^{-1} s^{-1}. This rate constant of k_{-1} = ~5 × 10^9 M^{-1} s^{-1} was used to calculate the values of k_{H_2O} from the observed ratios of k_{-1}/k_{H_2O} shown in Table 2.

Figure 4 shows that the rate of the solvolysis reaction has a large dependence on the basicity of the nitrogen atom of the aniline, with a value of β_{dg} = 0.79 ± 0.06. This indicates that the nitrogen atom provides a large amount of electron donation to assist $CH_2{-}S$ bond cleavage, and develops a positive charge that is close to 1.0 in a late transition state. The Hammett correlation of the rate constants for the solvolysis reaction, k_{solv}, for substituents on the aniline (Figure 6) shows that the rate of the solvolysis reaction is very sensitive to substituents on the aniline ring and follows σ^- with a slope of ϱ^- = −3.3 ± 0.3. The Hammett plot shows a better correlation with σ^- than with σ, which indicates that there is a large amount of electron donation by resonance in the transition state of the reaction. Since the back-reaction of the thiophenoxide anion with the iminium ions is diffusion controlled, with ϱ = 0, the value of ϱ^- for the formation of the iminium cation at equilibrium is −3.3. This value shows that the amount of charge development that is indicated by a Hammett correlation when iminium ions are formed at equilibrium is essentially the same as for the formation of oxocarbenium ions from acetophenone dimethyl ketals at equilibrium, which follows a value of ϱ = −3.6,[22] and for the formation of triarylcarbenium ions from the corresponding triarylcarbinols at equilibrium, which follows ϱ^+ = −3.35.[23]

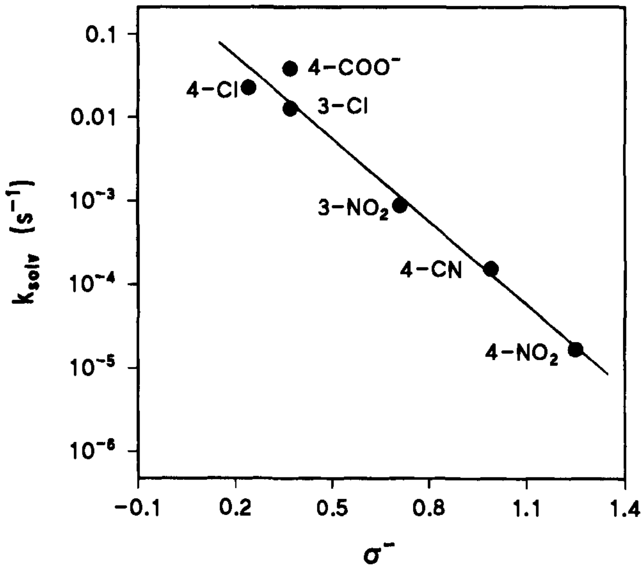

Figure 6. A Hammett plot of the observed rate constants for the solvolysis of $XC_6H_4N(CH_3)CH_2S\text{-}2\text{-}COO^-$ in 0.05 M CHES or carbonate buffer of pH 10.0–10.5 and μ = 1.0 (NaCl) at 25 °C. log k_{solv} against σ^-, X = 4-NO_2, 4-CN, 3-NO_2, 4-NO_2, 3-Cl, and 4-COO^-, follows ϱ^- = −3.3 ± 0.3.

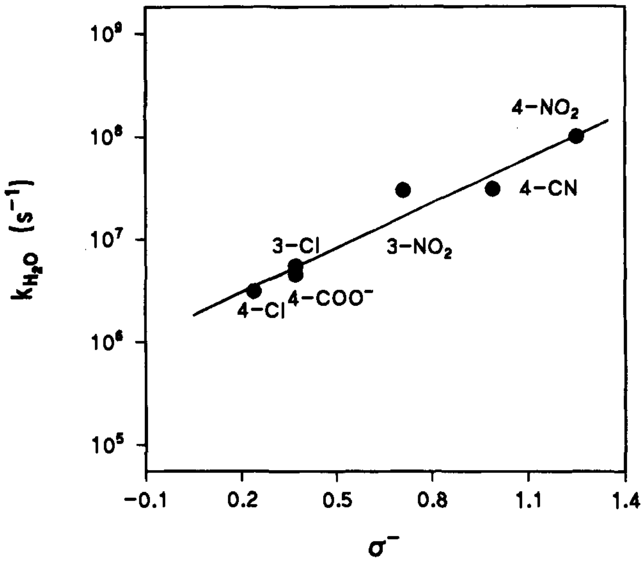

Figure 7. A Hammett plot of the rate constants for the hydration of $H_2C{=}N^+(CH_3)C_6H_4X$, X = 4-NO_2, 4-CN, 3-NO_2, 4-NO_2, 3-Cl, and 4-COO^-, which follows ϱ^- = 1.5 ± 0.2.

The rate constants for the reaction of the iminium cation with water, k_{H_2O}, are less sensitive to the substituent on the aniline ring, with ϱ^- = 1.5 ± 0.2 (Figure 7) and β_{dg} = −0.35 ± 0.03 (Figure 8); i.e., the reaction of the iminium cation with water is about half as sensitive to substituents as the solvolysis reaction. This relatively small sensitivity presumably reflects the high reactivity of the iminium ion intermediate.

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[21] Quoted in Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239.

[22] Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238.

[23] Deno, N. C.; Evans, W. L. *J. Am. Chem. Soc.* **1957**, *79*, 5804.

