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Relative Reactivities of a Strongly Nucleophilic Alkene and Azide Ion in Aqueous Methanol

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In recent years there have been extensive studies of structure−reactivity effects on the reactions of carbenium ions with alkenes in organic solvents[1] and with nucleophilic anions and solvent in mixed alcohol/water solvents.[2] The nucleophilic reactivity of the solvent water has been estimated to be lower than the reactivity of the strongly activated alkene pyrrole toward addition to resonance-stabilized carbocations.[1b] However, this estimate is based upon a comparison of data for the reaction of these nucleophiles with different electrophiles in different solvents. We are not aware of any direct determination of the relative nucleophilicity of alkenes and inorganic anions toward carbenium ions in nucleophilic solvents, and it is not known whether alkenes can compete effectively with the large concentrations of these solvents to give significant yields of an alkene adduct.

We report that $\mathbf{1}^+$ (Scheme 1) exhibits a large selectivity for reaction with the strongly activated alkene **2** and a direct comparison of the nucleophilicities of **2** and the inorganic nucleophile azide ion toward this electrophile.

The reaction of **1-PFB** (10^{-4} M, PFB = pentafluorobenzoate) in 50/50 (v/v) trifluoroethanol/water ($I = 0.50$, $NaClO_4$) gives the following products: the solvent adducts **1-OSolv**, 42% (38% **1-OH** and 4% **1-OCH$_2$CF$_3$**); the cyclization product **2**, 5%; and the dimeric product **3**, 53%. The addition of 1 mM NaN_3 does not affect the observed first-order rate constant ($k_{obsd} = 4.2 \times 10^{-3}$ s^{-1}) for reaction of **1-PFB**, but it causes a change in the reaction products to a quantitative yield of the azide ion adduct **1-N$_3$** (Scheme 1). By contrast, the reaction of 5×10^{-5} M **1-PFB** in 50/50 (v/v) methanol/water ($I = 0.50$, $NaClO_4$) gives a 98% total yield of the solvent adducts **1-OH** (30%) and **1-OMe** (68%), only 2% of **3**, and no detectable **2**.

We know of no precedent for the observed “self-assembly” of **3** by reaction of a very low concentration of **1-PFB** via heterolytic pathways in a protic, nucleophilic solvent. All of the rate and product data for these reactions are consistent with the mechanism shown in Scheme 1. The reaction of **1-PFB** in 50/50 (v/v) trifluoroethanol/water is kinetically zero order in the concentration of azide ion, and all of the products of this reaction are formed by partitioning of a common intermediate, $\mathbf{1}^+$, which undergoes quantitative trapping by 1 mM azide ion. This intermediate is either the open α-thioamide-substituted carbenium ion, a cyclic closed ion, or an equilibrium mixture of the two (Scheme 1).[3] We favor the open ion as the most reasonable precursor to **2**. However, acetolysis of enantiomerically enriched **1-OCOCF$_3$** occurs with partial retention of configuration, which is consistent with the presence of a mixture of the open and closed ions in acetic acid.[4] Whatever its structure, our results show that in 50/50 (v/v) trifluoroethanol/water a major reaction of $\mathbf{1}^+$ is its cyclization to give **2**. However, there is no large accumulation of **2** because it subsequently undergoes rapid nucleophilic addition to $\mathbf{1}^+$ that is formed continuously during the reaction of **1-PFB.**

In the more nucleophilic solvent of 50/50 (v/v) methanol/water, **3** is formed only as a minor product of the reaction of $\mathbf{1}^+$. A selectivity of $k_{az}/k_s = 70\,000$ M^{-1} for partitioning of $\mathbf{1}^+$ between reaction with azide ion and solvent was determined from the yields of the products of the reaction of **1-PFB** (5×10^{-5} M) according to eq 1, where [**1-N$_3$**]/[**1-OSolv**] is the ratio of the yields of the azide ion adduct and the sum of the yields of the solvent adducts (**1-OH** and **1-OMe**). In this solvent, the electrophile $\mathbf{1}^+$ is also trapped by *added* **2** to form **3** (Scheme 2). A rate constant ratio of $k_{az}/k_{alk} = 1.0$ for partitioning of $\mathbf{1}^+$ was determined from the yields of the nucleophile adducts **1-N$_3$** and **3**, which are formed from reaction of **1-PFB** (2×10^{-5} M) in the presence of both azide ion and the alkene **2**. It is not known if the rate constants for reaction of these two nucleophiles with $\mathbf{1}^+$ are identical because both reactions take place at the diffusion-controlled limit or because there is a coincidental equality of the barriers to two activation-limited reactions.

