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Substituent Effects on the Formation and Nucleophile Selectivity of Ring-Substituted Phenonium Ions in Aqueous Solution

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Abstract

The reaction of 2-(4-methylphenyl)ethyl tosylate (**Me-1-OTs**) in 50/50 (v/v) trifluoroethanol/water at 25 °C is first-order in the concentration of azide anion nucleophile. A carbon-13 NMR analysis of the products of the reactions of **Me-1-[α-¹³C]OTs** in 50/50 (v/v) trifluoroethanol/water at 25 °C shows the formation of **Me-1-[β-¹³C]OH**, **Me-1-[β-¹³C]OCH₂CF₃** and **Me-1-[β-¹³C]N₃** from the trapping of a symmetrical 4-methylphenonium ion reaction intermediate **Me-2⁺**. The formation of **Me-1-[α-¹³C]N₃** by concerted bimolecular displacement of azide ion at **Me-1-[α-¹³C]OTs** ($k_N = 3.8 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$) and of **Me-1-[α-¹³C]OH** and **Me-1-[α-¹³C]OCH₂CF₃** by concerted bimolecular displacement of solvent ($k_{\text{solv}} = 1.8 \times 10^{-8} \text{ s}^{-1}$) is also observed. An analysis of the rate and product data provides a value of $k_{\text{az}}/k_s = 32 \text{ M}^{-1}$ for partitioning of **Me-2⁺** between addition of azide ion and solvent that is nearly 3-fold smaller than $k_{\text{az}}/k_s = 83 \text{ M}^{-1}$ reported in an earlier study on the partitioning of **MeO-2⁺** [*J. Org. Chem.* **2011**, 76, 9568]. This change is attributed to a decrease in nucleophile selectivity with increasing electrophile reactivity for the activation-limited addition of solvent and azide anion to **X-2⁺**. These data set a limit of $1/k_s$ 10^{-7} s for the lifetime of **Me-2⁺** in aqueous solution.

The barriers for addition of the solvent water to many simple carbocations^[1] and carbocation-anion pairs have been determined.^[2–5] There is good evidence that solvolysis at secondary carbon is by an enforced concerted reaction mechanism, because secondary carbocations are too unstable to exist in water for the time of a bond vibration.^[6–9] A value $k_s \approx 3 \times 10^{12} \text{ s}^{-1}$ (Scheme 1) has been estimated for addition of a largely aqueous solvent to a simple tertiary carbocation, and it was proposed that solvent reorganization with a rate constant $k_r \approx 10^{11} \text{ s}^{-1}$ is the rate-limiting step for the overall carbocation-nucleophile combination reaction.^[10, 11] Electron-donating α-substituents, such as methoxy^[12] and 4-methoxyphenyl,^[13–15] (Scheme 1) are sufficient to give a carbocation with a lifetime long enough to permit diffusion-controlled bimolecular trapping by added nucleophiles. Surprisingly, the lifetimes of α-substituted 4-methoxybenzyl carbocations are not strongly affected by a strongly electron-withdrawing substituent at the α-carbon, such as α-CF₃ and α-COOEt.^[16–20] This is because the increase in k_s due to the strong inductive substituent effect is offset by a decrease in k_s due to an increasing intrinsic reaction barrier that arises from the tendency of these strongly electron-withdrawing groups to enhance resonance delocalization of charge onto the 4-methoxyphenyl ring substituent.^[21, 22]

Bridging phenonium ions were at one time the subject of *intense* interest in studies to characterize internal [anchimeric] nucleophilic assistance to solvolysis,^[23] and the chemical community continues to study the generation and reaction of these electrophiles.^[24, 25]

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However, relatively little is known about the absolute barrier for addition of solvent to ring-substituted phenonium ions. We are interested in designing experiments to examine these reaction barriers, so that they may be compared with barriers to nucleophile addition to related ring-substituted 1-phenylethyl carbocations.^[26–29]

