Nucleofugality of the Benzotriazole Group in Solvolysis

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We report that the (N-1)-benzotriazole anion is $\approx 10^{14}$-fold less reactive as a leaving group in solvolysis than the chloride ion.

The utility of benzotriazoles as a route to stabilized carbanion synthons is widely recognized.[1] There is also compelling evidence that moderately stable electrophiles such as iminium and amidinium ions form as intermediates of synthetically useful reactions of neutral benzotriazole precursors[2] (leaving group $pK_a = 8.4$);[3] however, the nucleofugality of the benzotriazole group has not been determined. This property is of general interest because there are few reports of the use of substrates with leaving groups having $pK_a = 6-12$ as precursors for the generation of moderately stable electrophiles as intermediates of solvolysis reactions.

Benzotriazole **1-Bt** (α-(N-1)-benzotriazole-α-methoxytoluene) was prepared by a published procedure.[4] Two sharp isosbestic points were observed when the solvolysis of **1-Bt** in water at 25 °C ($I = 1.0$, KCl) was followed by UV spectroscopy; no reaction intermediates were detected by HPLC analyses, and the same pseudo-first-order rate constant, k_{obsd} (s^{-1}), was found to govern the disappearance of **1-Bt** and the appearance of the product benzaldehyde (**3**). These observations show that the solvolysis of **1-Bt** follows the same stepwise mechanism (Scheme 1) observed for the reactions of the corresponding acetals (**1-OR**),[5a,b] α-acetoxy ethers (**1-OAc**),[5c] and α-azido ethers (**1-N$_3$**)[6] and that the hemiacetal reaction intermediate does not accumulate to any significant extent.[5c]

A logarithmic plot of the pseudo-first-order rate constants for the solvolysis of **1-Bt**, determined over a broad range of pH by monitoring the formation of **3** at 250 nm, is shown in Figure 1. There is no detectable catalysis of the reaction of **1-Bt** by buffers (≤ 0.05 M) used to maintain constant pH. The data in Figure 1 were fit to eq 1, using $k_{solv} = 2.1 \times 10^{-7}$ s^{-1} for spontaneous solvolysis of **1-Bt** and $k_H = 9.2$ M^{-1} s^{-1} for the specific acid-catalyzed reaction (Scheme 1).

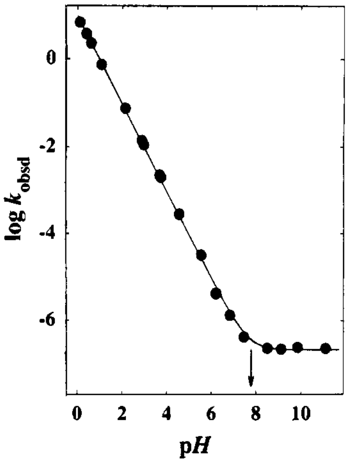
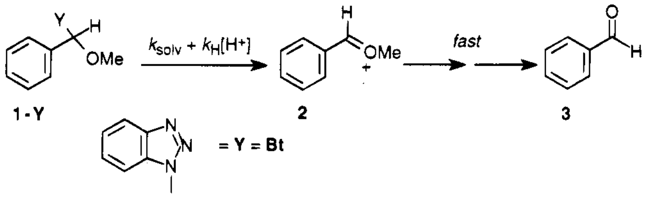


Figure 1. pH rate profile for solvolysis of **1-Bt** in water at 25 °C ($I = 1.0$, KCl). The solid line shows the fit of the data to eq 1, using $k_{solv} = 2.1 \times 10^{-7}$ s^{-1} and $k_H = 9.2$ M^{-1} s^{-1}. The arrow shows the pH at which $k_{solv} = k_H[H^+]$.

Scheme 1



$$k_{obsd} = k_{solv} + k_H[H^+] \qquad (1)$$

The sluggish pH-independent conversion of **1-Bt** to the α-(methoxybenzyl)oxocarbenium ion ($t_{1/2} \sim 40$ days) strongly suggests that electrophiles more stable than oxocarbenium ions, such as amidinium and iminium ions, should be readily accessible as intermediates in the solvolysis of appropriate benzotriazole precursors.

A value of $k_{solv} = 6 \times 10^{-18}$ s^{-1} for the solvolysis of 1-phenylethyl (N-1)-benzotriazole in 80% ethanol in water at 75 °C was estimated from the value of k_{solv} for reaction of **1-Bt** in water, as described in Table 1. Table 1 lists rate constants for $D_N + A_N$ (S_N1)[7] solvolysis of other 1-phenylethyl derivatives in 80% ethanol/water at 75 °C taken from the literature[8] and an estimate of k_{solv} for 1-phenylethyl azide. These data extend the range of nucleofugalities for heterolytic bond cleavage at carbon by *ca.* 10 million-fold, and they show that the benzotriazole anion is $\approx 10^{14}$-fold less reactive than chloride as a leaving group in solvolysis.

