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# How Does Organic Structure Determine Organic Reactivity? Nucleophilic Substitution and Alkene-Forming Elimination Reactions of α-Carbonyl and α-Thiocarbonyl Substituted Benzyl Derivatives

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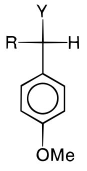
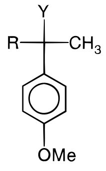
**Abstract:** The effect of α-(*N*,*N*-dimethylcarbamoyl) and α-(*N*,*N*-dimethylthiocarbamoyl) substituents on the rate constants for partitioning of α-substituted 1-(4-methoxyphenyl)ethyl carbocations between nucleophilic addition of 50:50 (v:v) MeOH/$H_2O$ ($k_s$, $s^{-1}$) and deprotonation by this solvent ($k_e$, $s^{-1}$) have been investigated. The data show that these α-amide and α-thioamide substituents result in 80-fold and ≥30 000-fold decreases, respectively, in $k_s$ for capture of the 4-methoxybenzyl carbocation by solvent, but that they lead to much smaller changes in $k_e$ for deprotonation of the corresponding α-substituted 1-(4-methoxyphenyl)ethyl carbocations by solvent. The large effect of the α-thioamide substituent on the partitioning of α-substituted 1-phenylethyl carbocations between formation of the products of solvolysis and elimination is therefore due primarily to the effect of this α-substituent on $k_s$ for capture of the carbocation by solvent. The results of experimental and computational studies are consistent with the conclusion that the relative magnitude of the rate constants $k_s$ and $k_e$ for partitioning of α-substituted 1-phenylethyl carbocations is strongly controlled by the relative thermodynamic stabilities of the neutral products of these reactions.

The reactions of the liberated carbocation intermediates of the stepwise reactions of simple α-methylbenzyl derivatives in nucleophilic solvents give mainly the products of solvolysis and less than 1% of the corresponding alkene product of an elimination reaction.[1,2] We were therefore surprised to learn that the substitution of an α-thioamide group for an α-methyl group at ring-substituted cumyl esters leads to a dramatic change in the product distribution for the reaction of these substrates in nucleophilic solvents, from mainly the solvent adducts, to the exclusive formation of the alkene product of an elimination reaction (Scheme 1).[3] This shows that the α-thioamide group causes a profound change in the partitioning of ring-substituted cumyl carbocations, from the predominant nucleophilic addition of solvent ($k_e/k_s \ll 1$, Scheme 1), to the virtually exclusive loss of a proton to form the α-substituted styrene ($k_e/k_s \gg 1$, Scheme 1).

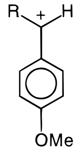
We report here experiments and calculations which were aimed at characterization of the effect of α-thiocarbonyl and α-carbonyl substituents on the following: (1) the rate constant $k_s$ ($s^{-1}$) for the addition of solvent to R-**1**$^+$ and R-**2**$^+$, (2) the rate constant $k_e$ ($s^{-1}$) for deprotonation of R-**2**$^+$ to form the α-substituted 4-methoxystyrene R-**3**, and (3) the relative thermodynamic stabilities of the alkene R-**3** and the corresponding water adduct (alcohol) R-**2**-OH.



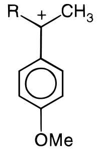
R-**1**-Y



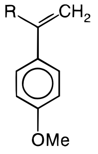
R-**2**-Y



R-**1**$^+$



R-**2**$^+$



R-**3**

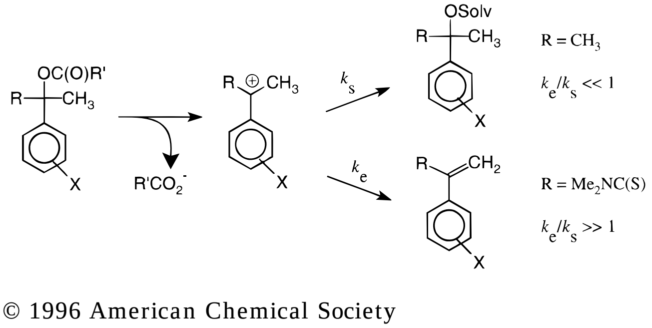
R = $Me_2NC(S)$, $Me_2NC(O)$, EtOC(O), $CH_3$

## Experimental Section

**Materials.** Unless noted otherwise, inorganic salts and organic chemicals were reagent grade from commercial sources and were used without further purification. Tetrahydrofuran was distilled from sodium/benzophenone and dichloromethane was distilled from calcium hydride. The water used for kinetic studies and HPLC analyses was distilled and then passed through a Milli-Q water purification system.

**Synthesis.** α-(Ethoxycarbonyl)-4-methoxybenzyl alcohol (EtOC(O)-**1**-OH)[4] and its pentafluorobenzoate ester (EtOC(O)-**1**-(pentafluorobenzoate)),[4] 2-(4-methoxyphenyl)-2-propyl 4-nitrobenzoate ($CH_3$-**2**-(4-nitrobenzoate)),[4] and 1-(*N*,*N*-dimethylthiocarbamoyl)-1-(4-methoxyphenyl)ethanol ($Me_2NC(S)$-**2**-OH)[3] were prepared by literature procedures. The procedures for the synthesis of the following compounds,

**Scheme 1**



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along with spectroscopic and analytical data for these compounds, are given in the Supporting Information: Me$_2$NC(S)-**1**-OH; Me$_2$NC(O)-**2**-OH; Me$_2$NC(O)-**1**-OH; EtOC(O)-**2**-OH; Me$_2$NC(S)-**1**-N$_3$; Me$_2$NC(S)-**2**-N$_3$; Me$_2$NC(S)-**2**-(4-nitrobenzoate); Me$_2$NC(S)-**2**-(4-methoxybenzoate); Me$_2$NC(O)-**2**-(4-nitrobenzoate); Me$_2$NC(O)-**2**-(pentafluorobenzoate); EtOC(O)-**2**-(pentafluorobenzoate); Me$_2$NC(S)-**1**-(4-nitrobenzoate); Me$_2$NC(S)-**1**-(3,5-dinitrobenzoate); Me$_2$NC(S)-**1**-(pentafluorobenzoate); Me$_2$NC(O)-**1**-(pentafluorobenzoate); Me$_2$NC(S)-**3**; Me$_2$NC(O)-**3**; EtOC(O)-**3**.

**HPLC Analyses.** The products of the reactions of R-**1**-Y and R-**2**-Y were separated by HPLC as described previously,[1,2,5,6] except that peak detection was by a Waters 996 diode array detector. The products were detected by their UV absorbance at the following wavelengths, which are $\lambda_{max}$ for the corresponding alcohols: Me$_2$NC(S)-**1**-Y, 271 nm; Me$_2$NC(O)-**1**-Y, 275 nm; EtOC(O)-**1**-Y, 275 nm; Me$_2$NC(O)-**2**-Y, 275 nm; EtOC(O)-**2**-Y, 274 nm; CH$_3$-**2**-Y, 273 nm. The products of the reactions of Me$_2$NC(S)-**2**-Y were detected at 266 nm, which is $\lambda_{max}$ for Me$_2$NC(S)-**3**.

The products of the reaction of solvent and azide ion with R-**1**-Y and R-**2**-Y were identified as described in earlier work.[1,2,6] The azide ion adducts Me$_2$NC(S)-**1**-N$_3$ and Me$_2$NC(S)-**2**-N$_3$ were also isolated and characterized by NMR and IR spectroscopy (see Supporting Information). The alkenes R-**3** formed from the reactions of R-**2**-Y were identified by comparison of their HPLC retention times with those for authentic materials.

**Procedures for Product Studies.** Product studies were carried out at room temperature (22 ± 2 °C). Control experiments showed that the product ratios obtained at room temperature and at 25 °C are identical. Aqueous solutions of sodium azide were adjusted to pH $\approx$ 7 with concentrated HClO$_4$ before use. Reactions were initiated by making a 100-fold dilution of a solution of substrate ($10^{-2}-10^{-3}$ M) in acetonitrile into 50:50 (v:v) TFE/H$_2$O or 50:50 (v:v) MeOH/H$_2$O at $I = 0.50$ (NaClO$_4$). The reactions of Me$_2$NC(S)-**2**-(4-nitrobenzoate) in 50:50 (v:v) MeOH/H$_2$O containing both azide and acetate ions were buffered with 1 or 5 mM sodium phosphate. These solutions were prepared by dilution of 20 mM sodium phosphate buffer in water at pH = 7.0 to the appropriate final concentration in 50:50 (v:v) MeOH/H$_2$O ($I = 0.50$, NaClO$_4$). The dehydration of Me$_2$NC(S)-**2**-OH to give Me$_2$NC(S)-**3** was carried out in 50:50 (v:v) TFE/H$_2$O containing 0.05−0.50 M perchloric acid ($I = 0.50$, NaClO$_4$).

The yields of the products of the reaction of Me$_2$NC(S)-**2**-(4-methoxybenzoate) with azide ion in 50:50 (v:v) MeOH/H$_2$O were determined during the first 3 h of the reaction, because at later times there was significant conversion of the azide ion adduct to the alkene Me$_2$NC(S)-**3**. For all other R-**1**-Y and R-**2**-Y, the products were shown to be stable for at least three halftimes of the reaction of the substrate.

Ratios of product yields ([P$_1$]/[P$_2$]) were calculated using eq 1, where $A_1/A_2$ and $\epsilon_{P_2}/\epsilon_{P_1}$ are the ratios of the peak areas from HPLC analysis and the extinction coefficients of the two products at the wavelength of the analysis, respectively. The reproducibility of the product ratios

$$[\mathrm{P}_1]/[\mathrm{P}_2] = (A_1/A_2)(\epsilon_{\mathrm{P}_2}/\epsilon_{\mathrm{P}_1}) \tag{1}$$

$$\epsilon_{\mathrm{alkene}}/\epsilon_{\mathrm{RN}_3} = \Delta A_{\mathrm{alkene}}/\Delta A_{\mathrm{RN}_3} \tag{2}$$

from HPLC analysis was ±10%. For R-**1**-Y, EtOC(O)-**2**-Y, and CH$_3$-**2**-Y, the extinction coefficients of the alcohols and the corresponding methanol and azide ion adducts were shown to be identical by solvolyzing the corresponding benzoate esters in the presence of increasing concentrations of methanol or azide ion and showing, by HPLC analysis of a constant amount of total product, that the decrease in the HPLC peak area for the alcohol product is equal to the increase in the HPLC peak area for the methanol or azide ion adduct. The extinction coefficients of Me$_2$NC(O)-**2**-N$_3$ and Me$_2$NC(O)-**2**-OH at 275 nm were assumed to be identical because the absorbance of these compounds at this wavelength is due primarily to the 4-methoxyphenyl group. A ratio of $\epsilon_{\mathrm{alkene}}/\epsilon_{\mathrm{ROH}} = (12\,600\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1})/(1800\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}) = 7.0$ at 275 nm for Me$_2$NC(O)-**3** and Me$_2$NC(O)-**2**-OH in 50:50 (v:v) MeOH/H$_2$O was determined using authentic materials. A ratio of $\epsilon_{\mathrm{alkene}}/\epsilon_{\mathrm{RN}_3} = 2.7$ at 266 nm for Me$_2$NC(S)-**3** and Me$_2$NC(S)-**2**-N$_3$ was calculated using eq 2, where $\Delta A_{\mathrm{alkene}}$ and $\Delta A_{\mathrm{RN}_3}$ are the changes in the HPLC peak areas for Me$_2$NC(S)-**3** and Me$_2$NC(S)-**2**-N$_3$, respectively, observed for reaction of a constant amount of Me$_2$NC(S)-**2**-(4-nitrobenzoate) in the presence of increasing concentrations of azide ion. The reproducibility of the extinction coefficient ratios determined in different experiments was better than ±10%. The relative extinction coefficients of the alkene EtOC(O)-**3** and the corresponding nucleophile adducts EtOC(O)-**2**-Y were not determined.