Isomerization of the parent phenonium cation to the 1-phenylethyl carbocation in a super acidic medium is estimated to be favored by 12 kcal/mol.^[30] This predicts a larger thermodynamic driving force for addition of solvent to the phenonium cation, that will reduce the kinetic barrier for k_s for solvent addition, compared with k_s for addition to the 1-phenylethyl carbocation (Scheme 2). On the other hand, nucleophile addition to phenonium ions presumably proceeds by a concerted bimolecular displacement reaction through a pentavalent transition state that avoids formation of the more unstable primary carbocation intermediate of a stepwise reaction. This requirement for the development of unfavorable bonding for pentacoordinate carbon should result in an increase the intrinsic barrier for bimolecular substitution at the phenonium cation, compared to the intrinsic barrier for thermodynamically favorable collapse of the 1-phenylethyl carbocation to the solvent adduct (Scheme 2).^[21, 31]

We recently reported the generation and trapping of the 4-methoxyphenonium ion **MeO-2⁺** as an intermediate of the solvolysis reaction of 2-(4-methoxyphenyl)ethyl tosylate in the largely aqueous solvent of 50/50 (v/v) trifluoroethanol water.^[32] The relative yields of the products of addition of azide anion and solvent to **MeO-2⁺** were determined and used to calculate a value of $k_{az}/k_s = 83 \text{ M}^{-1}$ for partitioning of the electrophile between capture by azide anion and solvent. Combining this rate constant ratio and an upper-limit of $k_{az} \leq 5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ gave $k_s \leq 6 \times 10^7 \text{ s}^{-1}$ for addition of an aqueous solvent to **MeO-2⁺**.^[29] Arguments were presented that the actual value of k_s lies below this limit.^[32]

X = -OCH₃, -CH₃

X-2⁺

We report here the generation of **Me-2⁺** as an intermediate of the solvolysis reaction of 2-(4-methylphenyl)ethyl tosylate in the largely aqueous solvent of 50/50 (v/v) trifluoroethanol/water. The 4-Me- for 4-MeO- substitution results in a < 3-fold decrease in k_{az}/k_s that is consistent with a modest decrease in nucleophile selectivity, with increasing electrophile reactivity, due to a shift to a transition state with weakened bonding of the nucleophile/leaving group to the central carbon. The results provide strong evidence that there is a significant chemical activation barrier to concerted bimolecular displacement reactions of azide anion and solvent at the strained cyclopropyl rings of **X-2⁺** so that the absolute lifetimes of these intermediates generated by laser flash photolysis might be obtained by direct measurement.

EXPERIMENTAL

[¹³C]-Carbon dioxide (99% enriched) was purchased from Aldrich. All other organic and inorganic chemicals were reagent grade from commercial sources and were used without further purification.

Syntheses

2-(4-Methylphenyl)-[1- ^{13}C]ethanol [**Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OH}$**] was synthesized by the procedure of Tsuno and coworkers.^[33] The product was purified by silica-gel column chromatography eluting by n-hexane/ether; yield 54 %, ^1H NMR (400 MHz, CDCl_3): δ 7.13 (m, 4H, ArH), 3.84 (dq, 2H, $J_{\text{H}13\text{C}} = 143$ Hz, $J_{\text{HCCH}} = J_{\text{HCOH}} = 6$ Hz, $^{13}\text{CH}_2\text{OH}$), 2.84 (dt, 2H, $J_{13\text{CCH}} = 5$ Hz, $J_{\text{HCCH}} = 6$ Hz, CH_2), 2.33 (s, 3H, PhCH_3), 1.39 (1H, dt, $J_{13\text{CCOH}} = 3$ Hz, $J_{\text{HCOH}} = 6$ Hz, OH), ^{13}C NMR (100.4 MHz, CDCl_3): δ 63.8.

