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Swain–Scott Relationships for Nucleophile Addition to Ring-Substituted Phenonium Ions

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Abstract

The products of the reactions of 2-(4-methoxyphenyl)ethyl tosylate (**MeO-1-Ts**) and 2-(4-methylphenyl)ethyl tosylate (**Me-1-Ts**) with nucleophilic anions were determined for reactions in 50/50 (v/v) trifluoroethanol/water at 25°C. In many cases the nucleophile selectivity k_{Nu}/k_s (M^{-1}) for reactions of nucleophile and solvent, calculated from the ratio of product yields, depends upon $[\text{Nu}^-]$. This demonstrates the existence of competing reaction pathways, which show different selectivities for reactions with nucleophiles. A carbon-13 NMR analysis of the products of the reactions of substrate enriched with carbon-13 at the α -carbon, **X-1- $[\alpha\text{-}^{13}\text{C}]$ Ts**, ($\text{X} = \text{-OCH}_3$, -Me) with nucleophilic anions in 50/50 (v/v) trifluoroethanol/water at 25°C shows the formation of **X-1- $[\beta\text{-}^{13}\text{C}]$ OH**, **X-1- $[\beta\text{-}^{13}\text{C}]$ OCH₂CF₃** and **X-1- $[\beta\text{-}^{13}\text{C}]$ Nu** ($\text{Nu} = \text{Br, Cl, CH}_3\text{CO}_2, \text{Cl}_2\text{CHCO}_2$) from the trapping of symmetrical 4-substituted phenonium ion reaction intermediates **X-2⁺**. The observation of excess label in the α -position, $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}] > 1.0$, for both the water and nucleophile adducts, shows that water and anionic nucleophiles also react by direct substitution at **X-1- $[\alpha\text{-}^{13}\text{C}]$ Ts**. The ratios of product yields, $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}]$, and observed nucleophile selectivity $(k_{\text{Nu}}/k_s)_{\text{obs}}$ were used to dissect the contribution of direct nucleophile addition at **Me-1-Ts** and trapping of **X-2⁺** to the product yields. The product yields from partitioning of the intermediate gave the nucleophile selectivity k_{Nu}/k_s (M^{-1}) for **X-2⁺**. Swain-Scott plots of $\log(k_{\text{Nu}}/k_s)$ are correlated by slopes of $s = 0.78$ and $s = 0.73$ for reactions of **MeO-2⁺** and **Me-2⁺**, respectively. This shows that the sensitivity of bimolecular substitution at **X-2⁺** to changes in nucleophile reactivity is smaller than for nucleophilic substitution at the methyl iodide. Evidence is presented that nucleophile addition to **X-2⁺** proceeds through an “exploded” transition state.

Graphical Abstract

Absolute rate constants have been reported for nucleophile addition to classical carbocations,^{1–3} such as tertiary alkyl carbocations,⁴ oxocarbenium ions,⁵ ring-substituted 1-phenylethyl carbocations,^{6,7} α -substituted 1-phenylethyl carbocations,^{8–18} and carbocation-anion pairs (Chart 1).^{19–22} By contrast, much less is known about the rate constants for nucleophile addition to bridging phenonium ions **X-2⁺**, which form as intermediates of nucleophilic substitution reactions at **X-1-Ts** (Scheme 1A).²³ We are interested in estimating absolute rate constants for nucleophile addition to the strained cyclopropyl ring of **X-2⁺**,^{24,25} and in comparing these with rate constants for nucleophile addition to classical carbocations, such as those shown in Chart 1.

The bimolecular substitution reactions at bridging cations **X-2⁺** are reminiscent of nucleophile addition to bridging bromonium ions (Scheme 1B).²⁶ The structure and reactivity of simple bromonium ions were characterized in classic studies by R. Stan Brown coworkers. This work stands as an enduring benchmark for excellence in the study of reactive intermediates.^{26–32} I dedicate our paper to Prof. Brown, in recognition of his continuing contributions to Science, and to his efforts to promote the interests of the North American Chemical Community.