**Calculation of Rate Constant Ratios.** Dimensionless rate constant ratios for the reactions of nucleophiles Nu1 and Nu2 with R-**1**-Y and R-**2**-Y were calculated from the product yields using eq 3. The rate

$$k_{\mathrm{Nu}_1}/k_{\mathrm{Nu}_2} = [\mathrm{RNu1}][\mathrm{Nu2}]/[\mathrm{RNu2}][\mathrm{Nu1}] \tag{3}$$

constant ratios $k_e/k_s$ for reaction of solvent as a Brønsted base to form the elimination product ($k_e$) and as a nucleophile to form the solvolysis products ($k_s$) were calculated directly as the ratio of the yields of these products. Rate constant ratios $k_{az}/k_s$ (M$^{-1}$) for partitioning of R-**1**-Y and R-**2**-Y between reaction with azide ion and solvent were calculated using eq 4. The estimated error in these rate constant ratios is ±10%, the uncertainty in $A_1/A_2$ (eq 1), plus any uncertainty in the value of $\epsilon_{P_2}/\epsilon_{P_1}$ (see above).

$$k_{\mathrm{az}}/k_{\mathrm{s}}\ (\mathrm{M}^{-1}) = [\mathrm{RN}_3]/\sum[\mathrm{ROSolv}][\mathrm{N}_3^{\ -}] \tag{4}$$

Rate constant ratios for partitioning of the carbocation intermediates R-**2**$^+$ of the reactions of R-**2**-Y in the presence of azide ion alone, or in the presence of both azide and acetate ions, were determined from the nonlinear least squares fit of the product data to the appropriate equation (see Discussion), using SigmaPlot from Jandel Scientific.

**Kinetic Methods.** Kinetic studies were carried out in 50:50 (v:v) TFE/H$_2$O or 50:50 (v:v) MeOH/H$_2$O at 25 °C and $I = 0.50$ (NaClO$_4$). Aqueous solutions of sodium azide were adjusted to pH $\approx$ 7 with concentrated HClO$_4$ before use. The reactions were initiated by making a 100-fold dilution of a solution of substrate ($10^{-2}-10^{-3}$ M) in acetonitrile into the appropriate reaction mixture. For reactions that were monitored by HPLC analysis, the reaction mixture also contained *ca.* $10^{-5}$ M of 9-hydroxy-9-methylfluorene or 9-methoxyfluorene as an internal standard to correct for small variations in the HPLC injection volume.

The reactions of substituted benzoate esters were monitored by following either (a) the change in UV absorbance at the following wavelengths: Me$_2$NC(S)-**1**-(pentafluorobenzoate), 275 nm; Me$_2$NC(S)-**2**-(4-nitrobenzoate), 274 nm; or (b) the disappearance of the substrate by HPLC at the following wavelengths: Me$_2$NC(S)-**2**-(4-methoxybenzoate), 266 nm; Me$_2$NC(S)-**1**-(4-nitrobenzoate), 269 nm; Me$_2$NC(S)-**1**-(3,5-dinitrobenzoate), 271 nm; Me$_2$NC(O)-**2**-(4-nitrobenzoate), 262 nm; Me$_2$NC(O)-**2**-(pentafluorobenzoate), 273 nm; Me$_2$NC(O)-**1**-(pentafluorobenzoate), 273 nm; EtOC(O)-**2**-(pentafluorobenzoate), 273 nm; EtOC(O)-**1**-(pentafluorobenzoate), 273 nm.

The progress of the dehydration of Me$_2$NC(S)-**2**-OH to give Me$_2$NC(S)-**3** in 50:50 (v:v) TFE/H$_2$O containing 0.05 − 0.50 M perchloric acid ($I = 0.50$, NaClO$_4$) was monitored by HPLC analysis at 271 nm.

For all reactions, good first-order kinetics were observed over at least three half-lifes. First-order rate constants were determined from the slopes of linear semilogarithmic plots of reaction progress against time. The second-order rate constant for the acid-catalyzed dehydration of Me$_2$NC(S)-**2**-OH was determined as the slope of the linear plot of $k_{obsd}$ against [HClO$_4$]. Rate constants determined spectrophotometrically were reproducible to ±5%, and rate constants determined by HPLC analysis were reproducible to ±10%.

**Ab Initio Calculations.** The potential energy surfaces of α-substituted 1-phenylethanols and the corresponding α-substituted styrenes were examined with the semiempirical AM1 Hamiltonian[7] using MOPAC 4.0[8] on an IBM ES9121-400 computer at Miami University,

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**Table 1.** Observed First-Order Rate Constants for the Reactions of R-**1**-Y and R-**2**-Y in 50:50 (v:v) Methanol/Water and 50:50 (v:v) Trifluoroethanol/Water at 25 °C and $I = 0.50$ ($NaClO_4$)[a]

R-**1**-Y

| | | $k_{obsd}$ ($s^{-1}$) | |
|---|---|---|---|
| R | leaving group | 50:50 (v:v) $MeOH/H_2O$ | 50:50 (v:v) $TFE/H_2O$ |
| $CH_3$ | 4-nitrobenzoate | | $1.3 \times 10^{-4}$ [b] |
| | pentafluorobenzoate | | $1.5 \times 10^{-2}$ [c] |
| $Me_2NC(S)$ | 4-nitrobenzoate | $3.6 \times 10^{-5}$ | $3.7 \times 10^{-5}$ |
| | 3,5-dinitrobenzoate | $2.7 \times 10^{-4}$ | $3.1 \times 10^{-4}$ |
| | pentafluorobenzoate[d] | $5.3 \times 10^{-3}$ | $4.2 \times 10^{-3}$ |
| $Me_2NC(O)$ | pentafluorobenzoate | $1.9 \times 10^{-6}$ | $2.3 \times 10^{-6}$ |
| EtOC(O) | pentafluorobenzoate | $7.0 \times 10^{-7}$ | $5.5 \times 10^{-7}$ [b] |

R-**2**-Y

| | | $k_{obsd}$ ($s^{-1}$) | | |
|---|---|---|---|---|
| R | leaving group | 50:50 (v:v) $MeOH/H_2O$ | 50:50 (v:v) $TFE/H_2O$ | α-Me/ α-H[e] |
| $CH_3$ | 4-nitrobenzoate | | 0.090[b] | 690[g] |
| $Me_2NC(S)$ | 4-methoxybenzoate | $3.7 \times 10^{-5}$ | $2.0 \times 10^{-5}$ | |
| | 4-nitrobenzoate[d] | $1.3 \times 10^{-3}$ | $7.1 \times 10^{-4}$ | 36[f] |
| | | | | 19[g] |
| $Me_2NC(O)$ | 4-nitrobenzoate | $1.4 \times 10^{-6}$ | $8.5 \times 10^{-7}$ | |
| | pentafluorobenzoate | $1.6 \times 10^{-4}$ | $9.4 \times 10^{-5}$ | 84[f] |
| | | | | 41[g] |
| EtOC(O) | pentafluorobenzoate | $4.0 \times 10^{-5}$ | $3.5 \times 10^{-5}$ | 57[f] |
| | | | | 64[g] |

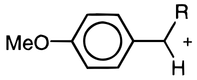
[a] Unless noted otherwise, rate constants were determined by following the disappearance of the substrate by HPLC as described in the Experimental Section. [b] Data from ref 4. [c] Estimated from $k_{obsd} = 1.3 \times 10^{-4}$ $s^{-1}$ for $CH_3$-**1**-(4-nitrobenzoate) and a rate constant ratio of 114 for reaction of $Me_2NC(S)$-**1**-(pentafluorobenzoate) and $Me_2NC(S)$-**1**-(4-nitrobenzoate) in 50:50 (v:v) trifluoroethanol/water (this work). [d] Determined spectrophotometrically as described in the Experimental Section. [e] Effect of the addition of an α-methyl group on $k_{obsd}$ for reaction of R-**1**-Y, calculated as the ratio of rate constants for reaction of R-**2**-Y and R-**1**-Y. [f] In 50:50 (v:v) methanol/water. [g] In 50:50 (v:v) trifluoroethanol/water.

or MOPAC 93[9] on a DEC 5000 workstation at the University of New England, Australia. After the initial optimization of geometry, the bonds between the benzylic carbon and the phenyl ring and the benzylic carbon and the α-substituent were systematically rotated and the energy recalculated, in order to ensure that a global minimum had been located.

The AM1 global minimum was used as the starting geometry for the ab initio calculations, which were performed using Gaussian 92[10] on a Cray Y-MP8/864 computer at the Ohio Supercomputer Center. Complete geometry optimization was performed by restricted Hartree−Fock calculations with the split-valence 3-21G basis set.[11,12] The calculations were performed without symmetry restrictions and all geometric parameters were fully optimized. Single-point calculations with the polarization basis set 6-31G*[13] were performed on each minimum energy structure that was located with the 3-21G basis set.

## Results

**Table 2.** Rate Constant Ratios for Partitioning of α-Substituted 4-Methoxybenzyl Carbocations R-**1**$^+$ between Reaction with Nucleophilic Reagents in 50:50 (v:v) Methanol/Water[a]



| R | $k_{MeOH}/k_{HOH}$[b] | $k_{az}/k_s$[c] ($M^{-1}$) |
|---|---|---|
| $Me_2NC(S)$[d] | 5 | $7 \times 10^4$ [e] |
| $Me_2NC(O)$[f] | 22 | 210[g] |
| EtOC(O)[h] | 11 | 44 |
| $CH_3$[i] | 9.0 | 7.2 |

[a] At 22 ± 2 °C and $I = 0.50$ ($NaClO_4$) and determined from product analysis by HPLC. [b] Dimensionless ratio of second-order rate constants for reaction of the carbocation with methanol and with water (eq 3). [c] Rate constant ratio for partitioning of the carbocation between reaction with azide ion and with solvent, calculated using a first-order rate constant for the reaction of solvent (eq 4). [d] Identical results were obtained using $Me_2NC(S)$-**1**-(4-nitrobenzoate), $Me_2NC(S)$-**1**-(3,5-dinitrobenzoate), or $Me_2NC(S)$-**1**-(pentafluorobenzoate) as the precursor to the carbocation. [e] Average (±10%) of four determinations in the range $[N_3^-] = 0.5-1.0$ mM. [f] Determined using $Me_2NC(O)$-**1**-(pentafluorobenzoate) as the precursor to the carbocation. [g] Average (±10%) of five determinations in the range $[N_3^-] = 1.0-10$ mM. [h] Determined using EtOC(O)-**1**-(pentafluorobenzoate) as the precursor to the carbocation. [i] Data from ref 1.