2-(4-Methylphenyl)ethyl 1- ^{13}C tosylate [**Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$**] was synthesized from the corresponding alcohol and 4-toluenesulfonyl chloride by the procedure of Tipson;^[34] yield 68 %, mp 67–68 °C, ^1H NMR (400 MHz, CDCl_3): δ 7.69 (A_2B_2 , 2H, $J = 8$ Hz, ArH), 7.28 (A_2B_2 , 2H, $J = 8$ Hz, ArH), 7.06 (A_2B_2 , 2H, $J = 8$ Hz, ArH), 6.99 (A_2B_2 , 2H, $J = 8$ Hz, ArH), 4.17 (dt, 2H, $J_{\text{H}13\text{C}} = 151$ Hz, $J_{\text{HCCH}} = 7$ Hz, $^{13}\text{CH}_2\text{OTos}$), 2.91 (q, 2H, $J_{13\text{CCH}} = J_{\text{HCCH}} = 7$ Hz, CH_2), 2.44 (s, 3H, PhCH_3), 2.31 (s, 3H, PhCH_3), ^{13}C NMR (100.4 MHz, CDCl_3): δ 70.8.

Carbon-13 NMR Analyses

Proton-decoupled ^{13}C NMR spectra were recorded on a JEOL AL-400 FT-NMR spectrometer operating at 100.4 MHz. Chemical shifts were reported in ppm, relative to a value of $\delta = 77.0$ ppm for CDCl_3 . The signals for the $[\alpha\text{-}^{13}\text{C}]$ and $[\beta\text{-}^{13}\text{C}]$ positions of the products of solvolysis of **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$** were monitored using a pulse angle of 45° and relaxation delay of 70 s to obtain spectra centered at 55.0 ppm, which spanned 7042.25 Hz and contained 65,000 data points (0.107 Hz/pt). Generally > 1,000 FT transients were averaged before determining the final spectra.

Kinetic Studies

The solvolysis reactions of **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$** in the absence or in the presence of azide anion were initiated by making a 200-fold dilution of a solution of substrate in acetonitrile into 50/50 (v/v) TFE/ H_2O ($I = 0.5$, NaClO_4) to give a final substrate concentration of 0.2 mM. The reactions were carried out under pseudo-first order conditions, where the concentration of azide anion is >10-fold larger than the concentration of substrate. The reaction progress was monitored for 60 days by HPLC analyses as described in earlier work.^[13, 17, 29] Values of the observed first order reaction rate constants for these reactions were determined as the slopes of semilogarithmic plots of reaction progress against time.

HPLC Product Analyses

The solvolysis reactions of **Me-1-OTs** were initiated by making a 200-fold dilution of a solution of substrate in acetonitrile into 50/50 (v/v) TFE/ H_2O ($I = 0.5$, NaClO_4) to give a final substrate concentration was 0.20 mM. The reactions were carried out at room temperature and after a reaction time of *ca* two months the relative yields of the azide anion (**Me-1- N_3**), water (**Me-1-OH**) and trifluoroethanol (**Me-1- OCH_2CF_3**) adducts were determined directly from the relative peak areas from HPLC analysis, with peak detection at 265 nm. This is λ_{max} for the 2-(4-methylphenyl)ethyl alcohol, and it was shown in an earlier study of the reactions of 1-(4-methylphenyl)ethyl derivatives that the molar extinction coefficients for products of the nucleophilic substitution reactions of azide anion (4- $\text{MeC}_6\text{H}_4\text{CH}(\text{CH}_3)\text{N}_3$ and solvent [(4- $\text{MeC}_6\text{H}_4\text{CH}(\text{CH}_3)\text{OH}$), (4- $\text{MeC}_6\text{H}_4\text{CH}(\text{CH}_3)\text{OCH}_2\text{CF}_3$) adducts are the same.^[29]

Carbon-13 NMR Product Analyses

The solvolysis reactions of **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$** in the absence or in the presence of N_3^- were initiated by preparing 20 mg of substrate in acetonitrile and adding this to 400 mL of 50/50

(v/v) TFE/H₂O (*I* = 0.5, NaClO₄) to give a final substrate concentration of 0.18 mM. After a *ca* two-month reaction time the reaction products were extracted into toluene. The toluene layer was washed with water, dried over MgSO₄ and removed by evaporation. The resulting residue was dissolved in 0.6 mL of CDCl₃, and analyzed by ¹³C NMR to determine relative yields of products labeled with ¹³C at the α- and β-positions. The relative product yields were determined by integration of the following peaks for the [¹³C]-enriched carbons: **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OH}$** , 63.77 ppm; **Me-1- $[\beta\text{-}^{13}\text{C}]\text{OH}$** , 38.72 ppm; **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OCH}_2\text{CF}_3$** , 73.77 ppm; **Me-1- $[\beta\text{-}^{13}\text{C}]\text{OCH}_2\text{CF}_3$** , 35.67 ppm; **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{N}_3$** , 52.56 ppm; **Me-1- $[\beta\text{-}^{13}\text{C}]\text{N}_3$** , 34.19 ppm.