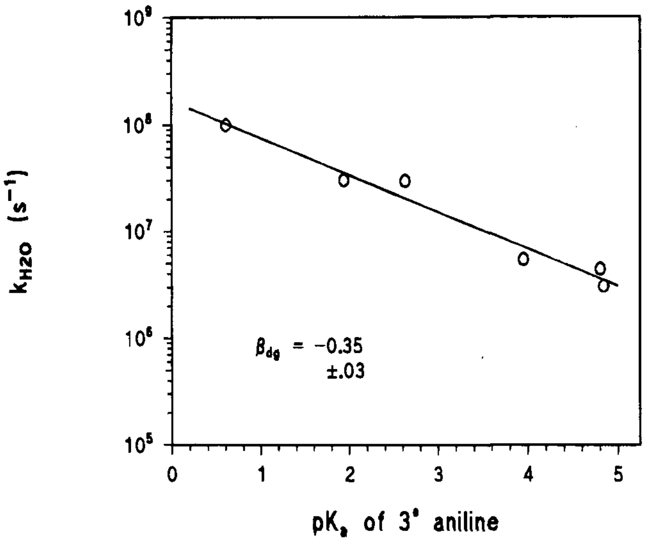

Figure 8. A Brønsted correlation of the rate constants for the hydration of $H_2C{=}N^+(CH_3)C_6H_4X$: log k_{H_2O} against the pK_a values of the corresponding *N,N*-dimethylanilines $(CH_3)_2NC_6H_4X$, X = 4-NO_2, 4-CN, 3-NO_2, 4-NO_2, 3-Cl, and 4-COO^-, with $\beta_{dg} = -0.35 \pm 0.03$.

We have shown that the rate constant for the reaction of $H_2C{=}N^+(CH_3)C_6H_4\text{-}4\text{-}NO_2$ with water is $1 \times 10^8\ s^{-1}$. The N^+ scale of nucleophilic reactivities[24] predicts that thiophenoxide ion will be more reactive toward the cation than water by a factor of $\sim 10^8$. This would predict a rate constant of $\sim 10^{16}$ $M^{-1}\ s^{-1}$ for the reaction of $H_2C{=}N^+(CH_3)C_6H_4\text{-}4\text{-}NO_2$ with the ArS^- leaving group.[25] This value is too large to be quantitatively significant, but it would surely result in a first-order rate constant that would be too large to represent a significant barrier for the collapse of the encounter complex $H_2C{=}N^+(CH_3)C_6H_4\text{-}4\text{-}NO_2\cdot{}^-SAr$ to give the addition product. This requires that the reaction of the parent anilinothioether with such a nucleophile must proceed as a concerted bimolecular substitution reaction, because there is no significant barrier for the reaction with an iminium cation intermediate. We have observed such a bimolecular reaction, as will be described in a later publication.

We believe that the solvolysis of **1**−SR does not proceed through the classical $D_N + A_N$ mechanism (S_N1 reaction), in which a bond-breaking step is followed by a diffusional separation step to form a solvent-separated ion pair. The absence of a significant lifetime for the encounter complex $H_2C{=}N^+(CH_3)C_6H_4\text{-}4\text{-}NO_2\cdot{}^-SAr$ requires that the transition state for the formation of $\mathbf{1}^+$ must involve both bond-breaking and diffusional separation.

Relevance to the Mechanism of Reaction of Thymidylate Synthase. These results show that iminium cations derived from formaldehyde, $H_2C{=}N^+(CH_3)C_6H_4X$ (X = 4-NO_2, 4-CN, 3-NO_2, 4-NO_2, 3-Cl, 4-^-OOC, and 4-Cl), have significant barriers for their reaction with water. Therefore, the iminium ion that is generated from N^5,N^{10}-methylenetetrahydrofolate, $\mathbf{2}^+$, could, in principle, have a significant lifetime in aqueous solution. The Brønsted plot for the dependence of log k_{H_2O} on the pK_a of the corresponding aniline in Figure 8 shows that the lifetime of the iminium ion increases with increasing basicity of the nitrogen atom of the parent amine. Assuming that the pK_a of N^5 in 5-methyltetrahydrofolate is not significantly different from that reported[26] for the same nitrogen atom in tetrahydrofolate, 4.8, the lifetime in aqueous solution of the iminium ion N^5,N^{10}-methylenetetrahydrofolate, $\mathbf{2}^+$, may be estimated by extrapolation from the Brønsted plot of Figure 8 to be $\sim 2.5 \times 10^{-7}$ s ($k_{H_2O} \approx 4 \times 10^6\ s^{-1}$).

The estimated lifetime for the iminium ion $\mathbf{2}^+$ is short enough that it is possible that the intramolecular nucleophilic group −HNR that is in close proximity to the cationic center would rapidly attack the iminium cation, preventing the iminium ion from existing for a significant time. Therefore, the transfer of methylene groups from N^5,N^{10}-methylenetetrahydrofolate, as in the conversion of dUMP to dTMP catalyzed by thymidylate synthase, may proceed through a concerted bimolecular substitution mechanism in which formation of the free iminium ion is circumvented.

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[24] Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239.

[25] There are a few examples in the literature in which Ritchie's N^+ scale of nucleophilicity has failed (Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689. McClelland, R. A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 2929). However, Richard and Jencks in their study of different reactivity−selectivity behavior of substituted 1-phenylethyl carbocations demonstrated that the selectivities governed by the Ritchie N^+ scale are obtained when the rate constant k_{nuc} is activation limited and that there is no selectivity when k_{nuc} becomes diffusion limited. In this study we are estimating the first-order rate constant for the collapse of an encounter complex, in which the diffusional step is not involved.

[26] Kallen, R. G.; Jencks, W. P. *J. Biol. Chem.* **1966**, *241*, 5845.