Table 1 gives the observed first-order rate constants, $k_{obsd}$ ($s^{-1}$), for the reactions of R-**1**-Y and R-**2**-Y in 50:50 (v:v) $MeOH/H_2O$ ($I = 0.50$, $NaClO_4$) and 50:50 (v:v) $TFE/H_2O$ ($I = 0.50$, $NaClO_4$), which were determined by monitoring the reaction progress by UV spectroscopy or HPLC analysis, as described in the Experimental Section. There was no significant change in $k_{obsd}$ (±10%) for reaction of any of these substrates when the concentration of azide ion was increased from zero to 0.50 M at $I = 0.50$ ($NaClO_4$). At $[N_3^-] = 0.50$ M, the yields of the corresponding azide ion adducts from these reactions were at least 40%.

The yields of the products of the reactions of R-**1**-Y and R-**2**-Y in 50:50 (v:v) $MeOH/H_2O$ ($I = 0.50$, $NaClO_4$) in the presence of increasing concentrations of azide ion were determined by HPLC analyses. Tables 2 and 3 give the dimensionless product rate constant ratios $k_{MeOH}/k_{HOH}$ for partitioning of R-**1**-Y and R-**2**-Y between reaction with methanol and with water in 50:50 (v:v) $MeOH/H_2O$, which were calculated from the yields of the methyl ethers and the corresponding alcohols using eq 3. Tables 2 and 3 also give the values of $k_{az}/k_s$ ($M^{-1}$) for the reactions of R-**1**-Y and R-**2**-Y with azide ion and solvent, which were calculated from the yields of the azide ion adduct and the solvent adducts using eq 4. There was no detectable formation of solvent adducts from the reactions of $Me_2NC(S)$-**2**-Y.

The rate constant ratio $k_s/k_e = 1.2$ (Table 3) for the partitioning of $Me_2NC(O)$-**2**-(pentafluorobenzoate) between solvolysis ($k_s$) and elimination ($k_e$) in 50:50 (v:v) $MeOH/H_2O$ was calculated directly as the ratio of the yields of the products of these reactions. The observed ratio of the HPLC peak areas for the solvolysis and elimination products of the reaction of EtOC(O)-**2**-(pentafluorobenzoate) in 50:50 (v:v) $MeOH/H_2O$ was used to calculate $k_s/k_e \approx 50$ (Table 3). This probably underestimates this ratio because the molar absorbtivity of the conjugated alkene EtOC(O)-**3** at 274 nm (the wavelength used for HPLC analysis) is expected to be larger than that of the solvent adducts EtOC(O)-**2**-OSolv ($\epsilon_{alkene} > \epsilon_{ROSolv}$, eq 1). There was no detectable formation of solvent adducts from the reactions of $Me_2NC(S)$-**2**-Y in 50:50 (v:v) $MeOH/H_2O$, and the yield of the alkene $CH_3$-**3** from the reaction of $CH_3$-**2**-(4-nitrobenzoate) in this solvent is less than 1%.[14] Therefore, the values of $k_s/k_e$ (Table 3) for the reactions of $Me_2NC(S)$-**2**-Y and $CH_3$-**2**-(4-nitrobenzoate) are upper and lower limits, re-

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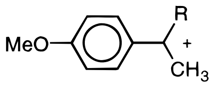
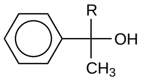
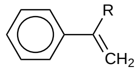
**Table 3.** Rate Constant Ratios for Partitioning of α-Substituted 1-(4-Methoxyphenyl)ethyl Carbocations R-**2**$^+$ between Nucleophilic Addition and Base-Catalyzed Deprotonation in 50:50 (v:v) Methanol/Water[a]



| R | $k_{MeOH}/k_{HOH}$[b] | $k_s/k_e$[c] | $k_{az}/k_s$[d] ($M^{-1}$) | $k_{az}/k_e$ ($M^{-1}$) | $k_{az}/k_B$[b] | $k_B/k_{Ac}$[b] |
|---|---|---|---|---|---|---|
| Me$_2$NC(S)[e] | | $<0.01$[f] | | 65[g] | 0.59[h] | 4.5[i] |
| Me$_2$NC(O)[j] | 31 | 1.2 | 1400 | 1700[k] | 10[h] | |
| EtOC(O)[l] | 14 | ≈50[m] | 84 | ≈4200[k] | large | |
| CH$_3$[n] | 9.0 | $>100$[o] | 18 | $>1800$[k] | large | |

[a] At 22 ± 2 °C and $I = 0.50$ (NaClO$_4$) and determined from product analysis by HPLC. [b] Dimensionless ratio of second-order rate constants. [c] Dimensionless ratio of first-order rate constants, calculated as the ratio of the yields of the solvent adducts and the alkene. [d] Rate constant ratio for partitioning of the carbocation between reaction with azide ion and with solvent and an average (±10%) of values determined at five or more concentrations of azide ion (eq 4). [e] Identical results were obtained using Me$_2$NC(S)-**2**-(4-methoxybenzoate) or Me$_2$NC(S)-**2**-(4-nitrobenzoate) as the precursor to the carbocation. [f] Upper limit calculated with the assumption that a 1% yield of the solvent adducts could have been detected by HPLC analysis. [g] Determined from the nonlinear least squares fit of the product data in Figure 1A to eqs 6 and 8 (see text). [h] The ratio of the constant limiting yields of the azide ion adduct and the alkene at high [N$_3^-$] (see Figure 1). [i] Calculated from $k_B/k_e = 110$ M$^{-1}$ (see text) and $k_{Ac}/k_e = 24.5$ M$^{-1}$ that was determined from the nonlinear least squares fit of the product data in Figure 2 to eqs 9 and 10 (see text). [j] Determined using Me$_2$NC(O)-**2**-(pentafluorobenzoate) as the precursor to the carbocation. [k] Calculated as $(k_s/k_e)(k_{az}/k_s)$. [l] Determined using EtOC(O)-**2**-(pentafluorobenzoate) as the precursor to the carbocation. [m] Calculated from the ratio of the observed HPLC peak areas for the solvent adducts and the alkene with the assumption that $\epsilon_{alkene} \approx \epsilon_{ROSolv}$ (eq 1). [n] Determined using CH$_3$-**2**-(4-nitrobenzoate) as the precursor to the carbocation. [o] The yield of the alkene is less than 1% and the upper limit was calculated with the assumption that a 1% yield of the alkene could have been detected by HPLC analysis.

**Table 4.** Ab Initio Energies of the Geometry Optimized Structures of α-Substituted 1-Phenylethanols R-**9**-OH and the Corresponding α-Substituted Styrenes R-**10**[a]

| | energy (hartrees)[b] | |
|---|---|---|
| | 3-21G//3-21G | 6-31G*//3-21G |
| |  | |
| CH$_3$ | −420.321749 | −422.659327 |
| MeOC(O) | −606.880681 | −610.262997 |
| Me$_2$NC(O) | −625.963840 | −629.452363 |
| Me$_2$NC(S) | −947.075646 | −952.077792 |
| |  | |
| CH$_3$ | −344.692880 | −346.621141 |
| MeOC(O) | −531.250113 | −534.224382 |
| Me$_2$NC(O) | −550.337389 | −553.416676 |
| Me$_2$NC(S) | −871.449629 | −876.047629 |

[a] Geometries were fully optimized by standard RHF procedures at the 3-21G level (see the Experimental Section) and the results of these calculations are given in the Supporting Information. [b] 1 hartree = 627.51 kcal/mol.

spectively, that were calculated with the assumption that 1% yields of Me$_2$NC(S)-**2**-OSolv and CH$_3$-**3** could have been detected by HPLC analysis.

Figure 1A shows the effect of increasing concentrations of azide ion on the fractional yields of the products of the reactions of Me$_2$NC(S)-**2**-(4-nitrobenzoate) and Me$_2$NC(S)-**2**-(4-methoxybenzoate) in 50:50 (v:v) MeOH/H$_2$O ($I = 0.50$, NaClO$_4$), and Figure 1B shows the corresponding data for the reaction of Me$_2$NC(O)-**2**-(pentafluorobenzoate).

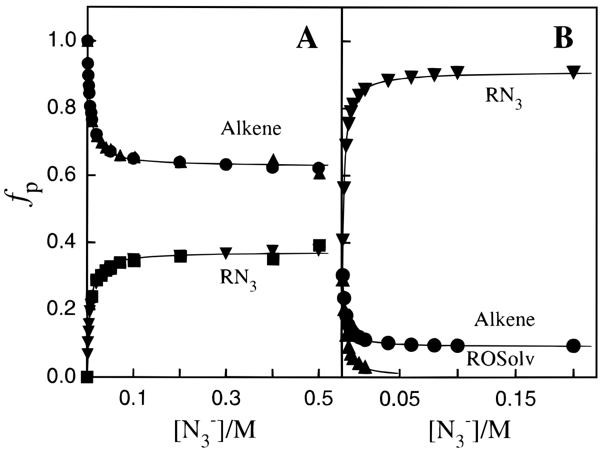


**Figure 1.** (A) Effect of azide ion on the fractional yields of the azide ion adduct Me$_2$NC(S)-**2**-N$_3$ and the alkene Me$_2$NC(S)-**3** from the reactions of Me$_2$NC(S)-**2**-Y in 50:50 (v:v) methanol/water at 22 ± 2 °C and $I = 0.50$ (NaClO$_4$). Key: ● and ▼, Y = 4-nitrobenzoate; ▲ and ■, Y = 4-methoxybenzoate. (B) Effect of azide ion on the fractional yields of the azide ion adduct Me$_2$NC(O)-**2**-N$_3$, the solvent adducts Me$_2$NC(O)-**2**-OSolv, and the alkene Me$_2$NC(O)-**3** from the reaction of Me$_2$NC(O)-**2**-(pentafluorobenzoate) in 50:50 (v:v) methanol/water at 22 ± 2 °C and $I = 0.50$ (NaClO$_4$).

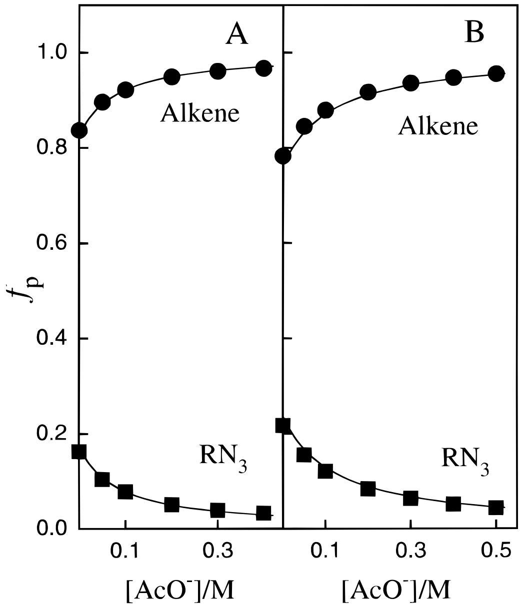


**Figure 2.** Effect of acetate ion on the fractional yields of the alkene Me$_2$NC(S)-**3** and the azide ion adduct Me$_2$NC(S)-**2**-N$_3$ from the reaction of Me$_2$NC(S)-**2**-(4-nitrobenzoate) in 50:50 (v:v) methanol/water at 22 ± 2 °C and $I = 0.50$ (NaClO$_4$) in the presence of 5 mM sodium phosphate buffer (pH = 7 in water) and a constant concentration of azide ion: (A) [N$_3^-$] = 5 mM; (B) [N$_3^-$] = 10 mM.