RESULTS

The first-order rate constant ($k_{\text{solv}}\text{)}_{\text{obs}} = 2.5 \times 10^{-7} \text{ s}^{-1}$ was determined for solvolysis of **Me-1-OTs** in the absence of azide anion by monitoring the disappearance of substrate by HPLC. Figure 1 shows a plot of values of the pseudo first-order rate constants k_{obs} against the concentration of added azide anion for reactions of **Me-1-OTs** in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) at 25 °C. The second-order rate constant ($k_{\text{Nu}}\text{)}_{\text{obs}} = 3.8 (\pm 0.1) \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ was determined as the slope of a linear plot of k_{obs} against $[\text{N}_3^-]$ (Figure 1). The yields of the products of the nucleophilic substitution reactions of azide anion (**Me-1-N₃**), water (**Me-1-OH**) and trifluoroethanol (**Me-1-OTFE**) with **Me-1-OTs** in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) and at 25 °C, determined by HPLC analyses, are reported in Table 1. The reactions of **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$** with azide anion were examined in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) at 25 °C. The relative yields of **Me-1-N₃**, **Me-1-OH**, and **Me-1-OTFE** labeled with carbon-13 in the α-position [$\alpha\text{-}^{13}\text{C}$] and the β position [$\beta\text{-}^{13}\text{C}$] were determined by carbon-13 NMR analyses, and the product ratios [$\alpha\text{-}^{13}\text{C}$]/[$\beta\text{-}^{13}\text{C}$] are reported in Table 2.

DISCUSSION

The observed first-order rate constant ($k_{\text{solv}}\text{)}_{\text{obs}} = 2.5 \times 10^{-7} \text{ s}^{-1}$ for solvolysis of **Me-1-OTs** in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) and at 25 °C is eight-fold smaller than ($k_{\text{solv}}\text{)}_{\text{obs}} = 1.95 \times 10^{-6} \text{ s}^{-1}$ determined for solvolysis of **MeO-1-OTs** under the same reaction conditions.^[32] This is consistent with internal nucleophilic push by the methoxyphenyl ring to ionization of **MeO-1-OTs** to form **MeO-2⁺**. The solvolysis of **MeO-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$** in 50/50 (v/v) TFE/H₂O gives equal yields of products **MeO-1-OH** and **MeO-1-OTFE** labeled with [$\alpha\text{-}^{13}\text{C}$] and with [$\beta\text{-}^{13}\text{C}$], so that there is no detectable solvolysis by a concerted bimolecular displacement mechanism. This shows that ($k_{\text{solv}}\text{)}_{\text{obs}}$ is equal to k_{Δ} for intramolecular displacement of tosylate anion by the aromatic ring to give the phenonium cation **MeO-2⁺**.^[32]