Azide anion selectivities of $k_{\text{az}}/k_s = 83 \text{ M}^{-1}$ and $k_{\text{az}}/k_s = 32 \text{ M}^{-1}$ (Scheme 2) were reported, respectively, for nucleophile addition to **MeO-2⁺** and **Me-2⁺** in 50/50 (v/v) TFE /water.^{24,25} This decrease in nucleophile selectivity is substantially smaller than the decrease from $k_{\text{az}}/k_s = 100 \text{ M}^{-1}$ and $k_{\text{az}}/k_s = 1.1 \text{ M}^{-1}$ determined for **MeO-3⁺** and **Me-3⁺** in the same solvent,^{6,33} which reflects the sharp increase in k_s relative to the essentially constant value of $k_{\text{Nu}} \approx 5 \times 10^9 \text{ M}^{-1}$ for the diffusion-limited reaction of azide anion.^{2,6,33,34} These results are consistent with a small decrease in the nucleophile selectivity of **X-2⁺**, with increasing electrophile reactivity, for reactions that are limited by the chemical barrier to nucleophile addition ($k_{\text{Nu}} < k_d \approx 5 \times 10^9 \text{ M}^{-1}$). The azide anion selectivity sets upper limits of $k_s < 2 \times 10^7 \text{ M}^{-1}$ and $k_s < 6 \times 10^7 \text{ M}^{-1}$, respectively, for addition of solvent to **MeO-2⁺** and **Me-2⁺**.

In this paper we apply experimental methods developed in our earlier work to study nucleophilic substitution reactions of a broad range of nucleophilic anions, whose relative reactivity have been characterized both for bimolecular substitution reactions of alkyl halides,^{35–37} and for carbocation nucleophile addition.^{38,39} These data provide values of the Swain-Scott electrophilicity parameter s for nucleophile addition to **MeO-2⁺** and **Me-2⁺**,³⁷ which show that the rate constants for nucleophile addition to **X-2⁺** are less sensitive to changes in the reactivity of anion nucleophiles than observed for the reference reaction of

nucleophile addition to methyl iodide. The larger reactivity of azide anion compared to bromide anion is similar to that observed for carbocation nucleophile addition reactions,^{38–40} and for bimolecular substitution reactions, which proceed through “exploded” transition states.^{41,42}

EXPERIMENTAL

All organic and inorganic chemicals were reagent grade from commercial sources, and were used without further purification. 2-(4-Methoxyphenyl)ethyl 1-¹³C]tosylate [**MeO-1- α -¹³C]Ts**] [99% enrichment] and 2-(4-methylphenyl)ethyl 1-¹³C]tosylate [**Me-1- α -¹³C]Ts**] [99% enrichment] were synthesized by published procedures.^{24,25}

Carbon-13 NMR Analyses

Proton-decoupled ¹³C 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 CDCl₃. The signals for the [α -¹³C] and [β -¹³C] positions of the products of solvolysis of **Me-1- α -¹³C]Ts** were monitored using a pulse angle of 45° and a 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.

HPLC Product Analyses

The solvolysis reactions of **Me-1-Ts** and **MeO-1-Ts** were initiated by making a 200-fold dilution of a solution of substrate in acetonitrile into 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) to give a final substrate concentration was 0.20 mM, as described in earlier work.^{24,25} The reactions were allowed to proceed to completion at room temperature, at which time the relative yields of the nucleophile (**X-1-Nu**, Nu = Br, Cl, CH₃CO₂, Cl₂CHCO₂), water (**X-1-OH**) and trifluoroethanol (**X-1-OCH₂CF₃**) adducts were determined from the relative peak areas from HPLC analysis, with peak detection at 276 nm and 265 nm, for **MeO-1-Y** and **Me-1-Y** respectively, which is λ_{max} for the respective water adducts.^{24,25} It was shown in previous work that the molar extinction coefficients for products of the substitution reactions of nucleophiles and of solvent 1-(4-methoxyphenyl)ethyl derivatives and at 1-(4-methylphenyl)ethyl derivatives are the same.^{6,42}

Carbon-13 NMR Product Analyses

The solvolysis reactions of **X-1- α -¹³C]Ts** (X = MeO, Me) in the absence or in the presence of Nu[−] (Br[−], Cl[−], CH₃CO₂[−], Cl₂CHCO₂[−]) were initiated by preparing 20 mg of substrate in acetonitrile and adding this to 20 mL of 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) to give a final substrate concentration of 3 mM. After > 2 reaction halftimes 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. The relative yields of products labeled with carbon-13 in the α - and β -position were determined by integration of the following product peaks: (a) **MeO-1- α -¹³C]X**: X = -OH, 63.83; X = -OCH₂CF₃; 73.87; X = -N₃, 52.69; X = Br, 33.35; X = Cl, 45.21; X = -O₂CCH₃, 65.17; X = -O₂CCHCl₂, 68.07 ppm. (b) **MeO-1- β -¹³C]X**: X = -OH,