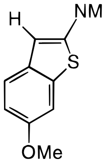
Figure 2 shows the effect of increasing concentrations of acetate ion on the fractional yields of the products of the reaction of Me$_2$NC(S)-**2**-(4-nitrobenzoate) in 50:50 (v:v) MeOH/H$_2$O ($I = 0.50$, NaClO$_4$) in the presence of 5 mM sodium phosphate buffer (pH = 7.0 in water) and 5 mM (Figure 2A) or 10 mM (Figure 2B) azide ion. The dilute phosphate buffer was added in order to minimize the reactions of hydroxide and methoxide ions as specific bases. It was shown that the product yields are unaffected by a decrease from 5 to 1 mM phosphate buffer.

The progress of the dehydration of Me$_2$NC(S)-**2**-OH to give the alkene Me$_2$NC(S)-**3** in 50:50 (v:v) TFE/H$_2$O containing 0.05−0.50 M perchloric acid ($I = 0.50$, NaClO$_4$) was followed by HPLC. The plot of $k_{obsd}$ against [HClO$_4$] is linear over this range of acid concentration, which shows that there is no detectable protonation of the α-thioamide group of the substrate by 0.50 M $HClO_4$. The second-order rate constant for the acid-catalyzed dehydration of $Me_2NC(S)$-**2**-OH, determined from the slope of this plot, is $k_H = 7.2 \times 10^{-5}$ $M^{-1}$ $s^{-1}$. After ten reaction halftimes no detectable $Me_2NC(S)$-**2**-OH (< 1%) remained, which shows that $K_{alk} = [alkene]_{eq}/[alcohol]_{eq} > 100$. It was not possible to monitor the dehydration of $Me_2NC(O)$-**2**-OH or EtOC(O)-**2**-OH to the corresponding alkenes, because the acid-catalyzed hydrolysis of the α-amide or α-ester group of these substrates is significantly faster than the dehydration reaction.

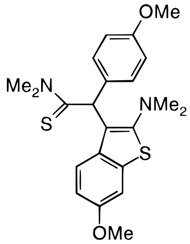
**Calculations.** The minimum-energy conformations of α-substituted 1-phenylethanols and the corresponding α-substituted styrenes, and the energies of these conformers were determined using ab initio methods, as described in the Experimental Section. The results of these calculations are summarized in Table 4. The geometries of the optimized structures of these compounds are given in the Supporting Information.

## Discussion

The reaction of $Me_2NC(S)$-**1**-(pentafluorobenzoate) ($1 \times 10^{-4}$ M) in 50:50 (v:v) TFE/$H_2O$ ($I = 0.50$, $NaClO_4$) gives the following products: 44% of the solvent adducts $Me_2NC(S)$-**1**-OH and $Me_2NC(S)$-**1**-$OCH_2CF_3$; 5% of 2-dimethylamino-6-methoxybenzothiophene, **4**; and 52% of the dimeric product **5**.[15] The formation of **4** and **5** is consistent with a stepwise mechanism and a rapid intramolecular cyclization of the carbocation intermediate $Me_2NC(S)$-$\mathbf{1}^+$ to give the benzothiophene **4**.[16] However, this activated alkene does not accumulate to any large extent, but rather it undergoes nucleophilic addition to a second molecule of $Me_2NC(S)$-$\mathbf{1}^+$—which is formed continuously during the reaction of $Me_2NC(S)$-**1**-(pentafluorobenzoate)—to give **5**.[15] In order to minimize the formation of **4** and **5**, the product studies for the reaction of $Me_2NC(S)$-**1**-Y described in this work were carried out in the more nucleophilic solvent of 50:50 (v:v) MeOH/$H_2O$. In this solvent, the trapping of $Me_2NC(S)$-$\mathbf{1}^+$ by solvent competes effectively with its intramolecular cyclization, and the yields of **4** and **5** from the reaction of $Me_2NC(S)$-**1**-(pentafluorobenzoate) are zero and 2%, respectively.[15]



**4**



**5**

**Reaction Mechanism.** For all the R-**1**-Y and R-**2**-Y in Table 1, reaction in 50:50 (v:v) MeOH/$H_2O$ in the presence of 0.50 M $NaN_3$ gives at least a 40% yield of the product of nucleophilic substitution by azide ion, in a reaction that is zero-order in the concentration of this nucleophile. These observations show that these substrates react by a stepwise $D_N + A_N$ ($S_N1$)[17] mechanism through the liberated carbocation intermediates R-$\mathbf{1}^+$ and R-$\mathbf{2}^+$ which can be trapped by azide ion. It has been shown in earlier work that 1-(*N*,*N*-dimethylthiocarbamoyl)-1-phenylethyl trifluoroacetate,[3,18] $CH_3$-**1**-Y,[1,19] $CH_3$-**2**-Y,[2,20] and EtOC(O)-**1**-(pentafluorobenzoate)[4,21] react by a stepwise mechanism through carbocation intermediates.

**Substituent Effects on Carbocation Formation.** The observed first-order rate constants, $k_{obsd}$ ($s^{-1}$, Table 1), for the stepwise reactions of the α-thioamide substituted benzyl derivatives $Me_2NC(S)$-**1**-Y and $Me_2NC(S)$-**2**-Y are much larger than those for reaction of their α-amide and α-ester substituted counterparts, but they are smaller than those for reaction of the corresponding α-methyl substituted derivatives. This shows that the interaction of the α-thioamide group with the developing positive charge in the transition state for ionization of $Me_2NC(S)$-**1**-Y and $Me_2NC(S)$-**2**-Y is less destabilizing than the corresponding interactions of α-amide and α-ester groups. This is due to the smaller destabilization of the developing positive charge by the polar electron-withdrawing effect, and its larger stabilization by the resonance electron-donating effect of the α-thioamide group compared with the α-amide group.[3,18,22] These results and conclusions are in good agreement with those of earlier studies of the effects of α-carbonyl and α-thiocarbonyl substituents on the rate constants for solvolysis reactions.[3,18,23]

The addition of an α-methyl group leads to a 690-fold increase in $k_{obsd}$ ($s^{-1}$) for the stepwise reaction of $CH_3$-**1**-(4-nitrobenzoate), but to significantly smaller increases of *ca.* 30-fold, *ca.* 60-fold, and 60-fold in $k_{obsd}$ for the stepwise reactions of $Me_2NC(S)$-**1**-(4-nitrobenzoate), $Me_2NC(O)$-**1**-(pentafluorobenzoate), and EtOC(O)-**1**-(pentafluorobenzoate), respectively (Table 1). The addition of the strongly electron-withdrawing α-amide and α-ester groups to the 4-methoxybenzyl carbocation results in an increase in the delocalization of positive charge away from the benzylic carbon and onto the 4-methoxyphenyl ring,[24] which serves to minimize the destabilizing polar electron-withdrawing effects of these substituents;[25] there may also be some direct resonance delocalization of positive charge onto these groups.[26] Therefore, the relatively small effect of the addition of an α-methyl group on $k_{obsd}$ for reaction of the α-thiocarbonyl and α-carbonyl substituted benzyl derivatives is probably due to the tendency of these electron-withdrawing groups to effect delocalization of the developing positive charge in the transition state away from the benzylic carbon. This in turn will reduce the magnitude of the stabilizing hyperconjugative interaction between positive charge at this center and an added α-methyl group. An α-thioamide group is less polar electron-withdrawing[3,18] but more resonance electron-donating than an α-amide group.[3,18,22,26] These differences will lead to larger and smaller, respectively, effects of the addition of an α-methyl group effect on $k_{obsd}$ for $Me_2NC(S)$-**1**-Y than for $Me_2NC(O)$-**1**-Y, with the net result being a 2-fold smaller effect for the former (Table 1).

**Rate and Equilibrium Constants for the Formation and Reaction of α-Substituted 4-Methoxybenzyl Carbocations.** Table 5 gives the absolute rate constants $k_s$ ($s^{-1}$) for reaction of R-$\mathbf{1}^+$ with a solvent of 50:50 (v:v) MeOH/$H_2O$ that were

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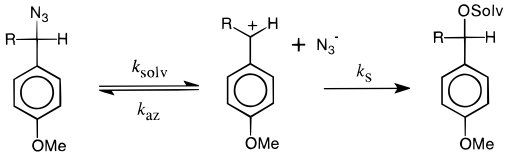
**Table 5.** Equilibrium Constants for Formation of α-Substituted 4-Methoxybenzyl Carbocations R-**1**$^+$ from the Corresponding Neutral Azide Ion Adducts and Rate Constants for Reaction of the Carbocations with Solvent (Scheme 2)[a]

| R | $K_{az}$[b] (M) | $k_s$[c] ($s^{-1}$) |
|---|---|---|
| $Me_2NC(S)$ | $\geq 1.7 \times 10^{-17}$ [d,e] | $\leq 7 \times 10^{4}$ [e] |
| $Me_2NC(O)$ | $6.1 \times 10^{-21}$ [d] | $2.4 \times 10^{7}$ |
| EtOC(O) | $1.8 \times 10^{-21}$ [f] | $1.1 \times 10^{8}$ |
| $CH_3$ | $2.6 \times 10^{-17}$ [f] | $6.9 \times 10^{8}$ |
| H | $7.4 \times 10^{-20}$ [f] | $2.0 \times 10^{9}$ [g] |

[a] In 50:50 (v:v) methanol/water at 25 °C and $I = 0.50$ ($NaClO_4$). [b] Equilibrium constant for formation of the carbocation R-**1**$^+$ from the azide ion adduct R-**1**-$N_3$, calculated as $K_{az} = k_{solv}/k_{az}$, where $k_{solv}$ is the rate constant for the stepwise reaction of R-**1**-$N_3$[4] and $k_{az} = 5 \times 10^9$ $M^{-1}$ $s^{-1}$ for the diffusion-limited reaction of azide ion with R-**1**$^+$, unless noted otherwise. [c] First-order rate constant for reaction of the carbocation with solvent, calculated from $k_{az}/k_s$ ($M^{-1}$, Table 2) and $k_{az} = 5 \times 10^9$ $M^{-1}$ $s^{-1}$ for the diffusion-limited reaction of azide ion with R-**1**$^+$, unless noted otherwise. [d] $k_{solv}$ for the reaction of R-**1**-$N_3$ was estimated from $k_{obsd}$ for the reaction of R-**1**-(pentafluorobenzoate) (Table 1) and the $6.2 \times 10^4$-fold larger value of $k_{obsd}$ for the stepwise reactions of R-**1**-(pentafluorobenzoate) than of R-**1**-$N_3$ that was calculated from the data in ref 4. [e] This is a limit because the rate constant for the reaction of azide ion with $Me_2NC(S)$-**1**$^+$ may be smaller than that for a diffusion-limited reaction. [f] Calculated using $k_{solv}$ for the reaction of R-**1**-$N_3$ in 50:50 (v:v) trifluoroethanol/water (ref 4), because the rate constants for the reaction of other R-**1**-Y in 50:50 (v:v) methanol/water differ from those for reaction in 50:50 (v:v) trifluoroethanol/water by less than 2-fold (Table 1). [g] Calculated from $k_{az}/k_s = 2.5$ $M^{-1}$ that was estimated from $k_{az}/k_s = 25$ $M^{-1}$ in 50:50 (v:v) trifluoroethanol/water (ref 4) and the 8-fold and 15-fold smaller values of $k_{az}/k_s$ for partitioning of EtOC(O)-**1**$^+$ and $CH_3$-**1**$^+$, respectively, in 50:50 (v:v) methanol/water (data from Table 2) than in 50:50 (v:v) trifluoroethanol/water (data from ref 4).