By contrast, carbon-13 NMR analyses of the products of solvolysis of **Me-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$** in 50/50 (v/v) TFE/H₂O show a small excess of carbon-13 label at the α-carbon for both **Me-1-OH** and **Me-1-OTFE**, for which [$\alpha\text{-}^{13}\text{C}$]/[$\beta\text{-}^{13}\text{C}$] = 1.16 and 1.08 respectively (Table 2). This solvolysis reaction therefore proceeds mainly by a unimolecular stepwise D_N + A_N mechanism,^[35] with rate constant k_{Δ} and scrambling of the label at the α- and β-carbons; and, by a slower concurrent concerted bimolecular A_ND_N mechanism,^[35] with rate constant k_{solv} , for direct addition of solvent to the α-carbon (Scheme 2) to form products labeled with carbon-13 at this carbon. The relationship between the product ratio [$\alpha\text{-}^{13}\text{C}$]/[$\beta\text{-}^{13}\text{C}$] and the rate constants k_{Δ} and k_{solv} is given by eq 1. Substitution of [$\alpha\text{-}^{13}\text{C}$]/[$\beta\text{-}^{13}\text{C}$] = 1.16 for the reaction of HOH into eq 1 gives a value of $k_{\text{solv}}/k_{\Delta} = 0.080$. Combining the observed rate constant ($k_{\text{solv}}\text{)}_{\text{obs}} = 2.50 \times 10^{-7} \text{ s}^{-1} = k_{\text{solv}} + k_{\Delta}$ with $k_{\text{solv}}/\Delta = 0.080$ gives values of $k_{\Delta} = 2.23 \times 10^{-8}$ and $k_{\text{solv}} = 1.8 \times 10^{-8} \text{ s}^{-1}$ (Scheme 3).

Eq 1 and 2 were used to partition the total yield of solvolysis reaction products, $f_{\text{Me-1-OSol}}$ (Table 1), into the product yields from the $D_N + A_N$ [$(f_{\text{ROSol}})_{D_N + A_N}$] and $A_N D_N$ [$(f_{\text{ROSol}})_{A_N D_N}$] solvolysis reactions (Table 3).^[35] The yield of **Me-1-OTFE** is low (7% of total solvolysis products, and we therefore make the simplifying assumption that $k_{\text{solv}}/k_{\Delta} = 0.080$ for the reactions of both water and trifluoroethanol. The use of the smaller observed ratio of $k_{\text{solv}}/k_{\Delta} = 0.04$ for the reaction of trifluoroethanol does not cause a significant change (0.2%) in the product yields for **Me-1-OSol** = **Me-1-OH** + **Me-1-OTFE** reported in Table 3.

$$\left(\frac{\alpha-^{13}\text{C}}{\beta-^{13}\text{C}}\right) = \left(\frac{k_{\text{solv}} + 0.5k_{\Delta}}{0.5k_{\Delta}}\right) \quad (1)$$

$$(f_{\text{ROSol}})_{D_N + A_N} = (f_{\text{ROSol}})_{\text{obs}} \left(\frac{k_{\Delta}}{k_{\text{solv}} + k_{\Delta}}\right) \quad (2)$$

$$(f_{\text{ROSol}})_{A_N D_N} = (f_{\text{ROSol}})_{\text{obs}} - (f_{\text{ROSol}})_{D_N + A_N} \quad (3)$$

The second-order rate constant $k_{\text{Nu}} = 3.8 \times 10^{-6} \text{ M}^{-1}\text{s}^{-1}$ for bimolecular substitution of azide anion at **Me-1-OTs** in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) is similar to $k_{\text{Nu}} = 3.6 \times 10^{-6} \text{ M}^{-1}\text{s}^{-1}$ for the substitution reaction at **MeO-1-OTs** under the same conditions.^[32] This shows that there is no significant push by the 4-OMe group to nucleophilic displacement of azide anion at **MeO-1-OTs**. Table 1 reports the observed product rate constant ratios ($k_{\text{az}}/k_{\text{s}})_{\text{obs}}$ (M^{-1}) for the reaction of azide anion and solvent with **Me-1-OTs**, calculated from the product yields using eq 4. The observed product rate constant ratio $(k_{\text{az}}/k_{\text{s}})_{\text{obs}} = 48 \text{ M}^{-1}$ is substantially larger than the rate constant ratio $(k_{\text{Nu}})_{\text{obs}}/(k_{\text{solv}})_{\text{obs}} = 15.2 \text{ M}^{-1}$ determined by kinetic analyses. This shows that a large fraction of the total yield of **Me-1-N₃** forms by trapping of the symmetrical intermediate **Me-2⁺**.