38.24; X = -OCH₂CF₃; 35.23; X = -N₃, 34.19; X = Br, 38.57; X = Cl, 38.32; X = -O₂CCH₃, 34.19; X = -O₂CCHCl₂, 33.77 ppm. (c) **Me-1-[α-¹³C]X**: X = -OH, 63.77; X = -OCH₂CF₃; 73.77; X = -N₃, 52.56; X = Br, 33.13; X = Cl, 45.12; X = -O₂CCH₃, 65.03; X = -O₂CCHCl₂, 67.96 ppm. (d) **Me-1-[β-¹³C]X**: X = -OH, 38.72; X = -OCH₂CF₃; 35.67; X = -N₃, 34.19; X = Br, 39.01; X = Cl, 39.01; X = -O₂CCH₃, 34.63; X = -O₂CCHCl₂, 34.25 ppm.

RESULTS

The reactions of **MeO-1-Ts** and **Me-1-Ts** with nucleophilic anions were studied in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) at 25 °C. The yields of the products of the substitution reactions of nucleophilic anions (**X-1-Nu**, X = -Me, -OMe), water (**X-1-OH**) and trifluoroethanol (**X-1-OTFE**) with **MeO-1-Ts** and **Me-1-Ts**, determined by HPLC analyses, are reported in Tables 1 and 2, respectively. The reactions of **MeO-1-[α-¹³C]Ts** and **Me-1-[α-¹³C]Ts** with nucleophilic anions were studied in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) at 25 °C. The relative yields of the reactions products labeled with carbon-13 in the α-position [α-¹³C] and the β position [β-¹³C] (Scheme 3), determined by carbon-13 NMR analyses, are reported in Table 3 as the product ratios [α-¹³C]/[β-¹³C].

DISCUSSION

Apparent nucleophile selectivities ($k_{\text{Nu}}/k_{\text{s}}$)_{obs} for reactions of **MeO-1-Ts** and **Me-1-Ts** in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) and at 25 °C, calculated using eq 1 [$f_{\text{ROSolv}} = f_{\text{ROH}} + f_{\text{ROTFE}}$] are reported in Tables 1 and 2, respectively. The values of ($k_{\text{Nu}}/k_{\text{s}}$)_{obs} for nucleophile addition to **MeO-1-Ts** are independent of nucleophile concentration, except for the 10% decrease in ($k_{\text{Nu}}/k_{\text{s}}$)_{obs} observed as [Br⁻] is increased from 0.10 to 0.50 M (Table 1). By contrast there are significant changes in ($k_{\text{Nu}}/k_{\text{s}}$)_{obs}, with increasing [Nu⁻], for nucleophile addition to **Me-1-Ts** (Table 2). The changes in ($k_{\text{Nu}}/k_{\text{s}}$)_{obs} in Tables 1 and 2 are consistent with competing pathways for direct addition of nucleophile and solvent to **X-1-Ts** and to the intermediate **X-2⁺** (Scheme 3).¹⁸ The procedure for dissection of the contribution of these pathways has been described in earlier studies on nucleophile addition of azide anion to **X-1-Ts**.^{24,25}

Nucleophile addition to the symmetrical intermediate **X-2⁺**, labeled with a single carbon-13 at the bridging position (Scheme 3), results in scrambling of the carbon-13 label between the [α]- and the [β]-positions. Equal yields of [α-¹³C]- and the [β-¹³C]-labeled adducts ([α-¹³C]/[β-¹³C] = 1.0, Table 3) are obtained when the reaction proceeds exclusively by the *k* pathway. The direct reaction of solvent [(k_{a})_{sol}, Scheme 3] or of nucleophile [(k_{a})_{Nu}] results in the exclusive formation of the corresponding [α-¹³C] labeled product and will result in an excess of the [α-¹³C] labeled adduct ([α-¹³C]/[β-¹³C] > 1.0, Table 3) when **X-1-Ts** reacts by competing *k*, (k_{a})_{sol} and (k_{a})_{Nu} reaction pathways (Scheme 3).