The effect of 1.0 M 2-mercaptoethanol on the products of the reaction of **1-Bt** at pH 4.6 (20 mM AcOH/AcO$^-$, I = 1.0 (KCl)) was determined in an effort to identify the position of bond cleavage for the specific acid-catalyzed reaction. The addition of 1.0 M thiol causes a 16% reduction in the yield of benzaldehyde but no change in the yield of benzotriazole. This result shows that $\geq 16\%$ of the reaction proceeds with carbon–nitrogen bond

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Table 1. Absolute and Relative Rate Constants for D_N + A_N (S_N1)[7] Solvolysis of 1-Phenylethyl Derivatives in 80% Ethanol/Water at 75 °C

leaving group	k_{solv} s^{-1}	relative rate[a]
benzotriazole anion	6×10^{-18b}	3×10^{-15}
N_3^-	6×10^{-13c}	3×10^{-10}
$CH_3CO_2^{-d}$	1×10^{-10}	5×10^{-8}
Cl^{-d}	1.9×10^{-3}	1
$CH_3SO_3^{-d}$	10.7	5600
$CF_3SO_3^{-d}$	2.2×10^{6}	1×10^{9}

[a] Rate constant for solvolysis relative to that of 1-phenylethyl chloride. [b] Estimated from k_{solv} for reaction of 1-phenylethyl azide in 80% EtOH/H_2O at 75 °C and a rate constant ratio of 1×10^5 for solvolysis of **1-N$_3$** ($k_{solv} = 0.022$ s^{-1})[6] and **1-Bt** ($k_{solv} = 2.1 \times 10^{-7}$ s^{-1}, this work) in water at 25 °C. [c] Estimated from k_{solv} for reaction of 1-phenylethyl chloride in 80% EtOH/H_2O at 75 °C and a rate constant ratio of 3×10^9 for solvolysis of 1-(4-methoxyphenyl)ethyl chloride ($k_{solv} = 400$ s^{-1}, footnote 7 in: Richard, J. P.; Amyes, T. L.; Bei, L.; Stubblefield, V. *J. Am. Chem. Soc.* **1990**, *112*, 9513–9519) and 1-(4-methoxyphenyl)ethyl azide ($k_{solv} = 1.3 \times 10^{-7}$ s^{-1}: Amyes, T. L.; Stevens, I. W.; Richard, J. P. *J. Org. Chem.* **1993**, *58*, 6057–6066) in 50/50 (v/v) trifluoroethanol/water at 25 °C. [d] Data from ref 8.

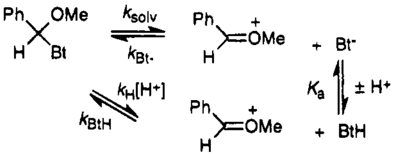
cleavage to form the oxocarbenium ion **2**, which is trapped by the thiol to give the mixed (O,S) acetal **1-SCH$_2$CH$_2$OH**,[9] which is 25-fold more stable in acid (k_H = 0.36 M^{-1} s^{-1})[10] than **1-Bt**. In fact, much more than 16% of the reaction in acid proceeds with carbon–nitrogen bond cleavage because only a poor yield of **1-SCH$_2$CH$_2$OH** will be obtained from trapping of the highly reactive and nonselective oxocarbenium ion **2** by 2-mercaptoethanol.[6]

The absence of an effect of 2-mercaptoethanol on the yield of benzotriazole shows that there is no detectable trapping of a nitrogen-stabilized carbenium ion to form a stable thiol adduct; however, the experimental results do not rigorously exclude the possibility that part of the reaction proceeds with C–O bond cleavage to give a nitrogen-stabilized carbenium ion, which decomposes to benzaldehyde through unstable tetrahedral adducts to water or 2-mercaptoethanol.

The similar second-order rate constants for specific acid-catalyzed cleavage of **1-Bt** (leaving group pK_a = 8.4,[3] k_H = 9.2 M^{-1} s^{-1}) and the acetal **1-OMe** (leaving group pK_a = 15.5,[3] k_H = 33 M^{-1} s^{-1})[5b] show that the rates of these reactions are relatively insensitive to changing basicity of the leaving group. Since protonation is favored for strongly basic leaving groups and bond cleavage is favored for weakly basic leaving groups, the observed insensitivity of k_H to leaving group basicity is consistent with a transition state in which full, preequilibrium, proton transfer to the leaving group is balanced by nearly complete cleavage of its bond to carbon.

Finally, we note that the pH at which equal pseudo-first-order rate constants are observed for the spontaneous and specific acid-catalyzed solvolysis of **1-Bt** (pH$_I$ = 7.6) is only 0.8 log units below the pK_a = 8.4 for ionization of the neutral benzotriazole leaving group. The relationship between pH$_I$ and pK_a for stepwise solvolysis (Scheme 2) is given by eq 2,[10] where k_{Bt^-} and k_{BtH} are the second-order rate constants for the reaction of **2** with the benzotriazole anion and neutral benzotriazole, respectively. Equation 2 holds because (1) in the reverse direction, the velocities for the conversion of **2 to 1-Bt** by reaction of anionic (Bt^-) and neutral (BtH) nucleophiles must also be equal at pH$_I$ and (2) the ratio of second-order rate constants k_{Bt^-}/k_{BtH} required to observe equal velocities for nucleophile addition to **2** at pH$_I$ = 7.6 is equal to $[BtH]_I/[Bt^-]_I$, the ratio of the concentration of the two nucleophiles at pH$_I$.