$$(k_{\text{az}}/k_{\text{s}})_{\text{obs}} = \left(\frac{f_{\text{RN3}}}{f_{\text{ROSol}} [\text{N}_3^-]}\right) \quad (4)$$

$$(f_{\text{RN3}})_{A_N D_N} = \left(\frac{k_{\text{Nu}} [\text{N}_3^-]}{(k_{\text{solv}})_{\text{obs}} + k_{\text{Nu}} [\text{N}_3^-]}\right) \quad (5)$$

$$(f_{\text{RN3}})_{D_N + A_N} = (f_{\text{RN3}})_{\text{obs}} - (f_{\text{RN3}})_{A_N D_N} \quad (6)$$

$$\left(\frac{\alpha-^{13}\text{C}}{\beta-^{13}\text{C}}\right) = \left(\frac{(f_{\text{RN3}})_{A_N D_N} + 0.5(f_{\text{RN3}})_{D_N + A_N}}{0.5(f_{\text{RN3}})_{D_N + A_N}}\right) \quad (7)$$

$$(k_{\text{az}}/k_{\text{s}})_{\text{C}+} = \left(\frac{(f_{\text{RN3}})_{D_N + A_N}}{(f_{\text{ROSol}})_{D_N + A_N} [\text{N}_3^-]}\right) \quad (8)$$

Eq 5 and 6, derived for Scheme 3, were used to partition the total yield of azide anion adduct **Me-1-N₃** (Table 1), into the product yields from the stepwise D_N + A_N [(f_{RN3})_{D_N+A_N}] and concerted A_ND_N [(f_{RN3})_{A_ND_N}] substitution reactions (Table 3). Substitution of these product yields into eq 7, derived for Scheme 3, gives the theoretical ratios [α-¹³C]/[β-¹³C] for **Me-1-N₃** labeled with carbon-13 at the α- and β-carbons. The good agreement between the calculated and observed ratios shows that Scheme 3 provides a complete and self-consistent rationalization of the experimental data. Table 3 also reports values for the rate constant ratio (*k*_{az}/*k*_s)_{C+} for trapping of the phenonium cation intermediate **X-2⁺**, determined from the product yields for the stepwise D_N + A_N reaction using eq 8.

Reactivity-Selectivity Relationships

Chart 1 reports the nucleophile selectivity *k*_{az}/*k*_s (M⁻¹) determined for addition of azide anion and solvent to several electrophiles, and the absolute rate constant *k*_s in the cases where these are known. The nucleophile selectivity (*k*_{Nu})_{obs}/*k*_{solv} = *k*_{az}/*k*_s = [3.8 × 10⁻⁶ M⁻¹s⁻¹]/[1.8 × 10⁻⁸ s⁻¹] = 210 M⁻¹ for the reaction of **Me-1-OTs** serves as a benchmark for a concerted bimolecular displacement reaction at a primary alkyl tosylate. The value of log (*k*_{az}/*k*_s) = 2.3 for this reaction is significantly smaller than the Swain-Scott nucleophilicity parameter *n* = log(*k*_{az}/*k*_s)_{MeBr} = 3.9 determined for the reaction of azide anion and solvent with methyl bromide in water.^[36] This difference in nucleophile selectivity is consistent with a stronger stabilization of the transition state for bimolecular substitution at aliphatic carbon by interactions of reactive nucleophiles with the bromide anion leaving group, compared to tosylate anion leaving group. Such transition state stabilization by interactions between nucleophile and leaving group across a pentavalent carbon transition state has been noted in other work, and given the name “symbiosis”.^[6, 37–40]

Chart 1 shows the very different effects of replacing a 4-Me by a 4-OMe ring substituent on nucleophile selectivity for addition of azide anion and a solvent of aqueous/trifluoroethanol to phenonium cations and to the ring substituted 1-phenylethyl carbocations **MeO-3⁺** and **Me-3⁺**. This difference is not related to a difference in the effect of these substitutions on the reaction thermodynamic driving force, because the 4-OMe substituent provides a similar stabilization of the **Me-2⁺** cation in bromide ion transfer reaction in the gas phase (Scheme 4A),^[41] and the **Me-3⁺** cation in a hydroxide ion transfer reaction in aqueous/trifluoroethanol (Scheme 4B).^[29]