$$(k_{\text{Nu}}/k_{\text{s}})_{\text{obs}} = \left(\frac{f_{\text{RNu}}}{f_{\text{ROSol}}[\text{Nu}]} \right) \quad (1)$$

$$(k_{\text{Nu}}/k_{\text{s}})_{\Delta} = \left(\frac{(f_{\text{RNu}})_{\Delta}}{(f_{\text{ROSol}})_{\Delta} [\text{Nu}]} \right) \quad (2)$$

In most cases, product ratios $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}] = 1.0$ were observed for the reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in the presence of nucleophilic anions (Table 3). This shows that these reactions proceed essentially exclusively by the k_{s} pathway (Scheme 3). The ratios as large as $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}] = 1.59$, observed for the product **MeO-1-OH** of the reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in the presence of bromide ion, show that the decrease in nucleophile selectivity $(k_{\text{Nu}}/k_{\text{s}})_{\text{obs}}$ with increasing $[\text{Br}^-]$ (Table 1) is due to a reaction that is first-order in $[\text{Br}^-]$, and which gives **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ OH** as the product. The bromide anion reaction may proceed by either direct nucleophilic addition of the anion to the sulfonyl group of **Me-1-Ts** to form **MeO-1-OH** and a sulfonyl bromide, or by Brønsted general base catalysis of nucleophilic addition of water to the α -carbon.

The electron-donating 4-MeO-promotes the reaction of **MeO-1-Ts** with internal nucleophilic assistance to formation of the symmetrical intermediate **MeO-2⁺**.^{23–25} By contrast, the assisted pathway is less important for the reactions of **Me-1-Ts**. Values of $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}] > 1.0$, and as large as $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}] = 3.15$, are observed for the alcohol (**Me-1-OH**) and the nucleophile adducts (**Me-1-Nu**, $\text{-Nu} = \text{-Br, -Cl, CH}_3\text{CO}_2^-, \text{Cl}_2\text{CHCO}_2^-$), which form as products of the reactions of **Me-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** (Table 3). These large product ratios show that the k_{s} , $(k_{\alpha})_{\text{sol}}$ and $(k_{\alpha})_{\text{Nu}}$ pathways are all significant for the reactions of these nucleophilic anions.

The product ratios $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}] = 1.0$ determined for the reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in the presence of chloride, acetate and dichloroacetate anions (Table 3) show that these substitution reactions proceed essentially exclusively by the k_{s} pathway. The observed nucleophile selectivities $(k_{\text{Nu}}/k_{\text{s}})_{\text{obs}}$ (eq 1) are therefore equal to the selectivities $(k_{\text{Nu}}/k_{\text{s}})$ (eq 2) for partitioning of **MeO-2⁺**. The ratios $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}] > 1.0$ determined for the alcohol product **MeO-1-OH** of the substitution reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in the presence of bromide anion require that the observed total yield of the solvent adducts be partitioned into the yields from the k_{s} and k_{α} pathways: $(f_{\text{ROSol}})_{\text{obs}} = (f_{\text{ROSol}})_{\text{s}} + (f_{\text{ROSol}})_{\alpha}$. Eq 3 gives the relationship between $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}]$ (Table 3) and the rate constants for reaction by the k_{s} and the k_{α} pathways, where k_{α} corresponds to either $(k_{\alpha})_{\text{sol}}$ or $(k_{\alpha})_{\text{Nu}}$ from Scheme 3. Eq 4 shows the relationship between the observed product yield $(f_{\text{R-X}})_{\text{obs}}$ [$\text{X} = \text{-OH, -Nu}$], $(f_{\text{R-X}})$ from partitioning of a symmetrical intermediate, and $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}]$.

Table 4 reports: (a) Values for $(f_{\text{R-OSol}})$ calculated from the values of $(f_{\text{R-OSol}})_{\text{obs}}$ (Table 1) and $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}]$ (Table 3) for the reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in the presence of bromide ion. (b) Values for $(f_{\text{R-OSol}})_{\alpha}$, calculated using eq 5, for these same reactions (c) Values of $(k_{\text{Nu}}/k_{\text{s}})$, determined using eq 2, for partitioning of **MeO-2⁺** between addition of bromide anion and solvent. These calculations assume that values of $[\alpha\text{-}^{13}\text{C}]/[\beta\text{-}^{13}\text{C}]$ for the water [**MeO-1-OH**] and the trifluoroethanol [**MeO-1-OTFE**] adduct are the same. This assumption should not affect our interpretation of these data, because the water adduct accounts for > 92% of the total solvolysis reaction products (Tables 1 and 2).