Scheme 2



$$pK_a - pH_I = \log(k_{Bt^-}/k_{BtH}) \qquad (2)$$

The value of pK_a − pH$_I$ = 0.8 for the reaction of **1-Bt**, which is among the smallest ever observed for solvolysis,[10] requires a small selectivity of (k_{Bt^-}/k_{BtH}) = 6 for partitioning of **2** between capture by the benzotriazole anion and neutral benzotriazole.[11] This small selectivity is in line with that expected for partitioning of the highly unstable ($k_{HOH} = 2 \times 10^9$ s^{-1} for reaction with solvent water)[6] and nonselective (k_{az}/k_{HOH} = 2.6 M^{-1} for partitioning between reaction with azide ion and solvent water)[6] oxocarbenium ion **2**.

Experimental Section

Materials. Inorganic and organic salts, benzaldehyde, and benzotriazole were reagent grade and were used without further purification. The water used for kinetic studies was distilled and then passed through a Milli-Q water purification apparatus. **1-Bt** was prepared and purified by literature procedures.[4,12]

Kinetic Studies. Rate constants for the solvolysis of **1-Bt** were determined in water at 25 °C and with constant ionic strength of 1.0 maintained with KCl. Solutions of **1-Bt** were prepared in acetonitrile, and the reactions were initiated by making a 300-fold dilution of this solution to give a final substrate concentration of 1×10^{-5}–6×10^{-5} M for reactions at pH < 6. The solvolysis reaction was followed by monitoring the appearance of **3** at 250 nm or the disappearance of **1-Bt** at 215 nm. The following buffers (potassium salts) were used to maintain constant pH: $H_2PO_4^-/HPO_4^{2-}$, pH 11.5–11; HCO_3^-/CO_3^{2-}, pH 9.8–9.3; $HP_2O_7^{3-}/P_2O_7^{4-}$, pH 9.3–8.5; $(CH_3)_2As(O)OH/(CH_3)_2As(O)O^-$, pH 6.2; $CH_3CO_2H/CH_3CO_2^-$, pH 5.6–3.6; $ClCH_2CO_2H/ClCH_2CO_2^-$, pH 2.8. Standard solutions of HCl were used at pH < 2.8.

Pseudo-first-order rate constants, k_{obsd} (s^{-1}), for reactions at pH < 6 were obtained from the slopes of semilogarithmic plots of reaction progress against time, which were linear for at least three half-times. The initial velocities of the slow reactions of **1-Bt** at pH 6–10 were determined by following the increase in absorbance at 250 nm over the first 3–5% of the reaction of **1-Bt** (1.2×10^{-4} M). Values of k_{obsd} were obtained from the slopes of linear plots of $(A - A_o)/(A_\infty - A_o)$, where $(A_\infty - A_o)$ is the total change in absorbance determined for the faster reaction of an identical concentration of **1-Bt** at low pH. It was shown in a control experiment that the change in absorbance at 250 nm for reaction of **1-Bt** is independent of pH.

The reactions of **1-Bt** in the presence of 0.10–1.0 M HCl were monitored at 250 nm using an SX.17MV stopped-flow spectrophotometer from Applied Photophysics. Pseudo-first-order rate constants, k_{obsd} (s^{-1}), were obtained from the fit of the absorbance data to a single exponential function using software supplied with the instrument.

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(9) We were unable to detect **1-SCH$_2$CH$_2$OH** by HPLC analysis because of its low yield (16%) and small extinction coefficient at 255 nm (ϵ_{255} = 300 M^{-1} cm^{-1} for **1-OMe**) compared to that of benzaldehyde (ϵ_{255} = 6250 M^{-1} cm^{-1}).

(10) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476–1488.

(11) If part of the acid-catalyzed reaction of **1-Bt** proceeds with C–O bond cleavage, then k_H for the reaction of **1-Bt** with C–N cleavage will be <9.2 M^{-1} s^{-1}, pH$_I$ for this reaction will shift to pH <7.6, and the value of k_{Bt^-}/k_{BtH} calculated using eq 2 will be >6.

(12) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 791–797.

HPLC Analyses. The products of solvolysis of **1-Bt** were analyzed by HPLC as described previously,[13] except that peak detection at 255 nm was with a Waters 996 diode array detector. The benzaldehyde and benzotriazole reaction products were identified by comparison of their UV spectra and retention times with those of authentic standards.

The effect of the addition of 1.0 M 2-mercaptoethanol on the products of the reaction of **1-Bt** at pH 4.6 (20 mM AcOH/AcO$^-$, I = 1.0 (KCl)) was determined using 3-(4-methoxyphenyl)-1-propanol as an internal injection standard.

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