**Scheme 2**



calculated from the product rate constant ratios $k_{az}/k_s$ ($M^{-1}$, Table 2) and $k_{az} = k_d = 5 \times 10^9$ $M^{-1}$ $s^{-1}$ for the diffusion-limited reaction of azide ion with unstable benzylic carbocations.[1,4,6,19,20,27] With the exception of $k_{az}/k_s = 7 \times 10^4$ $M^{-1}$ for the partitioning of $Me_2NC(S)$-**1**$^+$, the azide ion selectivities for partitioning of all the R-**1**$^+$ in Table 2 lie well below $k_{az}/k_s = 10^4$ $M^{-1}$, which is the approximate threshold for the change from a diffusion- to an activation-limited reaction of azide ion with benzylic carbocations.[25,27a] Therefore, the value of $k_s$ for the reaction of $Me_2NC(S)$-**1**$^+$ with solvent (Table 5) is an upper limit that was calculated using $k_{az} \leq 5 \times 10^9$ $M^{-1}$ $s^{-1}$.[45] Table 5 also gives equilibrium constants for formation of the carbocations R-**1**$^+$ from the corresponding neutral azide ion adducts in 50:50 (v:v) $MeOH/H_2O$, which were calculated as $K_{az} = k_{solv}/k_{az}$ (M), where $k_{solv}$ is the experimentally-determined, or estimated first-order rate constant for the stepwise reaction of R-**1**-$N_3$,[4] and $k_{az}$ is the second-order rate constant for the reverse reaction of the carbocation with azide ion (Scheme 2).

**Effects of α-Thiocarbonyl and α-Carbonyl Substituents at R-1$^+$.** Figure 3, constructed using the data in Table 5, illustrates the effects of α-thioamide, α-amide, α-ester, and α-methyl groups on the equilibrium stability (log $K_{az}$) and the kinetic reactivity towards solvent (log $k_s$) of the 4-methoxybenzyl carbocation in 50:50 (v:v) $MeOH/H_2O$. Despite its great thermodynamic instability, the α-ester substituted carbocation EtOC(O)-**1**$^+$ has a relatively long lifetime ($1/k_s$), and it is one of several α-substituted 4-methoxybenzyl carbocations whose lifetimes are nearly independent of their thermodynamic stability.[4,21,28] The data obtained in this work show that the α-amide group is yet another example of a strongly electron-withdrawing α-substituent that results in thermodynamic destabilization of the 4-methoxybenzyl carbocation relative to the neutral azide ion adduct ($K_{az}$), but to a small *decrease*, rather than the expected increase, in the rate constant for reaction of the carbocation with a nucleophilic solvent ($k_s$) (Figure 3 and Table 5). The detailed descriptions and explanations of these α-substituent effects have been presented in earlier work.[4,25,28]

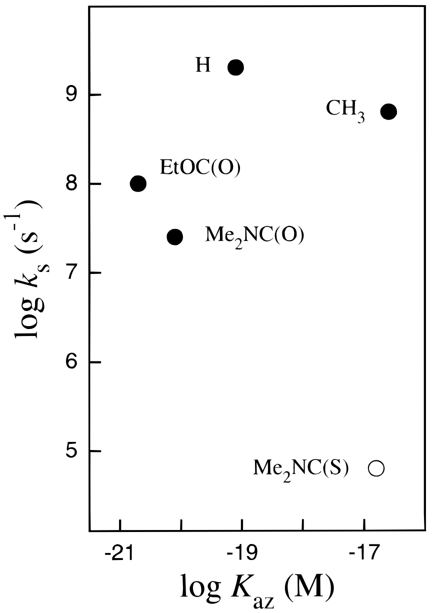


**Figure 3.** Logarithmic correlation between the rate constants for the reaction of α-substituted 4-methoxybenzyl carbocations R-**1**$^+$ with solvent ($k_s$, $s^{-1}$) and the equilibrium constants for their formation from the corresponding neutral azide ion adducts ($K_{az}$, M) in 50:50 (v:v) methanol/water at 25 °C and $I = 0.50$ ($NaClO_4$) (Scheme 2). The figure was constructed using the data in Table 5. The open circle denotes that the values of $k_s$ and $K_{az}$ for $Me_2NC(S)$-**1**$^+$ are upper and lower limits, respectively.

Figure 3 shows that $k_s$ ($s^{-1}$) for reaction of the α-thioamide substituted carbocation $Me_2NC(S)$-**1**$^+$ with 50:50 (v:v) $MeOH/H_2O$ is anomalously small in comparison with the rate constants for the addition of this solvent to other R-**1**$^+$. For example, thermodynamically, $Me_2NC(S)$-**1**$^+$ is at least as stable as the α-methyl carbocation $CH_3$-**1**$^+$, but it is also at least $10^4$-fold less reactive towards solvent (Table 5). This relatively large kinetic barrier to the capture of $Me_2NC(S)$-**1**$^+$ by solvent reflects the stabilizing interactions between the α-thioamide group and the benzylic cationic center, and the requirement for the relatively large *fractional loss* of these stabilizing interactions on proceeding from the ground to the transition state for reaction of the carbocation.[29,30] There are two stabilizing interactions between the α-thioamide group and the positive charge at the benzylic carbon that may contribute to the relatively large kinetic barrier to the reaction of $Me_2NC(S)$-**1**$^+$ with solvent.

(1) $Me_2NC(S)$-**1**$^+$ may be strongly stabilized by resonance delocalization of the positive charge at the benzylic carbon onto the weakly electronegative and strongly polarizable sulfur atom (A, R′ = 4-$MeOC_6H_4$, Scheme 3). The requirement for the

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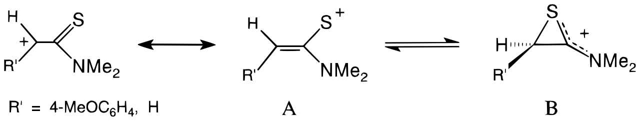
**Scheme 3**



relatively large fractional loss of such resonance stabilization of carbocations in the transition state for their capture by nucleophiles has been shown to result in the unusually low reactivities of several α-substituted benzyl carbocations toward solvent.[4,25,31]

(2) Me$_2$NC(S)-**1**$^+$ may also be stabilized by the nucleophilic addition of sulfur to the benzylic carbon to give the "closed" carbocation (B, R′ = 4-MeOC$_6$H$_4$, Scheme 3). However, if solvent reacts exclusively with an open carbocation that is the minor species in a mixture of open and closed carbocations, then sulfur bridging would result in a particularly large decrease in $k_s$ for the addition of solvent to Me$_2$NC(S)-**1**$^+$, because this stabilizing interaction will be *completely* lost in the transition state.[29,30]

The results of ab initio calculations at the Hartree−Fock 6-31G* level show that there is extensive delocalization of positive charge onto the α-thioamide group at the open form of the α-thioamide substituted methyl carbocation (A, R′ = H, Scheme 3) and that this substituent stabilizes the methyl carbocation by 35.7 kcal/mol (MP2/6-31G**) relative to the hydride ion adducts.[26] However, the conversion of the open carbocation to its closed form (B, R′ = H, Scheme 3) is stabilizing by a further 47.2 kcal/mol (MP2/6-31G**).[26] This suggests that both resonance delocalization and sulfur bridging to give a closed carbocation may contribute to the relatively low reactivity of Me$_2$NC(S)-**1**$^+$ toward solvent.

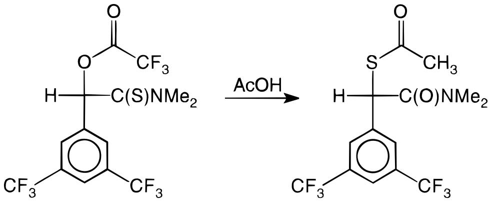
The following results are consistent with the conclusion that in strongly ionizing solvents Me$_2$NC(S)-**1**-Y reacts to form a significant concentration of the open α-thioamide substituted carbocation.

(1) The acetolysis of optically active Me$_2$NC(S)-**1**-O$_2$CCF$_3$ proceeds with partial loss of optical activity.[18] This requires formation of a symmetrical open carbocation intermediate for the reaction of this substrate in acetic acid.

(2) Neighboring group participation by the α-thioamide group would reduce the development of localized positive charge at the benzylic carbon in the transition state for ionization of Me$_2$NC(S)-**1**-Y, and this should lead to a reduction in the hyperconjugative stabilization of this transition state by an additional α-methyl group. However, the data in Table 1 show that the effects of the addition of an α-methyl group on $k_{obsd}$ for the reactions of Me$_2$NC(S)-**1**-Y, Me$_2$NC(O)-**1**-Y, and EtOC(O)-**1**-Y are similar (see above), which is consistent with the formation of similar, open, carbocation intermediates for all of these reactions.

(3) The UV−visible and $^{13}$C NMR spectra of the cationic species generated by ionization of 9-[*N*,*N*-dimethyl(thioformamidyl)]-9-fluorenyl chloride under stable ion conditions and by laser flash photolysis are consistent with an open structure for this carbocation in trifluoroethanol and methylene chloride.[46]

(4) The acetolysis of **6** gives an 86% yield of the rearranged product **7** which results from the nucleophilic addition of solvent to the closed carbocation, followed by rearrangement of the initial nucleophile adduct.[18] However, the change to the strongly electron-donating 4-methoxy ring substituent results in the exclusive formation of Me$_2$NC(S)-**1**-O$_2$CCH$_3$ from the addition of solvent to the benzylic carbon.[18] This shows that when the aromatic ring substituent(s) are strongly electron-withdrawing, the reactive intermediate is the closed carbocation, but that strongly electron-donating ring substituents favor formation of the products of attack on the open carbocation.



**6** **7**

**Reactions of Me$_2$NC(S)-2$^+$.** Figure 1A shows that the reactions of Me$_2$NC(S)-**2**-Y (Y = 4-nitrobenzoate or 4-methoxybenzoate) in 50:50 (v:v) MeOH/H$_2$O in the presence of increasing concentrations of azide ion lead to the formation of good yields of the azide ion adduct Me$_2$NC(S)-**2**-N$_3$, and a decrease in the yield of the alkene Me$_2$NC(S)-**3** from 100% in the absence of azide ion, to a *constant* limiting yield of 63% in the presence of large concentrations of azide ion. One consequence of this unusual result is that the observed rate constant ratios $(k_{az}/k_e)_{obsd}$ (M$^{-1}$) that are calculated from the yields of the azide ion adduct and the alkene at high concentrations of azide ion using eq 5, are inversely proportional to [N$_3^-$].

$$(k_{az}/k_e)_{obsd} = [RN_3]/[alkene][N_3^-] \qquad (5)$$

This is inconsistent with the simple partitioning of a carbocation intermediate between deprotonation by solvent and nucleophilic capture by azide ion, because this would require that the yield of the alkene approach zero at high [N$_3^-$], and that the partitioning ratio $(k_{az}/k_e)_{obsd}$ be independent of [N$_3^-$]. There are several possible explanations for the constant limiting yield of Me$_2$NC(S)-**3** from the reactions of Me$_2$NC(S)-**2**-Y in the presence of high concentrations of azide ion.

