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Brief Communication

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

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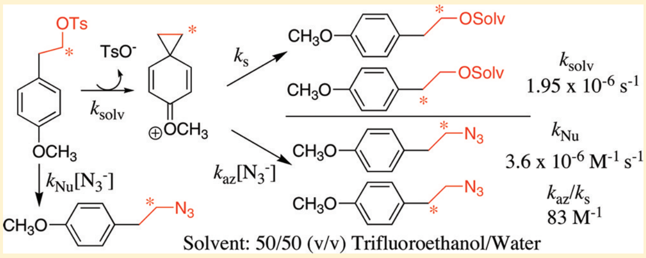
Supporting Information

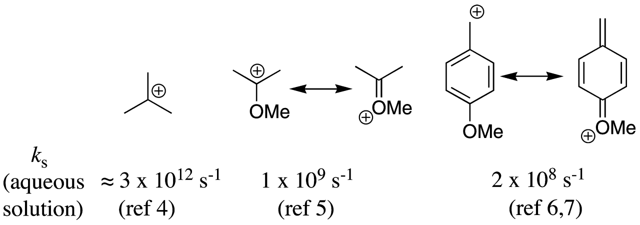
ABSTRACT: The reaction of 2-methoxyphenylethyl tosylate (**MeO-1-Ts**) is first-order in [N_3^-]. A carbon-13 NMR analysis of the products of the reactions of **MeO-1-[α-^{13}C]Ts** shows the formation of **MeO-1-[β-^{13}C]OH** and **MeO-1-[β-^{13}C]N_3** from the trapping of a symmetrical 4-methoxyphenonium ion reaction intermediate **2**$^+$. An analysis of the rate and product data provides a value of k_{az}/k_s = 83 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.



Solvent: 50/50 (v/v) Trifluoroethanol/Water

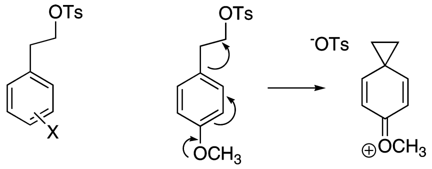
The barriers for addition of the solvent water to many simple carbocations are known.[1] There is good evidence that secondary alkyl carbocations are too unstable to exist in water for the time of a bond vibration[2,3] and that solvent reorganization with a rate constant $k_r \approx 10^{11}$ s^{-1} is the rate-limiting step for addition of water to simple tertiary carbocations ($k_s \approx 3 \times 10^{12}$ s^{-1}, Scheme 1).[4] Electron-donating α-substituents such as methoxy[5] 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.

Scheme 1



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 $\rho_X \geq -0.19$), but electron-donating substituents ($\rho^+_X < -0.19$) 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]

Scheme 2



X-1-Ts **MeO-1-Ts** **2**$^+$

We prepared **MeO-1-[α-^{13}C]Ts** and determined a value of k_{solv} = 1.95 × 10^{-6} s^{-1} for solvolysis in 50/50 (v/v) TFE/H_2O (I = 0.5, NaClO$_4$) at 25 °C. A value of $(k_{Nu})_{obs}$ = 3.6 (±0.1) × 10^{-6} M^{-1} s^{-1} under the same conditions was determined as the slope of a linear plot (not shown) of k_{obs} against [N_3^-]. Table 1 reports (1) the yields of the products of reactions of azide ion and solvent with **MeO-1-[α-^{13}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 and (2) the relative yields of **MeO-1-OH** and **MeO-1-N$_3$** labeled with carbon-13 in the α- and β-positions (Scheme

