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Formation and Stability of the 4-Methoxyphenonium Ion in Aqueous Solution

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Abstract

The reaction of 2-methoxyphenylethyl tosylate (**MeO-1-Ts**) is first-order in $[N_3^-]$. A carbon-13 NMR analysis of the products of the reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]\text{Ts}$** shows the formation of **MeO-1- $[\beta\text{-}^{13}\text{C}]\text{OH}$** and **MeO-1- $[\beta\text{-}^{13}\text{C}]\text{N}_3$** from the trapping of a symmetrical 4-methoxyphenonium ion reaction intermediate **2⁺**. An analysis of the rate and product data provides a value of $k_{\text{az}}/k_{\text{s}} = 83 \text{ M}^{-1}$ for partitioning of **2⁺** between addition of azide ion and solvent. These data set a limit for the lifetime of **2⁺** in aqueous solution.

The barriers for addition of the solvent water to many simple carbocations are known.¹ There is good evidence that secondary alkyl carbocations are too unstable to exist in water for the time of a bond vibration,^{2,3} and that solvent reorganization with a rate constant $k_{\text{r}} \approx 10^{11} \text{ s}^{-1}$ is the rate-limiting step for addition of water to simple tertiary carbocations ($k_{\text{s}} \approx 3 \times 10^{12} \text{ s}^{-1}$, Scheme 1).⁴ Electron-donating α -substituents such as methoxy⁵ and 4-methoxyphenyl^{6,7} (Scheme 1) are required to give carbocations with lifetimes long enough to permit diffusion-controlled bimolecular trapping by added nucleophiles. This leaves bridging phenonium ions, which were at one time the subject of *intense* interest in studies to characterize internal [anchimeric] nucleophilic assistance to solvolysis.⁸ The chemical community continues to study the generation and reaction of these electrophiles;^{9,10} however, there has been no work to determine their lifetimes in aqueous solution.

The first-order rate constant k_{AcOH} for acetolysis of ring substituted 2-phenylethyl tosylates (**X-1-Ts**) is insensitive to changes in electron-withdrawing substituents $-X$ at the aromatic ring (Hammett substituent constant $\rho^+ \geq 0.19$), but electron-donating substituents ($\rho^+ < -0.19$) cause large increases in k_{AcOH} . For example, acetolysis of **MeO-1-Ts** at 115 °C is 34- times faster than acetolysis of the parent 2-phenylethyl tosylate **H-1-Ts**.¹¹ This elegant study shows that acetolysis of **MeO-1-Ts** proceeds with intramolecular displacement of the tosylate ion leaving group to form the bridging 4-methoxyphenonium ion (**2⁺**, Scheme 2). The symmetrical cation **2⁺** has also been observed by proton NMR in strongly acidic solution.¹²

We prepared **MeO-1- $[\alpha\text{-}^{13}\text{C}]\text{Ts}$** and determined a value of $k_{\text{solv}} = 1.95 \times 10^{-6} \text{ s}^{-1}$ for solvolysis in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) at 25 °C. A value of $(k_{\text{Nu}})_{\text{obs}} = 3.6 (\pm$

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Supporting Information Available. The derivation of the relationship between the observed product selectivity $(k_{\text{az}}/k_{\text{s}})_{\text{obs}}$ and the rate constants from Scheme 3 is given as Supporting Information. This information is available free of charge via the Internet at <http://pubs.acs.org>.

$0.1) \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ under the same conditions was determined as the slope of a linear plot (not shown) of k_{obs} against $[\text{N}_3^-]$. Table 1 reports: (1) The yields of the products of reactions of azide ion and solvent with **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in 50/50 (v/v) TFE/ H_2O ($I = 0.5$, NaClO_4) and at 25°C that were determined by HPLC analyses. (2) The relative yields of **MeO-1-OH** and **MeO-1-N₃** labeled with carbon-13 in the α - and β positions (Scheme 3), that were determined by carbon-13 NMR analyses. There was only a low yield of the trifluoroethyl ether **MeO-1-OTFE** (Footnote a, Table 1).