$$\frac{[\alpha-^{13}\text{C}]}{[\beta-^{13}\text{C}]} = \left(\frac{k_{\alpha} + 0.5k_{\Delta}}{0.5k_{\Delta}} \right) \quad (3)$$

$$(f_{\text{R-X}})_{\Delta} = (f_{\text{R-X}})_{\text{obs}} \left(\frac{2}{\{[\alpha-^{13}\text{C}]/[\beta-^{13}\text{C}]\} + 1} \right) \quad (4)$$

$$(f_{\text{R-X}})_{\alpha} = (f_{\text{R-X}})_{\text{obs}} - (f_{\text{R-X}})_{\Delta} \quad (5)$$

Table 5 reports the fractional product yields ($f_{\text{R-OSol}}$) and ($f_{\text{R-Nu}}$) for the reactions of **Me-1- $[\alpha-^{13}\text{C}]$ Ts** by the k pathway. These were determined from the observed yields ($(f_{\text{R-OSol}})_{\text{obs}}$ and $(f_{\text{R-Nu}})_{\text{obs}}$ (Table 2), and the product ratios $[\alpha-^{13}\text{C}]/[\beta-^{13}\text{C}]$ (Table 3), by following the procedures described above for the reaction of **MeO-1- $[\alpha-^{13}\text{C}]$ Ts** in the presence of bromide ion. The product yields were used to calculate nucleophile selectivities ($k_{\text{Nu}}/k_{\text{s}}$) (eq 2) for partitioning of **Me-2 $^{+}$** . This dissection of product yields shown in Table 5 gives selectivities ($k_{\text{Nu}}/k_{\text{s}}$) that are independent of $[\text{Nu}^{-}]$.

The selectivities ($k_{\text{Nu}}/k_{\text{s}}$, M^{-1}) for partitioning of **X-2 $^{+}$** are summarized in Table 6. Figure 1 shows the logarithmic correlation of selectivities $k_{\text{Nu}}/k_{\text{s}}$ for reactions of **X-2 $^{+}$** with the Swain-Scott nucleophilicity parameter ($n_{\text{CH}_3\text{I}}$),³⁵ which include the azide anion selectivity reported in earlier work.^{24,25} These plots are correlated by slopes of $s = 0.78$ ($r^2 = 0.73$) and $s = 0.73$ ($r^2 = 0.70$) for reactions of **MeO-2 $^{+}$** and **Me-2 $^{+}$** , respectively.³⁷ The Swain-Scott correlations, which are no more than fair, show that the rate constants k_{Nu} for nucleophile addition to **X-2 $^{+}$** are less sensitive to changing nucleophile reactivity than observed for substitution reactions at the methyl iodide in methanol.³⁵ They show that the bond development to the nucleophile at the transition state for nucleophile substitution at **X-2 $^{+}$** is smaller than for this reference reaction.

Approximate two-point Brønsted correlations of $\beta_{\text{nuc}} = 0.09$ and 0.06 , respectively, for addition of substituted acetate anions to **MeO-2 $^{+}$** and **Me-2 $^{+}$** were determined as the slopes of two-point correlations of ($k_{\text{RCOO}}/k_{\text{s}}$) against $\text{p}K_{\text{a}}$, using values of $\text{p}K_{\text{a}} = 4.8$ and 1.3 for $\text{CH}_3\text{CO}_2^{-}$ and $\text{CHCl}_2\text{CO}_2^{-}$, respectively.⁴³ By comparison, Brønsted correlations of $\beta_{\text{nuc}} = 0.14$ and 0.13 have been reported, respectively, for nucleophilic substitution reactions of substituted alkyl amines at N-(methoxymethyl)-N,N-dimethyl(3-nitroanilinium) ion (**3 $^{+}$**),⁴¹ and for nucleophilic substitution reactions of substituted alkyl alcohols at (1-4-nitrophenyl)-2-propyl tosylate.⁴⁴