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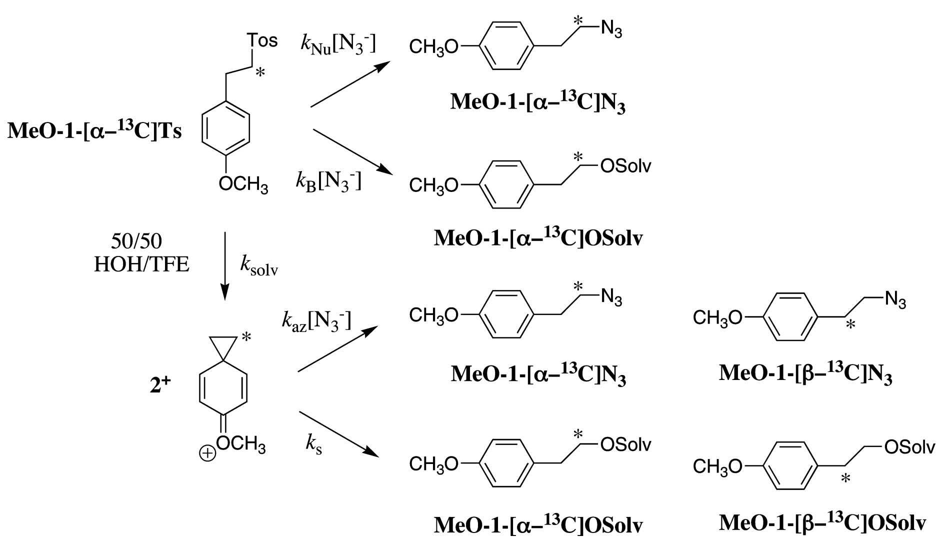
Table 1. Yields of the Products of the Reaction of MeO-1-[α-^{13}C]Ts in 50/50 (v/v) TFE/H_2O (I = 0.5, $NaClO_4$) and at 25 °C in the Absence and Presence of Azide Anion

$[N_3^-]$/M	$(f_{ROSol})_T$[a]	$([\alpha\text{-}^{13}C])/([\beta\text{-}^{13}C])$[b]	$(f_{RN3})_T$[c]	$([\alpha\text{-}^{13}C]$[d]$)/([\beta\text{-}^{13}C])$	**MeO-1-[α-^{13}C]N_3**[e]	**MeO-1-[β-^{13}C]N_3**[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

[a] The total yield of **MeO-1-OH** and **MeO-1-OTFE**. An average product ratio [**MeO-1-OH**]/[**MeO-1-OTFE**] = 16.9 ± 0.3 was determined for the reactions at $[N_3^-]$ = 0.0, 0.01, and 0.03 M. [b] The ratio of the yields of **MeO-1-[α-^{13}C]OH** and **MeO-1-[β-^{13}C]OH** determined by carbon 13 analyses. [c] The fractional yield of **MeO-1-N_3**. The values in parentheses 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 3 (see text). [d] The ratio of the yields of **MeO-1-[α-^{13}C]N_3** and **MeO-1-[β-^{13}C]N_3** determined by carbon-13 NMR analyses. [e] The fractional yield of products calculated from $(f_{RN3})_T$ and the ratio of [α-^{13}C] and [β-^{13}C] labeled **MeO-1-N_3**.

Scheme 3



3), which were determined by carbon-13 NMR analyses. There was only a low yield of the trifluoroethyl ether **MeO-1-OTFE** (Table 1, footnote *a*).

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

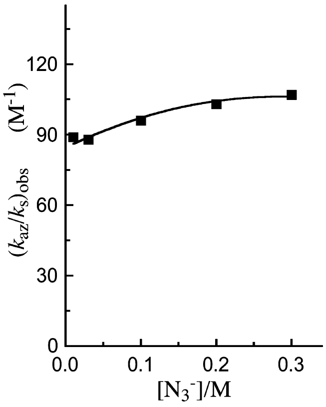


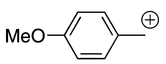
Figure 1. Effect of increasing $[N_3^-]$ on the observed rate constant ratio $(k_{az}/k_s)_{obs}$ calculated from the yields of the products of nucleophilic addition of azide anion and solvent to **MeO-[α-^{13}C]-1-Ts** (eq 1) in 50/50 (v/v) TFE/H_2O (I = 0.5, $NaClO_4$) and at 25 °C.

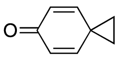
Figure 1 shows the effect of increasing $[N_3^-]$ on the azide ion selectivity $(k_{az}/k_s)_{obs}$ (eq 1) for the reaction of **MeO-1-[α-^{13}C]Ts**, where f_{RN3} and f_{ROSolv} are the fractional yields of **MeO-1-N_3** and (**MeO-1-OH** + **MeO-1-OTFE**), respectively (Table 1). A linear increase in $(k_{az}/k_s)_{obs}$ (M^{-1}) with increasing $[N_3^-]$ was observed in a previous 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-[α-^{13}C]OSolv** from azide anion catalysis of the direct addition of water to substrate [k_B (M^{-1} 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 [$(k_{Nu} + k_B)/k_{solv}$] = $(3.64 \times 10^{-6}\ M^{-1}\ s^{-1})/(1.95 \times 10^{-6}\ s^{-1}) = 1.9\ M^{-1}$ determined above and values of $k_{az}/k_s = 83\ M^{-1}$ and $k_B/k_{Nu} = 0.016$ 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-N$_3$** $(f_{RN3})_T$ and the theoretical yields calculated from eq 3 using the above three rate constant ratios.