The total yield of **MeO-1-N₃** is very much greater than expected if these products were formed exclusively by a bimolecular nucleophilic displacement reaction with $(k_{\text{Nu}})_{\text{obs}}/k_{\text{solv}} = 1.9 \text{ M}^{-1}$. For example only a 2% yield of **MeO-1-N₃** is predicted for the bimolecular substitution reaction of 0.01 M azide ion, but the observed yield is 47% (Table 1). The additional **MeO-1-N₃** forms by trapping of 2^+ (k_{az} , Scheme 3). Similar yields of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ N₃** and **MeO-1- $[\beta\text{-}^{13}\text{C}]$ N₃** from trapping of 2^+ are observed for the reaction of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in the presence of 0.01 M NaN_3 (Table 1). The increase in the excess of the α - compared to the β -labeled product for reactions at the higher $[\text{N}_3^-]$ is due to bimolecular substitution of N_3^- at **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts**. Essentially identical yields of the α - and β -carbon-13 labeled alcohol form as products of solvolysis of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** ($[\text{N}_3^-] = 0 \text{ M}$); but, an excess of the α -carbon-13 alcohol is observed for reactions at high $[\text{N}_3^-]$. This is consistent with azide ion catalysis of addition of water (k_{B} , Scheme 3) to either the sulfonyl group or to the $[\alpha\text{-}^{13}\text{C}]$ -carbon of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts**.

$$\left(\frac{k_{\text{az}}}{k_{\text{s}}}\right)_{\text{obs}} = \left(\frac{f_{\text{RN}_3}}{f_{\text{ROSolv}}}\right) \left(\frac{1}{[\text{N}_3^-]}\right) \quad (1)$$

Figure 1 shows the effect of increasing $[\text{N}_3^-]$ on the azide ion selectivity $(k_{\text{az}}/k_{\text{s}})_{\text{obs}}$ (eq 1) for the reaction of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts**, where f_{RN_3} and f_{ROSolv} are the fractional yields of **MeO-1-N₃**, and (**MeO-1-OH** + **MeO-1-OTFE**), respectively (Table 1). A linear increase in $(k_{\text{az}}/k_{\text{s}})_{\text{obs}}$ (M^{-1}) with increasing $[\text{N}_3^-]$ was observed in an earlier study of the reactions of 4-methoxybenzyl derivatives, which proceed by competing azide ion bimolecular substitution and trapping of the 4-methoxybenzyl carbocation intermediate.⁶ By comparison, the downward break in the correlation shown in Figure 1 is consistent with the formation of additional **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ OSolv** from azide anion catalysis of the direct addition of water to substrate [k_{B} , ($\text{M}^{-1} \text{ s}^{-1}$), Scheme 3]. The solid line shows the theoretical fit of data from Figure 1 to eq 2 derived for Scheme 3 [the derivation is given as Supporting Information], using $[(k_{\text{Nu}} + k_{\text{B}})/k_{\text{solv}}] = (3.64 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1})/(1.95 \times 10^{-6} \text{ s}^{-1}) = 1.9 \text{ M}^{-1}$ determined above; and, values of $k_{\text{az}}/k_{\text{s}} = 83 \text{ M}^{-1}$ and $k_{\text{B}}/k_{\text{Nu}} = 0.016$ for the variable parameters obtained from the nonlinear least squares fit of these data. There is good agreement between the total observed yields of **MeO-1-N₃** (f_{RN_3})_T, and the theoretical yields calculated from eq 3 using the above three rate constant ratios (Table 3).