**Explanation 1: The Elimination Reaction is Concerted.** The constant limiting yield of Me$_2$NC(S)-**3** may be the result of a concerted elimination reaction that bypasses the carbocation intermediate of the stepwise mechanism, with an observed rate constant that is independent of [N$_3^-$]. However, this possibility can be excluded because the overall KIE of $k(\alpha\text{-CH}_3)/k(\alpha\text{-CD}_3)$ = 1.03 for the reaction of Me$_2$NC(S)-**2**-(4-nitrobenzoate) in 80% ethanol in water[3] is very close to unity, so that it effectively rules out concerted proton transfer and cleavage of the bond to leaving group in the transition state.

**Explanation 2: The Carbocation Undergoes Deprotonation by the Leaving Group within an Ion Pair Intermediate.** The carbocation-leaving group ion pair intermediate Me$_2$NC(S)-**2**$^+$·Y$^-$ is expected to be too short-lived to be trapped by azide ion, because of its fast breakdown by diffusional separation to give the free ions.[32,33] Therefore, the constant limiting yield of Me$_2$NC(S)-**3** might result from very fast proton transfer from the carbocation to the leaving group within this ion pair. However, this is unlikely because the reactions of Me$_2$NC(S)-**2**-(4-nitrobenzoate) and Me$_2$NC(S)-**2**-(4-methoxybenzoate) in the presence of azide ion give identical yields of the alkene and the azide ion adduct (Figure 1A).

**Explanation 3: Azide Ion Reacts with the Carbocation as a Brønsted Base.** Azide ion normally reacts with α-methyl substituted carbocations exclusively as a nucleophile (Lewis base).[1,20] However, Me$_2$NC(S)-**2**$^+$ is an unusual α-methyl carbocation, because it exhibits an extremely large tendency to undergo loss of a proton to solvent to give the alkene Me$_2$NC-

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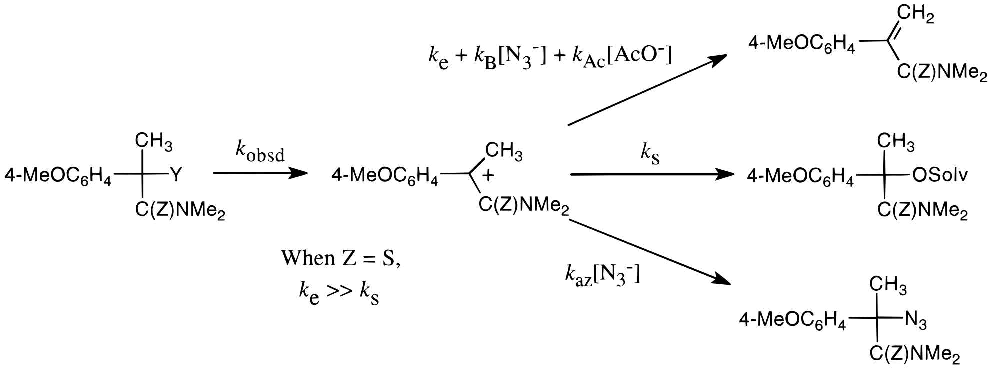
[31] McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823−6858.

[32] Richard, J. P. *J. Org. Chem.* **1992**, *57*, 625−629.

[33] Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7900−7909.

**Scheme 4**



(S)-**3** ($k_s/k_e$ < 0.01, Table 3). If $Me_2NC(S)$-**2**$^+$ exhibits the same tendency to undergo deprotonation by azide ion ($k_B$, Scheme 4), then the limiting ratio of the yields of the alkene and the azide ion adduct from the stepwise reaction of $Me_2NC(S)$-**2**-Y at high $[N_3^-]$ will represent the rate constant ratio $k_B/k_{az}$ for reaction of azide ion as a Brønsted base and as a nucleophile, as shown in Scheme 4. The solid lines in Figure 1A show that there is a good fit of the product data to eqs 6 and 8 ($k_e \gg k_s$), which were derived for the mechanism shown in Scheme 4. The nonlinear least squares fits were obtained using the relationship $k_B = 1.7k_{az}$ ($k_{az}/k_B = [RN_3]_{lim}/[alkene]_{lim} = 0.59$), to give $k_{az}/k_e = 65 \pm 2$ $M^{-1}$ as the single unknown parameter in eqs 6 and 8 (the error is the standard deviation).

We now consider whether it is reasonable that azide ion is sufficiently reactive as a Brønsted base to abstract a proton from $Me_2NC(S)$-**2**$^+$ to give the alkene $Me_2NC(S)$-**3** (Scheme 4). The rate constant ratios $k_{az}/k_B = 0.59$ and $k_{az}/k_e = 65$ $M^{-1}$ obtained from the fit of the product data in Figure 1A to eqs 6 and 8 can be combined to give $k_B/k_e = 110$ $M^{-1}$, so that the mechanism in Scheme 4 requires that 1.0 M azide ion be 110-fold more reactive than solvent as a Brønsted base for deprotonation of $Me_2NC(S)$-**2**$^+$. The p$K_a$s of acetic acid (4.76) and hydrazoic acid (4.72) are similar,[34] so that acetate and azide ions should show similar reactivities as Brønsted bases for deprotonation of $Me_2NC(S)$-**2**$^+$ if the mechanism shown in Scheme 4 is correct. The relative rates of deprotonation of $Me_2NC(S)$-**2**$^+$ by acetate and azide ions were determined from the effect of increasing concentrations of acetate ion on the product distribution for the reaction of $Me_2NC(S)$-**2**-(4-nitrobenzoate) in 50:50 (v:v) $MeOH/H_2O$ in the presence of fixed concentrations of 0.005 M (Figure 2A) or 0.010 M (Figure 2B) azide ion. Figure 2 shows that the addition of acetate ion results in an increase in the yield of the alkene $Me_2NC(S)$-**3** at the expense of the azide ion adduct; there was no detectable formation of the acetate ion adduct in these experiments. The solid lines in Figure 2 show that there is a good fit of the product data to eqs 9 and 10, which were derived for the mechanism shown in Scheme 4 ($k_e \gg k_s$). The nonlinear least squares fits were obtained using $k_B/k_e = 110$ $M^{-1}$ and $k_{az}/k_e = 65$ $M^{-1}$ determined in the absence of acetate ion (Figure 1A), to give $k_{Ac}/k_e = 23$ and 26 $M^{-1}$ for $[N_3^-] = 0.005$ and 0.010 M, respectively, as the single unknown parameter in eqs 9 and 10. The average value of $k_{Ac}/k_e = 24.5 \pm 1.5$ $M^{-1}$ can be combined with $k_B/k_e = 110$ $M^{-1}$ to give $k_B/k_{Ac} = 4.5$ as the rate constant ratio for deprotonation of $Me_2NC(S)$-**2**$^+$ by azide and acetate ions.

$$f_{alk} = \frac{1 + (k_B/k_e)[N_3^-]}{1 + (k_s/k_e) + (k_B/k_e + k_{az}/k_e)[N_3^-]} \quad (6)$$

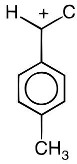
$$f_{ROS} = \frac{(k_s/k_e)}{1 + (k_s/k_e) + (k_B/k_e + k_{az}/k_e)[N_3^-]} \quad (7)$$

$$f_{RN_3} = \frac{(k_{az}/k_e)[N_3^-]}{1 + (k_s/k_e) + (k_B/k_e + k_{az}/k_e)[N_3^-]} \quad (8)$$

$$f_{alk} = \frac{1 + (k_B/k_e)[N_3^-] + (k_{Ac}/k_e)[AcO^-]}{1 + (k_B/k_e + k_{az}/k_e)[N_3^-] + (k_{Ac}/k_e)[AcO^-]} \quad (9)$$

$$f_{RN_3} = \frac{(k_{az}/k_e)[N_3^-]}{1 + (k_B/k_e + k_{az}/k_e)[N_3^-] + (k_{Ac}/k_e)[AcO^-]} \quad (10)$$

The data in Figure 2 for the effect of acetate ion are fully consistent with the mechanism shown in Scheme 4. The 4.5-fold greater reactivity of azide than of acetate ion as a Brønsted base for deprotonation of $Me_2NC(S)$-**2**$^+$ is not unusually large for bases of similar p$K_a$.[35] It may result from either (a) a smaller steric barrier to reaction of the linear azide ion or (b) a smaller barrier to formation of the carbocation−anion contact ion pair for azide than for acetate ion. Similarly, a difference in the barriers to ion pair formation has been proposed to explain the 10-fold larger rate constant for the encounter-limited nucleophilic reaction of azide than of acetate ion with the 1-(4-methylphenyl)ethyl carbocation (**8**).[19]



**8**

Table 3 summarizes the rate constant ratios for partitioning of $Me_2NC(S)$-**2**$^+$ that were obtained from the fits of the data in Figures 1A and 2 to eqs 6, 8, 9, and 10. $Me_2NC(S)$-**2**$^+$ should be even more stable than its counterpart without an α-methyl group, $Me_2NC(S)$-**1**$^+$, for which $k_{az} \leq 5 \times 10^9$ $M^{-1}$ $s^{-1}$ (see above). Therefore, the rate constant ratios $k_{az}/k_e$ ($M^{-1}$) and $k_{az}/k_B$ were combined with ($k_{az} + k_B$) $\leq 5 \times 10^9$ $M^{-1}$ $s^{-1}$ for the reaction of azide ion with $Me_2NC(S)$-**2**$^+$ as a nucleophile and as a Brønsted base to give the absolute rate constants $k_e$ ($s^{-1}$) and $k_B$ ($M^{-1}$ $s^{-1}$) for the deprotonation of $Me_2NC(S)$-**2**$^+$ by solvent and azide ion given in Table 6. An upper limit on $k_s$ ($s^{-1}$) for the reaction of $Me_2NC(S)$-**2**$^+$ with a solvent of 50:50

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[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.

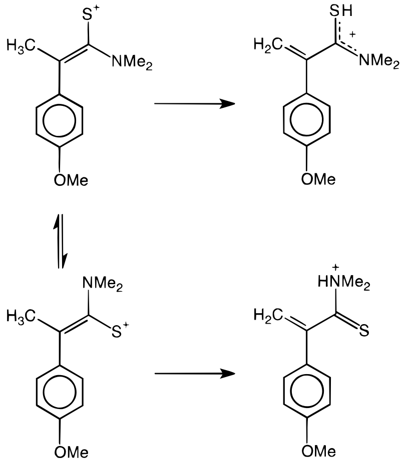
[35] See, for example, the deviations from the Brønsted correlation of rate constants for general-base-catalyzed deprotonation of triosephosphates: Richard, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 4926−4936.