The Swain-Scott nucleophilicity parameters for bromide ($n_{\text{CH}_3\text{I}} = 5.79$) and azide ($n_{\text{CH}_3\text{I}} = 5.78$) anion are essentially the same, while the Ritchie N_{r} parameter for azide anion (7.5) is larger than for bromide anion (2.2).⁴⁰ The larger selectivity ($k_{\text{Nu}}/k_{\text{s}}$) of azide compared with bromide anion for addition to **X-2 $^{+}$** is therefore consistent with a bimolecular substitution reaction that proceeds through an exploded or expanded carbocation-like transition state that shows stronger stabilizing interactions with azide compared with bromide anion (Scheme 4A). This behavior was previously reported for bimolecular nucleophilic substitution at N-(methoxymethyl)-N,N-dimethyl(3-nitroanilinium) ion (Scheme 4B),⁴¹ where the

carbocation intermediate of a stepwise reaction is strongly stabilized by the electron-donating α -methoxy group. Figure 2 shows the logarithmic correlation, with a slope of 0.60 ($r^2 = 0.85$), between the nucleophile selectivities for the reactions shown in Schemes 4A ($X = -OMe$) and 4B. This correlation is better than those from Figure 1. This provides support for the conclusion that the reaction shown in Scheme 4B is a better model for bimolecular substitution at $\mathbf{X-2}^+$ than is substitution at methyl iodide.

We briefly consider the factors that favor an “expanded” transition state for nucleophile addition to $\mathbf{X-2}^+$. The ground state for $\mathbf{X-2}^+$ should be strongly affected by the large cyclopropyl ring strain and the weak basicity of the substituted phenyl leaving group $\mathbf{X-2}^+$. This will favor a stretching and weakening of the bonds to the leaving group, along with corresponding a buildup of positive charge at the methylene carbons of $\mathbf{X-2}^+$.^{45–48} We propose that the “expanded” ground state of $\mathbf{X-2}^+$ is maintained at the transition state for nucleophilic substitution by anions (Scheme 4A).

The change in ring substituent from $X = -OMe$ to $X = -Me$ results in a decrease in the basicity of the phenyl leaving group at $\mathbf{X-2}^+$ and an increase in the reactivity of the phenonium ion towards nucleophilic substitution. The effect of this change is a decrease in the Swain-Scott nucleophilicity parameter from $s = 0.78$ to $s = 0.73$, that is consistent with a weakening in the bonding to the nucleophile and a shift to a more “open” transition state. This decrease in s with decreasing leaving group basicity has not been well documented for other nucleophilic substitution reactions at carbon. It may be rationalized by a three dimensional reaction energy diagram, which has separate coordinates for bonding to the nucleophile and leaving group.⁴⁹

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Figure 1. Swain-Scott correlations of nucleophile selectivities for reactions of X-2^+ in 50/50 (v/v) TFE/ H_2O ($I = 0.5$, NaClO_4) at 25 °C. The values of n were determined for substitution reactions of methyl iodide in methanol.³⁵ Key: (●), MeO-2^+ ; (■), Me-2^+ .

Figure 2.

Logarithmic correlation between nucleophile selectivities for reactions of N-(methoxymethyl)-N,N-dimethyl(3-nitroanilinium) ion ($\log(k_{\text{Nu}}/k_{\text{w}})_{\text{A}}$, Scheme 4B)⁴¹ and **MeO-2**⁺ ($\log(k_{\text{Nu}}/k_{\text{w}})_{\text{OMe}}$, X = -OMe, Scheme 4A).

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Chart 1.

Table 1

The Fractional Yields of Products and the Observed Nucleophile Selectivities ($k_{\text{Nu}}/k_{\text{s}})_{\text{obs}}$ for Reactions of **MeO-1-Ts** in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) at 25 °C, and at Different Fixed Concentrations of Nucleophilic Anion.

Nu ⁻	[Nu ⁻]/M	f_{RNu}^a	f_{ROH}^a	f_{ROTFE}^a	f_{ROSol}^b	$(k_{\text{Nu}}/k_{\text{s}})_{\text{obs}}$ (M ⁻¹) ^c
Br ⁻	0.10	0.805	0.182	0.014	0.195	41.3
	0.20	0.887	0.104	0.0083	0.113	39.4
	0.30	0.919	0.075	0.0060	0.081	37.8
	0.40	0.943	0.053	0.0042	0.057	41.1
	0.50	0.930	0.047	0.0037	0.050	37.7
Cl ⁻	0.10	0.553	0.423	0.024	0.447	12.4
	0.20	0.696	0.287	0.017	0.304	11.5
	0.30	0.770	0.218	0.012	0.230	11.2
	0.40	0.815	0.178	0.009	0.185	11.0
	0.50	0.850	0.143	0.008	0.150	11.3
CH ₃ CO ₂ ⁻	0.10	0.171	0.777	0.052	0.829	2.07
	0.20	0.285	0.669	0.047	0.716	1.99
	0.30	0.372	0.585	0.043	0.628	1.98
	0.40	0.439	0.522	0.040	0.561	1.96
	0.50	0.494	0.469	0.037	0.507	1.95
Cl ₂ CHCO ₂ ⁻	0.10	0.102	0.843	0.056	0.899	1.13
	0.20	0.173	0.780	0.048	0.827	1.05
	0.30	0.239	0.716	0.045	0.761	1.05
	0.40	0.287	0.672	0.042	0.713	1.01
	0.50	0.338	0.624	0.038	0.662	1.023