$$\left(\frac{k_{\text{az}}}{k_{\text{s}}}\right)_{\text{obs}} = \frac{\left(1 + \frac{k_{\text{az}}[\text{N}_3^-]}{k_{\text{s}}}\right) + \left(\frac{k_{\text{solv}}}{k_{\text{B}} + k_{\text{Nu}}}\right) \left(\frac{k_{\text{az}}}{k_{\text{s}}}\right) \left(1 + \frac{k_{\text{B}}}{k_{\text{Nu}}}\right)}{\left(\frac{k_{\text{B}}}{k_{\text{Nu}}}\right) \left(1 + \frac{k_{\text{az}}[\text{N}_3^-]}{k_{\text{s}}}\right) [\text{N}_3^-] + \left(\frac{k_{\text{solv}}}{k_{\text{B}} + k_{\text{Nu}}}\right) \left(1 + \frac{k_{\text{B}}}{k_{\text{Nu}}}\right)} \quad (2)$$

$$(f_{\text{RN3}})_T = \frac{\left(\frac{k_{\text{Nu}}}{k_{\text{solv}}}\right)[\text{N}_3^-]}{1 + \left(\frac{k_{\text{B}} + k_{\text{Nu}}}{k_{\text{solv}}}\right)[\text{N}_3^-]} + \frac{\left(\frac{k_{\text{az}}}{k_{\text{s}}}\right)[\text{N}_3^-]}{\left(1 + \left(\frac{k_{\text{B}} + k_{\text{Nu}}}{k_{\text{solv}}}\right)[\text{N}_3^-]\right)\left(1 + \frac{k_{\text{az}}[\text{N}_3^-]}{k_{\text{s}}}\right)} \quad (3)$$

The azide ion selectivity of $k_{\text{az}}/k_{\text{s}} = 83 \text{ M}^{-1}$ requires that the lifetime of 2^+ in water is sufficiently long to allow for its diffusion through the nucleophilic solvent, and *selection* for reaction with strongly nucleophilic azide anion.^{13,14} The *upper* limit for k_{az} is $k_{\text{d}} \approx 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for a diffusion-controlled reaction of 2^+ .¹⁵ Combining this and $k_{\text{az}}/k_{\text{s}} = 83 \text{ M}^{-1}$ gives an upper limit of $k_{\text{s}} \leq 6 \times 10^7 \text{ s}^{-1}$ for addition of solvent. We expect that k_{s} for addition of solvent to 2^+ is smaller than $2 \times 10^8 \text{ s}^{-1}$ observed for the 4-methoxybenzyl carbocation, because $k_{\text{s}} = 3.4 \times 10^{-3} \text{ s}^{-1}$ for addition of solvent to the neutral *spiro*[2,5]-octa-1,4-diene-3-one¹⁶ is 1000-fold smaller than $k_{\text{s}} = 3.3 \text{ s}^{-1}$ for addition of solvent to the unsubstituted *p*-quinone methide **4**,¹⁷ while O-methylation of **4** causes a 10^8 -fold increase in electrophile reactivity.¹⁸ We suggest that the rate constants for addition of nucleophiles to 2^+ lie closer to $k_{\text{s}} = 10^5 \text{ s}^{-1}$ and $k_{\text{az}} = 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the addition of azide ion and solvent, that are estimated from $k_{\text{az}}/k_{\text{s}} = 83 \text{ M}^{-1}$, and assuming that O-methylation causes similar $\approx 10^8$ -fold increases in k_{s} for addition of solvent to **3** and **4**.

The value of $\log(k_{\text{az}}/k_{\text{s}}) = 1.9$ for the reaction of 2^+ is smaller than the Swain-Scott nucleophilicity parameter of $n = 3.9$ determined for the reaction of azide anion with methyl bromide.¹⁹ This decrease in selectivity for nucleophile addition to the more reactive electrophile *might* reflect the different diffusion-limited ($k_{\text{d}} = k_{\text{az}} = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) and activation-limited rate constants for addition of azide ion and solvent to 2^+ , if $k_{\text{s}} = 6 \times 10^7 \text{ s}^{-1}$ for addition of solvent to 2^+ . However, we suggest that this decrease in selectivity with increasing electrophile reactivity is due to a change in the structure of the transition state for nucleophile addition, that results in a weakening in the bonding to the reacting nucleophile.²⁰ A similar shift in transition state structure has been proposed to rationalize the smaller selectivity of methyl perchlorate compared to methyl iodide towards reaction with nucleophilic anions.¹⁹