**Table 6.** Rate Constants for Reaction of α-Substituted 1-(4-Methoxyphenyl)ethyl Carbocations R-**2**$^+$ with Solvent and for Base-Catalyzed Deprotonation of the Carbocations by Solvent and Azide Ion (Scheme 4)[a]

| R | $k_s$[b] ($s^{-1}$) | $k_e$[c] ($s^{-1}$) | $k_B$[d] ($M^{-1}\ s^{-1}$) |
|---|---|---|---|
| $Me_2NC(S)$ | $\leq 1 \times 10^4$ [e] | $\leq 2.9 \times 10^7$ [f] | $\leq 3.1 \times 10^9$ [g] |
| $Me_2NC(O)$ | $3.6 \times 10^6$ | $2.9 \times 10^6$ [h] | $4.5 \times 10^8$ [i] |
| EtOC(O) | $6.0 \times 10^7$ | $\approx 1.2 \times 10^6$ [j] | |
| $CH_3$ | $2.8 \times 10^8$ | $< 2.8 \times 10^6$ [j] | |

[a] In 50:50 (v:v) methanol/water at 22 ± 2 °C and $I = 0.50$ ($NaClO_4$). [b] First-order rate constant for reaction of the carbocation with solvent, calculated from $k_{az}/k_s$ ($M^{-1}$, Table 3) and $k_{az} = 5 \times 10^9\ M^{-1}\ s^{-1}$ for the diffusion-limited reaction of azide ion with R-**2**$^+$, unless noted otherwise. [c] First-order rate constant for deprotonation of R-**2**$^+$ by solvent. [d] Second-order rate constant for deprotonation of R-**2**$^+$ by azide ion. [e] Upper limit calculated from $k_s \leq 7 \times 10^4\ s^{-1}$ for the reaction of $Me_2NC(S)$-**1**$^+$ with 50:50 (v:v) methanol/water (Table 5) and the 7-fold effect of the addition of an α-methyl group on $k_s$ ($s^{-1}$) for the reaction of this solvent with $Me_2NC(O)$-**1**$^+$ (Tables 5 and 6). [f] Calculated from $k_{az}/k_e$ ($M^{-1}$) and $k_{az}/k_B$ (Table 3) and $(k_{az} + k_B) \leq 5 \times 10^9\ M^{-1}\ s^{-1}$ for the reaction of azide ion with the carbocation as both a nucleophile and a Brønsted base. [g] Calculated from $k_{az}/k_B$ (Table 3) and $(k_{az} + k_B) \leq 5 \times 10^9\ M^{-1}\ s^{-1}$. [h] Calculated from $k_{az}/k_e$ ($M^{-1}$, Table 3) and $k_{az} = 5 \times 10^9\ M^{-1}\ s^{-1}$. [i] Calculated from $k_{az}/k_B$ (Table 3) and $(k_{az} + k_B) = 5 \times 10^9\ M^{-1}\ s^{-1}$. [j] Calculated from $k_s$ ($s^{-1}$) and the value of $k_s/k_e$ (Table 3).

**Scheme 5**



(v:v) MeOH/H$_2$O was obtained in two ways: (1) A limit of $k_s < 2.9 \times 10^5\ s^{-1}$ was calculated from $k_e \leq 2.9 \times 10^7\ s^{-1}$ (Table 6) and $k_s/k_e < 0.01$ (Table 3). (2) A smaller limit of $k_s \leq 1 \times 10^4\ s^{-1}$ (Table 6) was calculated from $k_s \leq 7 \times 10^4\ s^{-1}$ for the reaction of $Me_2NC(S)$-**1**$^+$ with 50:50 (v:v) MeOH/H$_2$O (Table 5), with the assumption that the addition of an α-methyl group leads to the same 7-fold decrease in $k_s$ as that observed for the reaction of $Me_2NC(O)$-**1**$^+$ (Tables 5 and 6).

**Explanation 4: Efficient Intramolecular Proton Transfer.** The quantitative yield of alkene obtained from the reaction of $Me_2NC(S)$-**2**$^+$ in the absence of azide ion might be a consequence of a high "effective molarity"[36] of the α-thioamide group as an intramolecular proton or hydride acceptor (Scheme 5). However, the observation that good yields of $Me_2NC(S)$-**3** are obtained from intermolecular general base catalysis of the deprotonation of $Me_2NC(S)$-**2**$^+$ by acetate and azide ions (Figures 1A and 2) effectively excludes the possibility of an efficient intramolecular pathway for formation of the alkene. The value of $k_{Ac}/k_e = 24.5\ M^{-1}$ for partitioning of $Me_2NC(S)$-**2**$^+$ between bimolecular and unimolecular elimination in 50:50 (v:v) MeOH/H$_2$O is even larger than $k_{Ac}/k_e = 2.0\ M^{-1}$ for the partitioning of **8** in 50:50 (v:v) TFE/H$_2$O,[37] for which intramolecular proton transfer is not possible. We conclude that the partitioning of $Me_2NC(S)$-**2**$^+$ between bimolecular deprotonation by acetate ion and a unimolecular reaction is even *more favorable* than for the partitioning of **8**, and that there is no efficient intramolecular pathway for the conversion of $Me_2NC(S)$-**2**$^+$ to $Me_2NC(S)$-**3**.

**Reactions of $Me_2NC(O)$-2$^+$.** Figure 1B shows that the reaction of $Me_2NC(O)$-**2**-(pentafluorobenzoate) in the presence of increasing concentrations of azide ion in 50:50 (v:v) MeOH/H$_2$O results in formation of good yields of the azide ion adduct $Me_2NC(O)$-**2**-$N_3$ at the expense of the solvent adducts $Me_2NC(O)$-**2**-OSolv and the alkene $Me_2NC(O)$-**3**. At high $[N_3^-]$, the yield of the solvent adducts decreases to zero, while the yield of the alkene decreases to a constant limiting yield of 9%. As discussed above for the reactions of $Me_2NC(S)$-**2**$^+$, these data are consistent with a mechanism in which azide ion acts as a Brønsted base to abstract a proton from $Me_2NC(O)$-**2**$^+$ to give the alkene $Me_2NC(O)$-**3** ($k_B$, Scheme 4). Table 3 summarizes the rate constant ratios for partitioning of $Me_2NC(O)$-**2**$^+$ that were evaluated from the product data for the reaction of $Me_2NC(O)$-**2**-(pentafluorobenzoate) as follows:

(1) The rate constant ratio $k_{az}/k_s = 1400\ M^{-1}$ for partitioning of $Me_2NC(O)$-**2**$^+$ between nucleophilic addition of azide ion and solvent (Scheme 4) was determined from the ratio of the yields of the azide ion adduct and the solvent adducts using eq 4.

(2) The rate constant ratio $k_s/k_e = 1.2$ for partitioning of $Me_2NC(O)$-**2**$^+$ between nucleophilic addition of solvent and deprotonation by solvent was determined as the ratio of the yields of the solvent adducts (54%) and the alkene (46%) in the absence of azide ion (Figure 1B).

(3) The rate constant ratio $k_{az}/k_B = 10$ for partitioning of $Me_2NC(O)$-**2**$^+$ between nucleophilic addition of azide ion and deprotonation by azide ion acting as a Brønsted base was calculated as $[RN_3]_{lim}/[alkene]_{lim} = 10$, which is the ratio of the limiting yields of the azide ion adduct (91%) and the alkene (9%) at high $[N_3^-]$ (Figure 1B).

The solid lines in Figure 1B show the fits of the product data to eqs 6−8, which were calculated using $k_s/k_e = 1.2$, $k_{az}/k_e = (k_s/k_e)(k_{az}/k_s) = 1700\ M^{-1}$, and $k_B/k_e = (k_{az}/k_e)(k_B/k_{az}) = 170\ M^{-1}$. The absolute agreement between the observed product yields and those expected for the mechanism shown in Scheme 4 is better than ±1%, so that this mechanism provides an entirely consistent and satisfactory explanation for the effect of azide ion on the product distribution for the reaction of $Me_2NC(O)$-**2**-(pentafluorobenzoate). The rate constant ratios for partitioning of $Me_2NC(O)$-**2**$^+$ were combined with $(k_{az} + k_B) = k_d = 5 \times 10^9\ M^{-1}\ s^{-1}$ for the diffusion-limited[27] reaction of azide ion with $Me_2NC(O)$-**2**$^+$ as a nucleophile and as a Brønsted base, to give the absolute rate constants $k_s$ ($s^{-1}$), $k_e$ ($s^{-1}$), and $k_B$ ($M^{-1}\ s^{-1}$) for the reactions of this carbocation given in Table 6.

**Reactions of EtOC(O)-2$^+$ and $CH_3$-2$^+$.** Table 3 gives the rate constant ratios for partitioning of EtOC(O)-**2**$^+$ and $CH_3$-**2**$^+$ between nucleophilic addition of azide ion and solvent that were calculated from the yields of the azide ion adduct and the solvent adducts using eq 4. The effect of azide ion on the low (≈2%, Table 3) yield of the alkene EtOC(O)-**3** from the reaction of EtOC(O)-**2**-(pentafluorobenzoate) in 50:50 (v:v) MeOH/H$_2$O was not determined.

Table 6 gives absolute rate constants for the reactions of EtOC(O)-**2**$^+$ and $CH_3$-**2**$^+$ that were calculated from the rate constant ratios in Table 3 and $k_{az} = k_d = 5 \times 10^9\ M^{-1}\ s^{-1}$ for

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[36] Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183−278.

[37] Calculated from $k_{Ac}/k_s = 1.43 \times 10^{-3}\ M^{-1}$ and $k_e/k_s = 7 \times 10^{-4}$ for partitioning of the 1-(4-methylphenyl)ethyl carbocation between deprotonation by acetate ion or solvent and the nucleophilic addition of solvent in 50:50 (v:v) TFE/H$_2$O.[19]

**Table 7.** Effects of α-Carbonyl and α-Thiocarbonyl Substituents on the Relative Stabilities of α-Substituted 1-Phenylethyl Alcohols and the Corresponding α-Substituted Styrenes (Scheme 6)[a]

| | Δ*H* (kcal/mol)[b] | | Δ*G* (kcal/mol)[c] | |
|---|---|---|---|---|
| α-substituent R | 3-21G//3-21G | 6-31G*//3-21G | expl | $k_e/k_s$[d] |
| $CH_3$ | 0 | 0 | 0 | <0.01 |
| MeOC(O) | 1.07 | 0.27 | nd | ≈0.02[e] |
| $Me_2NC(O)$ | −1.52 | −1.57 | nd | 0.83 |
| $Me_2NC(S)$ | −1.79 | −5.04 | <−3.9[f] | >100 |

[a] Energy changes are for the isodesmic reaction shown in Scheme 6, unless noted otherwise. [b] Calculated from the ab initio energies of R-**9**-OH and R-**10** given in Table 4. [c] For compounds with a 4-methoxy substituent at the aromatic ring. [d] Rate constant ratio for partitioning of R-$\mathbf{2}^+$ between deprotonation by solvent to give R-**3** and nucleophilic addition of solvent to give R-**2**-OSolv in 50:50 (v:v) methanol/water (Table 3). [e] For R = EtOC(O). [f] Calculated from $K_{alk}$ = 0.13 and >100, respectively, for the dehydration of $CH_3$-**2**-OH to give $CH_3$-**3** (ref 2) and of $Me_2NC(S)$-**2**-OH to give $Me_2NC(S)$-**3** (this work) in 50:50 (v:v) trifluoroethanol/water.

the diffusion-limited reaction of azide ion[27] as a nucleophile with these unstable carbocations.