The large decrease in nucleophile selectivity from (*k*_{az}/*k*_s) = 100 to 1.1 M⁻¹ for nucleophile addition to **MeO-3⁺** and **Me-3⁺** (Chart 1) reflects the increase in *k*_s for the activation-limited reaction of solvent, relative to the invariant value of *k*_{az} = 5 × 10⁹ for diffusion-limited addition of azide ion to **MeO-3⁺** and **Me-3⁺**.^[26, 29, 42, 43] By comparison, the smaller 2.6-fold change in nucleophile selectivity from *k*_{az}/*k*_s = 83 M⁻¹ for **MeO-2⁺** to 32 M⁻¹ for **Me-2⁺** is consistent with a shift to a “looser” transition state, with weakened bonding of the nucleophile and leaving group to the central carbon, as the p*K*_a of the carbon leaving group is decreased (Scheme 5).^[44] The alternative explanation is that the change in selectivity reflects a 2.6 fold increase in *k*_s relative to *k*_{az} = 5 × 10⁹ for the diffusion-limited reactions of azide ion. However, such a small 2.6 fold increase in *k*_s is inconsistent with the larger 8-fold difference in the values of *k*_Δ for the ionization of **Me-1-OTs** and **MeO-1-OTs** (ΔΔ*G*_Δ[‡] ≈ 1.2 kcal/mol) and still larger ca 3000-fold effect of **Me-** for **MeO-** substitution on *K*_{eq} = *k*_f/*k*_r for a bromide anion transfer reaction (ΔΔ*G*[°] ≈ 4.7 kcal/mol, Scheme 4). This ca. 3000-fold effect on *K*_{eq} must be expressed as changes in both the rate constant *k*_Δ for formation of the phenonium ion and in the rate constant for the reactions in the reverse direction, so that the **Me-** for **MeO-** substitution is predicted to cause a > 100- fold increase in *k*_s for solvent addition to **MeO-2⁺**.

Lifetime of Phenonium Ions

We conclude that the decrease in k_{az}/k_s from 83 M^{-1} for **MeO-2**⁺ to 32 M^{-1} for **Me-2**⁺ reflects a 2.6 fold decrease in the nucleophile selectivity for the activation-limited addition of solvent and azide anion to **MeO-2**⁺. This sets upper limits of $k_{az} = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $k_s = 1.6 \times 10^8 \text{ s}^{-1}$ for addition of azide anion and solvent to **Me-2**⁺. The lifetime of the neutral *spiro*[2,5]-octa-1,4-diene-3-one **4** in water ($k_s = 3.4 \times 10^{-3} \text{ s}^{-1}$)^[45] is 1000-fold longer than for the simple *p*-quinone methide **5**.^[46, 47] If there were a constant 1000-fold difference in reactivity for changing phenyl ring substituents, then the value of $k_s = 6 \times 10^9 \text{ s}^{-1}$ estimated for addition of aqueous/trifluoroethanol to **CH₃-3**⁺^[27, 29] and $(k_{az}/k_s) = 32 \text{ M}^{-1}$ for nucleophile addition to **CH₃-2**⁺ gives values of $k_s = 6 \times 10^6 \text{ s}^{-1}$ and $k_{az} = 2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for addition of solvent and azide anion to **CH₃-2**⁺.

Scheme 4 suggests that there is a smaller effect of changing phenyl ring substituents on the reactivity of **X-2**⁺ compared with **X-3**⁺ that would be reflected as an increase in the observed 10^3 -fold difference in the reactivity of **4** and **5**, with increasing electrophile reactivity. If this were the case, then $k_s = 6 \times 10^6 \text{ s}^{-1}$ and $k_{az} = 2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for nucleophile addition to **CH₃-2**⁺. In any case, these data set an approximate lower limit of $1/k_s = 10^{-7} \text{ s}$ for the lifetime of **Me-2**⁺ in aqueous solution and a longer lifetime for **CH₃O-2**⁺. These results suggest that the absolute lifetimes of these phenonium may be readily determined by experiment, provided efficient procedures for their generation by laser flash photolysis were developed.^[48]

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Figure 1.