EXPERIMENTAL

Potassium [^{13}C]-cyanide (99% enriched) was purchased from ISOTEC. All other organic and inorganic chemicals were reagent grade from commercial sources and were used without further purification. 2-(4-Methoxyphenyl)-[1- ^{13}C]ethanol [**MeO-1- $[\alpha\text{-}^{13}\text{C}]\text{OH}$**] was synthesized by a published procedures.²¹

Carbon-13 NMR Analyses

Proton-decoupled ^{13}C -NMR spectra were recorded at 100.4 MHz. Chemical shifts were measured in ppm, relative to a value of $\delta = 77.0 \text{ ppm}$ for CDCl_3 . A pulse angle of 45° was employed to obtain spectra centered at 55.0 ppm, which spanned 7042.25 Hz and contained 65,000 k data points (0.107 Hz/pt). Several delay times between FT pulses, ranging from 8 to 70 s, were examined. Identical ratios of the peak areas for carbon-1 and carbon-2 of 2-(4-methoxyphenyl)ethyl derivatives were observed 35 and 70 s delay times; and, the longer

relaxation time of 70 s was used for these spectra. Generally > 1,000 FT transients were averaged before determining the final spectra.

Kinetic and product studies

The progress of the reactions of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** in 50/50 (v/v) TFE/H₂O ($I = 0.5$, NaClO₄) and at 25 °C in the absence or in the presence of N₃[−] was monitored by HPLC analyses as described in earlier work.^{6,18} The reactions were initiated by making a 100-fold dilution of 2-(4-methoxyphenyl)ethyl tosylate dissolved in acetonitrile into 20 mL of 50/50 (v/v) TFE/H₂O ($I = 0.5$ (NaClO₄)). The final substrate concentration was 2 mM for reactions in the presence of 0, 0.1, 0.2 and 0.3 M azide anion and 0.3 mM for reactions in the presence of 0.01 and 0.03 M azide anion. At specified times aliquots of 100 μ L were applied directly onto an HPLC column for analysis. The reactant and products were separated by gradient elution using a mixed MeOH/H₂O solvent.²² The peaks for the substrate and product were monitored at 276 nm, which is λ_{max} for 2-(4-methoxyphenyl)ethyl alcohol and 2-(4-methoxyphenyl)ethyl azide. A value of $\epsilon_{\text{ROTs}}/\epsilon_{\text{R-Nu}} = 1.17$ for the ratio of extinction coefficients of **MeO-1-Ts** and **MeO-1-OH** at 276 nm was determined by comparing the HPLC peak areas at 276 nm of known concentrations of **MeO-1-Ts** and **MeO-1-OH**. The sum of the peak areas from HPLC analyses at 276 nm for **MeO-1-OH** and **MeO-1-N₃** remained constant as [N₃[−]] was increased from 0.00 [100% yield of **MeO-1-OSolv**] to 0.30 M [97% yield of **MeO-1-N₃**]. This shows that these products have the same extinction coefficient at $\lambda_{\text{max}} = 276$ nm.

The decrease in the HPLC peak area (A_{ROTs}) for the reactant **MeO-1-Ts** was monitored for *ca* 2-reaction halftimes; and, first-order reaction rate constants were determined as the slopes of semi-logarithmic plots of reaction progress f_s (eq 1) against time, where ΣA_{RNU} is the sum of the peak areas for the products **MeO-1-OH** (A_{ROH}) **MeO-1-OCH₂CF₃** (A_{ROTFE}) and **MeO-1-N₃** (A_{RN3}). The ratio of the yields of the products of the reactions of **MeO-1-Ts** in 50/50 (v/v) TFE/H₂O at $I = 0.5$ (NaClO₄) was determined directly from the ratio of the HPLC peak areas for the products using eq 5, because **MeO-1-OSolv** and **MeO-1-N₃** have the same extinction coefficient at $\lambda_{\text{max}} = 276$ nm (see above).

$$f_s = \frac{(A_{\text{ROTs}})/1.17}{(A_{\text{ROTs}})/1.17 + \Sigma A_{\text{RNU}}} \quad (4)$$

$$\left(\frac{f_{\text{RN3}}}{f_{\text{ROSolv}}} \right) = \left(\frac{A_{\text{RNu}}}{A_{\text{ROH}} + A_{\text{ROTFE}}} \right) \quad (5)$$