**Substituent Effects on the Reactivity of R-$\mathbf{2}^+$.** The effects of the change from an α-methyl substituent to an α-amide or an α-ester substituent on $k_s$ ($s^{-1}$) for the reactions of $CH_3$-$\mathbf{1}^+$ (Table 5) and $CH_3$-$\mathbf{2}^+$ (Table 6) with a solvent of 50:50 (v:v) MeOH/$H_2O$ are similar. However, there is no observable nucleophilic addition of solvent to the α-thioamide substituted carbocation $Me_2NC(S)$-$\mathbf{2}^+$, and solvent reacts with this carbocation exclusively as a Brønsted base to abstract a proton from the α-methyl group to give $Me_2NC(S)$-**3** ($k_s/k_e$ < 0.01, Table 3). $Me_2NC(S)$-$\mathbf{2}^+$ also shows an unusual resistance to the addition of nucleophilic anions, which react preferentially as Brønsted bases: there is no detectable nucleophilic addition of acetate ion to $Me_2NC(S)$-$\mathbf{2}^+$ (see above), and the potent nucleophile azide ion is 1.7-fold less reactive as a nucleophile than as a Brønsted base toward $Me_2NC(S)$-$\mathbf{2}^+$ (Table 3).

Table 3 shows that there is a progressive increase in the rate constant ratio $k_e/k_s$ for the partitioning of R-$\mathbf{2}^+$ between loss of a proton from the α-methyl group and the nucleophilic addition of solvent as the α-substituent R is changed along the series α-methyl, α-ester, α-amide, α-thioamide. The absolute rate constants for these reactions (Table 6) show that these changes in $k_e/k_s$ are a consequence of the relatively large decreases in $k_s$ along the series $CH_3$-$\mathbf{2}^+$, EtOC(O)-$\mathbf{2}^+$, $Me_2NC(O)$-$\mathbf{2}^+$, $Me_2NC(S)$-$\mathbf{2}^+$, relative to $k_e$, which shows a much smaller sensitivity to changes in the α-substituent at R-$\mathbf{2}^+$.

The changes in the rate constant ratio $k_e/k_s$ for partitioning of R-$\mathbf{2}^+$ between loss of a proton and the nucleophilic addition of solvent may be due to interactions which develop in the two different transition states for these reactions, and which are then lost on proceeding to the products; or they may simply be the consequence of changes in the overall thermodynamic driving force for formation of the two different products, which are partially expressed in the respective transition states for their formation (Figure 4). The change from an α-methyl group to an α-thioamide group results in a large increase in the equilibrium constant for the dehydration of R-**2**-OH to give the alkene R-**3**, from $K_{alk}$ = [alkene]$_{eq}$/[alcohol]$_{eq}$ = 0.13 for the dehydration of $CH_3$-**2**-OH to give $CH_3$-**3** in 50:50 (v:v) TFE/$H_2O$,[2] to $K_{alk}$ > 100 for the dehydration of $Me_2NC(S)$-**2**-OH to give $Me_2NC(S)$-**3** (this work), which corresponds to a change in Δ*G* for this reaction of more than 3.9 kcal/mol (Table 7). This shows that R-**3** is strongly stabilized relative to R-**2**-OH by the change in R from an α-methyl to an α-thioamide group (Figure 4). This large ground state effect is partly or entirely responsible for the dramatic effect of the change from an α-methyl to an α-thioamide group on $k_e/k_s$ for partitioning of R-$\mathbf{2}^+$ between loss of a proton and nucleophilic capture by solvent (Figure 4 and Table 7).

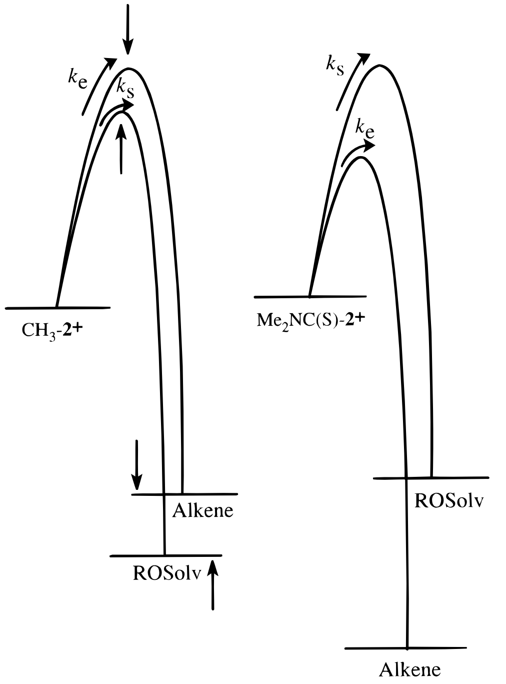
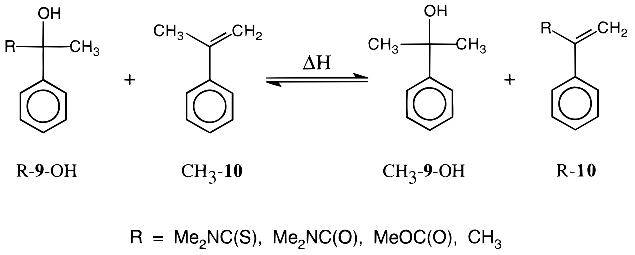


**Figure 4.** Hypothetical free energy profiles for the partitioning of $CH_3$-$\mathbf{2}^+$ and $Me_2NC(S)$-$\mathbf{2}^+$ between nucleophilic addition of solvent to give the solvent adducts ($k_s$) and deprotonation to give the alkene ($k_e$) in 50:50 (v:v) methanol/water. The arrows indicate the effect of a change from an α-methyl to an α-thioamide substituent at R-$\mathbf{2}^+$ on the relative stabilities of the two products and of the respective transition states for their formation.

**Scheme 6**



We were unable to determine the equilibrium constants for the acid-catalyzed dehydration of $Me_2NC(O)$-**2**-OH and EtOC(O)-**2**-OH, because these compounds undergo competing acid-catalyzed hydrolysis of the α-amide and α-ester groups. The energies of α-thioamide, α-amide, α-ester and α-methyl substituted 1-phenylethyl alcohols (R-**9**-OH) and the corresponding α-substituted styrenes (R-**10**) were therefore examined using ab initio methods (Table 4), and the results were used to calculate the enthalpy changes for the isodesmic reactions shown in Scheme 6 (Δ*H*, Table 7). The experimental value of Δ*G* < −3.9 kcal/mol for the reaction of $Me_2NC(S)$-**2**-OH with $CH_3$-**3** to give $CH_3$-**2**-OH and $Me_2NC(S)$-**3** (*cf.* Scheme 6) in 50:50 (v:v) TFE/$H_2O$ is close to Δ*H* = −5.04 kcal/mol for the corresponding reaction of $Me_2NC(S)$-**9**-OH (Scheme 6) determined from ab initio calculations at the 6-31G*//3-21G level (Table 7). This provides good evidence that the values of Δ*H* for the reactions shown in Scheme 6 determined by ab initio calculation provide reasonable estimates of Δ*G* for the corresponding reactions of the 4-methoxy compounds in TFE/$H_2O$.

The data in Table 7 show that there is good correlation between the increase in the rate constant ratio $k_e/k_s$ for partitioning of R-**2**$^+$ between loss of a proton to give the alkene R-**3** and nucleophilic capture by solvent to give R-**2**-OSolv and the change to a more negative value of ΔH for the reaction shown in Scheme 6. This supports the conclusion that the relative rate constants for loss of a proton from R-**2**$^+$ ($k_e$) and its nucleophilic capture by solvent ($k_s$) are strongly controlled by the relative stabilities of the alkene and alcohol products of these reactions. This provides yet another example of a substituent effect on rate constants for the interconversion of stable neutral and reactive charged species that is dominated by the substituent effect on the relative stabilities of neutral compounds.[38−41]

Our experiments and calculations do not allow for a detailed explanation of the effects of α-thiocarbonyl and α-carbonyl substituents on the observed changes in Δ*G* and the calculated changes in Δ*H* for the reaction shown in Scheme 6. However, we suggest that these changes are controlled largely by the balance between two opposing interactions of these α-substituents at the alkenes R-**3** or R-**10**.

(1) A *stabilizing* interaction between the adjacent sp$^2$-hybridized centers, which is of roughly equal magnitude for the α-thioamide, α-amide, and α-ester groups. This is not likely to be a simple resonance interaction, because the adjacent *π*-centers are not coplanar in the ground states of R-**10** optimized at the 3-21G level, but are twisted away from coplanarity by 70°, 60°, and 10° for $Me_2NC(S)$-**10**, $Me_2NC(O)$-**10** and MeOC(O)-**10**, respectively. Rather, the stabilization of the alkenes R-**10** by α-thiocarbonyl and α-carbonyl substituents (Table 4) is likely a consequence of the *σ*-bond between the sp$^2$-hybridized carbon of these α-substituents and that of the alkene double bond, which is expected to be stronger than the corresponding *σ*-bond between these α-substituents and the benzylic carbon at R-**9**-OH.[42,43]

(2) A *destabilizing* dipole−dipole interaction between the electron-deficient α-thiocarbonyl or α-carbonyl substituent and the electron-deficient alkene double bond at R-**10**[43] which decreases in magnitude on proceeding from the strongly electron-withdrawing α-ester substituent to the more weakly electron-withdrawing α-amide and α-thioamide substituents.[44]

The data in Table 7 suggest that these opposing effects described in 1 and 2 above cancel at MeOC(O)-**10**, which is of similar stability to $CH_3$-**10**, relative to the corresponding alcohols R-**9**-OH, but that the stabilizing interaction between adjacent sp$^2$-hybridized centers is responsible for the much greater stability of $Me_2NC(S)$-**10**.

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**Supporting Information Available:** Text giving details of procedures for the synthesis of the ring-substituted alcohols, azides, and benzoate derivatives R-**1**-Y and R-**2**-Y and the α-substituted styrenes R-**3** and spectroscopic and analytical data for these compounds and tables of 3-21G geometries of the optimized structures of $Me_2NC(S)$-**9**-OH, $Me_2NC(O)$-**9**-OH, MeOC(O)-**9**-OH, $CH_3$-**9**-OH, $Me_2NC(S)$-**10**, $Me_2NC(O)$-**10**, MeOC(O)-**10** and $CH_3$-**10** (16 pages). See any current masthead page for ordering and Internet access instructions.

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[44] The change in the geminal interactions between the α-substituent R and the hydroxyl group at R-**9**-OH with changing R has not been determined. The destabilizing *polar interactions* between the electron-withdrawing hydroxyl group and the geminal R substituent should decrease as R is changed from an α-ester to the more weakly electron-withdrawing α-amide and α-thioamide substituents. However, this would result in the stabilization of the alcohol $Me_2NC(S)$-**9**-OH relative to the alkene $Me_2NC(S)$-**10**, rather than the observed stabilization of the alkene R-**10** by the α-thioamide substituent (Table 7).

[45] The recently reported value of $k_{az} = 1.5 \times 10^9$ M$^{-1}$ s$^{-1}$ for reaction of the 9-[*N*,*N*-dimethyl(thioformamidyl)]-9-fluorenyl carbocation with azide ion in a solvent of trifluoroethanol lies below the diffusion-controlled limit.[46]

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