$$k_{az}/k_s = [\mathbf{1\text{-}N_3}]/[\mathbf{1\text{-}OSolv}][\mathrm{N_3}^-] \qquad (1)$$

The rate constant ratio k_s/k_c for partitioning of $\mathbf{1}^+$ between nucleophilic addition of solvent (k_s, Scheme 1) and intramolecular addition of the thioamide sulfur to the aromatic ring (k_c) is equal to the ratio of the yields of the products of the solvolysis (**1-OH** + **1-OSolv**) and the cyclization (**2** + **3**) reactions. These rate constants are closely matched for reaction in 50/50 (v/v) trifluoroethanol/water ([**1-OH** + **1-OSolv**]/[**2** + **3**] = $k_s/k_c = 0.74$), but in the more nucleophilic solvent of 50/50 (v/v) methanol/water **2** and **3** are minor reaction products, so that $k_s \gg k_c$.

In summary, we have shown that (1) at a concentration of 1.0 M, the alkene **2**, which is strongly activated for nucleophilic attack by electron-donating nitrogen and sulfur substituents, is 70 000-fold more reactive than the nucleophilic solvent 50/50 (v/v) methanol/water toward an electrophilic cation, and (2) the nucleophilic reactivity of the activated alkene **2** is the same as that of the highly reactive inorganic nucleophile azide ion. In addition, we now have in hand an experimental protocol that allows for the *direct* comparison of the reactivities of other alkenes and anionic nucleophiles toward electrophiles in strongly nucleophilic solvents.

Experimental Section

Synthesis. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini spectrometer at the University of Kentucky or at 300 or 400 MHz on Varian instruments at the University at Buffalo. Chemical shifts are reported downfield of an internal

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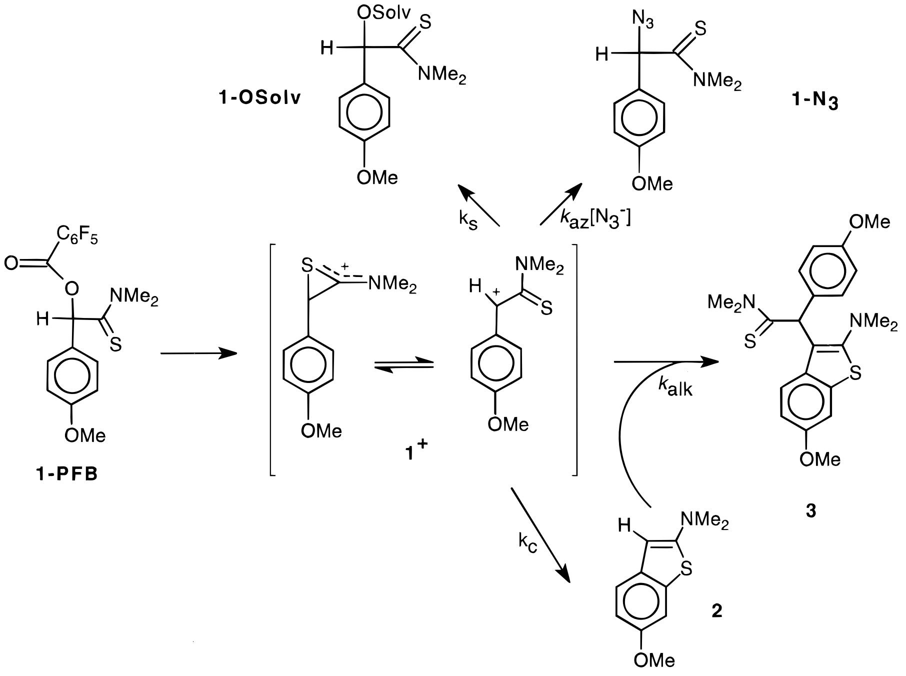
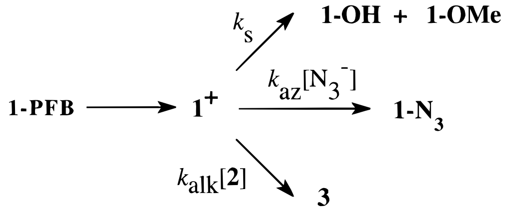
Scheme 1



Scheme 2



tetramethylsilane standard at 0 ppm. **2** was prepared by following a published procedure.[5]

α-(*N*,*N*-Dimethyl(thiocarbamoyl))-4-methoxybenzyl alcohol (**1**-OH) was prepared by the procedure used for the preparation of $Me_2NC(S)-$**2**-OH, except that 4-methoxybenzaldehyde was substituted for 4-methoxyacetophenone.[4b]