At *ca* two halftimes for the reaction of **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ Ts** the remaining substrate and the products were extracted into either ether or toluene. The organic layer was washed with water, dried over MgSO₄ and then removed using a rotary evaporator. The resulting sample was dissolved in 0.6 mL of CDCl₃ for ¹³C-NMR analysis. The relative yields of products labeled with carbon-13 in the α - and β -position were determined by integration of the following product peaks: **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ OH** at 63.83 ppm; **MeO-1- $[\beta\text{-}^{13}\text{C}]$ OH** at 38.24 ppm; **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ OCH₂CF₃** at 73.87 ppm; **MeO-1- $[\beta\text{-}^{13}\text{C}]$ OCH₂CF₃** at 35.23 ppm; **MeO-1- $[\alpha\text{-}^{13}\text{C}]$ N₃** at 52.69 ppm; **MeO-1- $[\beta\text{-}^{13}\text{C}]$ N₃** at 34.19 ppm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The effect of increasing $[N_3^-]$ on the observed rate constant ratio $(k_{az}/k_s)_{obs}$ calculated from the yields of the products of nucleophilic addition of azide anion and solvent to **MeO- $[\alpha\text{-}^{13}\text{C}]\text{-1-Ts}$** (eq 1) in 50/50 (v/v) TFE/ H_2O ($I = 0.5$, NaClO_4) and at 25 °C.

Scheme 1.

Scheme 2.

Scheme 3.

Table 1

The Yields of the Products of the Reaction of **MeO-1- $[\alpha$ - $^{13}\text{C}]$ Ts** in 50/50 (v/v) TFE/ H_2O ($I = 0.5$, NaClO_4) and at 25 °C in the Absence and Presence of Azide Anion.

$[\text{N}_3^-]/\text{M}$	f_{Roso}^a	$\frac{[\alpha - ^{13}\text{C}]}{[\beta - ^{13}\text{C}]}$ ^b	f_{RN3}^c	$\frac{[\alpha - ^{13}\text{C}]}{[\beta - ^{13}\text{C}]}$ ^d	MeO-1-$[\alpha$-$^{13}\text{C}]$N₃ ^e	MeO-1-$[\beta$-$^{13}\text{C}]$N₃ ^e
0	1.00	0.99	0.00			
0.01	0.53	1.01	0.47 (0.47)	1.06	0.24	0.23
0.03	0.27	1.05	0.73 (0.73)	1.12	0.39	0.34
0.10	0.094	1.19	0.91 (0.91)	1.42	0.53	0.38
0.20	0.046	1.40	0.95 (0.955)	1.86	0.62	0.33
0.30	0.030	1.61	0.97 (0.97)	2.33	0.68	0.29

^aThe total yield of **MeO-1-OH** and **MeO-1-OTFE**. An average product ratio $[\text{MeO-1-OH}]/[\text{MeO-1-OTFE}] = 16.9 \pm 0.3$ was determined for the reactions at $[\text{N}_3^-] = 0.0, 0.01$ and 0.03 M .

^bThe ratio of the yields of **MeO-1- $[\alpha$ - $^{13}\text{C}]$ OH** and **MeO-1- $[\beta$ - $^{13}\text{C}]$ OH** determined by carbon 13 analyses.

^cThe fractional yield of **MeO-1-N₃**. The values in parenthesis are the theoretical yields calculated using eq 3 and the partition rate constant ratios determined from the fit of the data in Figure 1 to eq 2 [see text].

^dThe ratio of the yields of **MeO-1- $[\alpha$ - $^{13}\text{C}]$ N₃** and **MeO-1- $[\beta$ - $^{13}\text{C}]$ N₃** determined by carbon-13 NMR analyses.

^eThe fractional yield of products calculated from f_{RN3}^c and the ratio of $[\alpha - ^{13}\text{C}]$ and $[\beta - ^{13}\text{C}]$ labeled **MeO-1-N₃**.