^aThe fractional product yields were determined by HPLC analyses.

^bThe sum of the fractional yields of the water and trifluoroethanol adducts.

^c Observed product rate constant ratio determined directly from the ratio of product yields using eq 1.

Table 2

The Fractional Yields of Products and the Observed Nucleophile Selectivities ($k_{\text{az}}/k_{\text{S}})_{\text{obs}}$ for Reactions of **Me-1-Ts** in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) at 25 °C, and at Different Fixed Concentrations of Nucleophilic Anion.

Nu ⁻	[Nu ⁻]/M	f_{RNu}^a	f_{ROH}^a	f_{ROTFE}^a	f_{ROSol}^b	$(k_{\text{Nu}}/k_{\text{S}})_{\text{obs}}$ (M ⁻¹) ^c
Br ⁻	0.10	0.646	0.332	0.022	0.354	18.2
	0.20	0.759	0.227	0.014	0.241	15.7
	0.30	0.816	0.176	0.0086	0.184	14.8
	0.40	0.849	0.145	0.0056	0.151	14.1
	0.50	0.871	0.123	0.0058	0.129	13.5
Cl ⁻	0.10	0.353	0.598	0.050	0.648	5.44
	0.20	0.509	0.455	0.037	0.482	5.28
	0.30	0.599	0.373	0.028	0.401	4.98
	0.40	0.662	0.314	0.024	0.336	4.92
	0.50	0.707	0.272	0.020	0.292	4.84
CH ₃ CO ₂ ⁻	0.10	0.125	0.807	0.069	0.875	1.42
	0.20	0.226	0.712	0.063	0.775	1.46
	0.30	0.311	0.633	0.056	0.689	1.51
	0.40	0.382	0.567	0.052	0.618	1.54
	0.50	0.444	0.508	0.048	0.556	1.60
Cl ₂ CHCO ₂ ⁻	0.10	0.065	0.866	0.069	0.935	0.696
	0.20	0.113	0.824	0.063	0.887	0.638
	0.30	0.182	0.758	0.060	0.818	0.742
	0.40	0.232	0.710	0.058	0.768	0.757
	0.50	0.269	0.682	0.049	0.731	0.737

^aThe fractional product yields were determined by HPLC analyses.

^bThe sum of the fractional yields of the water and trifluoroethanol adducts.

^c Observed product rate constant ratio determined directly from the ratio of product yields using eq 1.

Table 3

The Ratio of the Yields of the Products Enriched with Carbon-13 at the α - and β -Carbons for the Reactions of **X-1**-[α - ^{13}C]Ts in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) at 25 °C at Different Fixed Concentrations of Nucleophilic Anion.

	MeO-1-[α - ^{13}C]Ts		Me-1-[α - ^{13}C]Ts		
	[α - ^{13}C]/[β - ^{13}C] ^a				
	[Nu ⁻]/M	MeO-1-Nu	MeO-1-OH	MeO-1-Nu	MeO-1-OH
Br ⁻	0.10	1.01	1.16	1.31	1.70
	0.20	1.03	1.23	1.53	1.88
	0.30	1.02	1.31	1.75	2.32
	0.40	1.04	1.52	2.02	2.70
	0.50	1.03	1.59	2.26	3.15
Cl ⁻	0.10	1.00	1.04	1.12	1.24
	0.20	0.98	1.06	1.20	1.38
	0.30	0.99	1.10	1.27	1.52
	0.40	1.00	1.12	1.36	1.65
	0.50	1.01	1.14	1.49	1.78
CH ₃ CO ₂ ⁻	0.10	1.00	1.00	2.12	1.22
	0.20	1.05	1.00	2.60	1.25
	0.30	1.06	1.01	2.85	1.28
	0.40	1.12	1.01	3.04	1.31
	0.50	1.15	1.04	3.29	1.34
Cl ₂ CHCO ₂ ⁻	0.10	1.00	0.99	1.72	1.18
	0.20	1.01	1.01	1.83	1.20
	0.30	1.00	1.00	1.84	1.23
	0.40	1.00	0.99	1.95	1.26
	0.50	1.01	1.00	1.97	1.29