α-(*N*,*N*-Dimethylcarbamoyl)-4-methoxybenzyl pentafluorobenzoate (**1**-PFB) was synthesized from **1**-OH (0.13 g, 0.6 mmol) by adaptation of a published procedure for the synthesis of pentafluorobenzoate esters.[6] The final product was recrystallized from CH_2Cl_2/hexanes to give white crystals in a final yield of 60%: mp 109−110 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45, 6.95 (4H, A_2B_2, $J = 8.6$ Hz, Ar), 6.40 (1H, s, CH), 3.83 (3H, s, OCH_3), 3.01 (3H, s, NCH_3), 2.98 (3H, s, NCH_3); IR (cm^{-1}) 1740 (C=O), 1660 (C=O); UV λ_{max} 273 and 280 nm. Anal. Calcd for $C_{18}H_{14}F_5NO_4$: C, 51.55; H, 3.37; N, 3.34). Found: C, 51.40; H 3.40; N, 3.30.

Synthesis and Characterization of 3. **3** was isolated as a product of the reaction of **1-PFB** (100 mg) in CF_3CH_2OH (50 mL) for 5 h at room temperature. The solvent was removed by evaporation, and the products were separated by HPLC using a semipreparative octadecylsilane column (YMC), eluting with 80/20 (v/v) methanol/water. Evaporation of the solvent from the fractions containing **3** gave this compound as a white solid (40%): mp 88−90 °C; ^1H NMR (200 MHz, acetone-d_6, 20 °C, TMS) $\delta = 7.60$ (1H, d, $J = 9.0$ Hz, Ar), 7.27 (1H,d, $J = 2.4$ Hz, Ar), 7.12 (2H, d, $J = 8.4$ Hz, Ar), 6.82 (2H, d, $J = 8.4$ Hz, Ar), 6.69 (1H, dd, $J = 9.0$, 2.4 Hz, Ar), 6.13 (1H, s, CH), 3.79 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.51 (3H, s, $N(CH_3)_2$), 3.33 (3H, s, $N(CH_3)_2$), 2.66 (6H, s, $N(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 203.7$ (C=S), 158.1, 156.5, 153.4, 136.5, 132.9, 131.9, 130.3, 125.5, 124.1, 113.4, 113.3, 105.6, 55.5 (OCH_3), 55.1 (OCH_3), 53.9 (CH), 46.7 ($N(CH_3)_2$), 45.5 ($(C=S)N(CH_3)_2$), 41.8 ($(C=S)N(CH_3)_2$); $^{13}C-^1H$ DEPT analysis (100 MHz, $CDCl_3$) CH_3 $\delta = 55.5$, 55.1, 46.7, 45.5, 41.8; CH_2 none; CH $\delta = 130.3$, 125.5, 113.4, 113.3, 105.6, 53.9; MS found 414.1429, $C_{22}H_{26}N_2O_2S_2$ requires 414.1436.

Product Analyses by HPLC. The products of the addition of solvent and azide ion to $\mathbf{1}^+$ were identified by HPLC analysis as described in previous work.[7] The yields of the products of the reaction of **1-PFB** were calculated from the sum of their peak areas obtained from HPLC analysis with peak detection at 271 nm, which is λ_{max} for **1-OH**, and extinction coefficients for the various products at 271 nm in 50/50 (v/v) methanol/water determined as follows: Values of $\epsilon = 13\,000$ M^{-1} cm^{-1} for **1-OH** and $\epsilon = 11\,200$ M^{-1} cm^{-1} for **2** were determined using authentic materials. The former value was also used for **1-OCH₂CF₃** because the extinction coefficients of 4-methoxybenzyl alcohols and alkyl ethers are identical at λ_{max} for the alcohol.[8] Values of $\epsilon = 13\,000$ M^{-1} cm^{-1} for **1-OMe** and **1-N₃** and $\epsilon = 22\,000$ M^{-1} cm^{-1} for **3** were determined from $\epsilon = 13\,000$ M^{-1} cm^{-1} for **1-OH** and the ratio of the increase in the HPLC peak area for the nucleophile adduct (ΔA(**1-Nu**)) and the decrease in the sum of the peak areas for the solvent adducts (ΔA(**1-OSolv**)) observed for reaction of a fixed concentration of **1-PFB** in the presence of increasing concentrations of azide ion or **2** in 50/50 (v/v) methanol/water or of methanol in acetonitrile/water, according to eq 2.

$$\epsilon(\mathbf{1\text{-}Nu}) = (13\,000\ M^{-1}\ cm^{-1})(\Delta A(\mathbf{1\text{-}Nu})/\Delta A(\mathbf{1\text{-}OSolv})) \quad (2)$$

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