The increase in the observed pseudo first-order rate constant for the reactions of **Me-1-OTs** as the initial concentration of the azide anion nucleophile is increased.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

	Me-1-Ts	MeO-2 ⁺	Me-2 ⁺	MeO-3 ⁺	Me-3 ⁺

k_{az}/k_{solv} or k_{az}/k_s (M ⁻¹)	210	83	32	100	1.1
k_{solv} or k_s (s ⁻¹)	1.85 x 10 ⁻⁸			5 x 10 ⁷	6 x 10 ⁹

Chart 1.

Table 1

The Yields of the Products and the Observed Product Rate Constant Ratios $(k_{\text{az}}/k_{\text{s}})_{\text{obs}}$ for the Reaction of **Me-1-OTs** in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) at 25 °C and Different Fixed Concentrations of Azide Anion.

$[\text{N}_3^-]/\text{M}$	$f_{\text{RN}_3}^a$	f_{ROH}^a	f_{ROTFE}^a	f_{ROSol}^b	$(k_{\text{az}}/k_{\text{s}})_{\text{obs}} (\text{M}^{-1})^c$
0.0050	0.192	0.751	0.056	0.807	48
0.0060	0.223	0.725	0.052	0.777	48
0.0080	0.279	0.673	0.048	0.721	48
0.010	0.328	0.626	0.045	0.671	49

^a Fractional product yields determined by HPLC analyses.

^b The sum of the fractional yields of the water and trifluoroethanol adducts.

^c Observed product rate constant ratio determined from the ratio of product yields using eq 4.

Table 2

The Ratio of the Yields of Product Labeled with Carbon-13 in the α - and β -Positions for the Reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]\text{OTs}$** in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) at 25 °C and Different Fixed Concentrations of Azide Anion.

$[\text{N}_3^-]/\text{M}$	$[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}]^a$		
	MeO-1-N₃	MeO-1-OH	Me-1-OTFE
0.00		1.16	1.08
0.0050	2.25	1.15	1.06
0.0060	2.29	1.14	1.08
0.080	2.45	1.16	1.08
0.010	2.54	1.18	1.06

^a Determined as the ratio of the carbon-13 peak area for the products labeled with carbon-13 at the α - and β -carbon.

Table 3

Calculated Yields of the Azide Anion and Solvent Adducts to **MeO-1- α - ^{13}C]OTs** by competing $\text{D}_\text{N} + \text{A}_\text{N}$ and $\text{A}_\text{N}\text{D}_\text{N}$ Reaction Mechanisms in 50/50 (v/v) TFE/ H_2O ($I = 0.5$, NaClO_4) at 25 °C Determined by an Analysis of the Dependence of the Observed Rate Constants and Reaction Products on the Concentration of Azide Anion.

$[\text{N}_3^-]$	$(f_{\text{RN3}})\text{A}_\text{N}\text{D}_\text{N}^a$	$(f_{\text{RN3}})\text{D}_\text{N}+\text{A}_\text{N}^b$	$(f_{\text{ROSol}})\text{A}_\text{N}\text{D}_\text{N}^c$	$(f_{\text{ROSol}})\text{D}_\text{N}+\text{A}_\text{N}^d$	$(k_{\text{az}}/k_{\text{s}})_{\text{C}+}^e$	$\left[\frac{[\alpha-^{13}\text{C}]}{[\beta-^{13}\text{C}]} \right]_{\text{RN3}}^f$	
						Observed	Calculated ^g
0	0	0	0.074	0.926	-	-	-
0.005	0.071	0.121	0.060	0.747	32	2.25	2.24
0.006	0.084	0.139	0.058	0.719	32	2.29	2.21
0.008	0.108	0.171	0.053	0.668	32	2.45	2.26
0.010	0.132	0.197	0.050	0.621	32	2.54	2.34

^a Calculated using eq 5.

^b Calculated using eq 6.

^c Calculated using eq 3.

^d Calculated using eq 2.

^e Calculated using eq 8.

^f The ratio of the yields of **MeO-1- α - ^{13}C]-N₃** and **MeO-1- β - ^{13}C]-N₃** determined by carbon-13 NMR analyses.

^g Calculated using eq 7.