^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 4

Calculated Yields of the Nucleophile and Solvent Adducts to **MeO-1**-[α - ^{13}C]Ts, from Competing Reaction Pathways (Scheme 3) in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) at 25 °C.

[Nu ⁻]	f_{RNu} ^a	f_{ROSol} ^b	f_{ROSol} ^c	$(k_{\text{Nu}}/k_{\text{s}})$ ^d M ⁻¹
Br ⁻	0.1	0.805	0.181	0.014
	0.2	0.887	0.101	0.012
	0.3	0.919	0.070	0.011
	0.4	0.943	0.046	0.012
	0.5	0.930	0.039	0.011

^a $f_{\text{RNu}} = (f_{\text{RNu}})_{\text{obs}}$.

^b Calculated for data from Table 1 and 3 using eq 4.

^c Calculated using eq 5.

^d Calculated from the yields of the products from partitioning of **Me-2**⁺ using eq 2.

Calculated Yields of the Nucleophile and Solvent Adducts to **Me-1**-[α - ^{13}C]Ts, from Competing Reaction Pathways (Scheme 3) in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) at 25 °C.

Table 5

[Nu ⁻]	$(f_{\text{RNu}})^a$	$(f_{\text{ROSol}})^a$	$(f_{\text{RNu}})^b$	$(f_{\text{ROSol}})^b$	$(k_{\text{Nu}}/k_{\text{s}})^c$
Br ⁻	0.1	0.559	0.262	0.087	0.092
	0.2	0.600	0.167	0.159	0.074
	0.3	0.593	0.110	0.223	0.073
	0.4	0.562	0.082	0.287	0.069
	0.5	0.534	0.062	0.337	0.067
Cl ⁻	0.1	0.333	0.578	0.020	0.069
	0.2	0.462	0.405	0.046	0.078
	0.3	0.528	0.318	0.071	0.083
	0.4	0.561	0.254	0.101	0.083
	0.5	0.568	0.210	0.139	0.082
CH ₃ CO ₂ ⁻	0.1	0.080	0.789	0.045	0.087
	0.2	0.125	0.688	0.100	0.086
	0.3	0.162	0.604	0.150	0.085
	0.4	0.189	0.535	0.193	0.083
	0.5	0.207	0.475	0.237	0.081
Cl ₂ CHCO ₂ ⁻	0.1	0.048	0.858	0.048	0.077
	0.2	0.080	0.806	0.080	0.081
	0.3	0.128	0.734	0.128	0.084
	0.4	0.158	0.679	0.158	0.088
	0.5	0.181	0.638	0.181	0.092

^a Calculated for data from Table 2 and 3 using eq 4.

^b Calculated using eq 5.

^c Calculated from the yields of the products from partitioning of **Me-2**⁺ using eq 2.

Table 6 Nucleophile Selectivities for **X-2⁺** in 50/50 (v/v) TFE/H₂O (*I* = 0.5, NaClO₄) at 25 °C.

Nu ⁻	<i>n</i> _{CH₃I}	<i>k</i> _{Nu} / <i>k</i> _s (M ⁻¹)	<i>k</i> _{Nu} / <i>k</i> _s (M ⁻¹) ^{<i>e</i>}
N ₃ ⁻	5.8	83 ^{<i>a</i>}	32 ^{<i>b</i>}
Br ⁻	5.8	46 ^{<i>c</i>}	18
Cl ⁻	4.4	11.9 ^{<i>d</i>}	5.5
CH ₃ CO ₂ ⁻	4.5	2.0 ^{<i>d</i>}	0.91
Cl ₂ CHCO ₂ ⁻		1.0 ^{<i>d</i>}	0.58

^{*a*} Ref 25.^{*b*} Ref 24.^{*c*} Arithmetic average of nucleophile selectivities from Table 4.^{*d*} Arithmetic average of nucleophile selectivities from Table 1.^{*e*} Arithmetic average of nucleophile selectivities from Table 5.