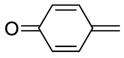
$$\left(\frac{k_{az}}{k_s}\right)_{obs} = \left(\frac{f_{RN3}}{f_{ROSolv}}\right)\left(\frac{1}{[N_3^-]}\right) \tag{1}$$

$$\left(\frac{k_{az}}{k_s}\right)_{obs} = \frac{\left(1 + \frac{k_{az}[N_3^-]}{k_s}\right) + \left(\frac{k_{solv}}{k_B + k_{Nu}}\right)\left(\frac{k_{az}}{k_s}\right)\left(1 + \frac{k_B}{k_{Nu}}\right)}{\left(\frac{k_B}{k_{Nu}}\right)\left(1 + \frac{k_{az}[N_3^-]}{k_s}\right)[N_3^-] + \left(\frac{k_{solv}}{k_B + k_{Nu}}\right)\left(1 + \frac{k_B}{k_{Nu}}\right)} \tag{2}$$

$$(f_{RN3})_T = \frac{\left(\frac{k_{Nu}}{k_{solv}}\right)[N_3^-]}{1 + \left(\frac{k_B + k_{Nu}}{k_{solv}}\right)[N_3^-]} + \frac{\left(\frac{k_{az}}{k_s}\right)[N_3^-]}{\left(1 + \left(\frac{k_B + k_{Nu}}{k_{solv}}\right)[N_3^-]\right)\left(1 + \frac{k_{az}[N_3^-]}{k_s}\right)} \tag{3}$$


$k_s = 2.5 \times 10^8\ s^{-1}$


3
$k_s = 3.4 \times 10^{-3}\ s^{-1}$


4
$k_s = 3.3\ s^{-1}$

The azide ion selectivity of $k_{az}/k_s = 83\ M^{-1}$ 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 $k_d \approx 5 \times 10^9\ M^{-1}\ s^{-1}$ for a diffusion-controlled reaction of **2**$^+$.[15] Combining this and $k_{az}/k_s = 83\ M^{-1}$ gives an upper limit of $k_s \leq 6 \times 10^7\ s^{-1}$ for addition of solvent. We expect that k_s for addition of solvent to **2**$^+$ is smaller than $2 \times 10^8\ s^{-1}$ observed for the 4-methoxybenzyl carbocation because $k_s = 3.4 \times 10^{-3}\ s^{-1}$ for addition of solvent to the neutral spiro[2,5]octa-1,4-diene-3-one[16] is 1000-fold smaller than $k_s = 3.3\ s^{-1}$ for addition of solvent to the unsubsituted *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 $k_s = 10^5\ s^{-1}$ and $k_{az} = 10^7\ M^{-1}\ s^{-1}$ for the addition of azide ion and solvent, that are estimated from $k_{az}/k_s = 83\ M^{-1}$, and assuming that O-methylation causes similar ~10^8-fold increases in k_s for addition of solvent to **3** and **4**.

The value of $\log(k_{az}/k_s) = 1.9$ 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 ($k_d = k_{az} = 5 \times 10^9\ M^{-1}\ s^{-1}$) and activation-limited rate constants for addition of azide ion and solvent to **2**$^+$, if $k_s = 6 \times 10^7\ s^{-1}$ 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 toward reaction with nucleophilic anions.[19]

EXPERIMENTAL SECTION

Potassium [^{13}C]-cyanide (99% enriched) was purchased from a commercial supplier. 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-[α-^{13}C]OH**] was synthesized according to a published procedure.[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 $\delta = 77.0$ 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 65000K 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 at 35 and 70 s delay times, and the longer relaxation time of 70 s was used for these spectra. Generally >1000 FT transients were averaged before the final spectra were determined.

Kinetic and Product Studies. The progress of the reactions of **MeO-1-[α-^{13}C]Ts** in 50/50 (v/v) TFE/H$_2$O ($I = 0.5$, NaClO$_4$) and at 25 °C in the absence or in the presence of N_3^- was monitored by HPLC analyses as described in previous 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/H$_2$O ($I = 0.5$ (NaClO$_4$). 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 μL were applied directly onto an HPLC column for analysis. The reactant and products were separated by gradient elution using a mixed MeOH/H$_2$O 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 $\varepsilon_{ROTs}/\varepsilon_{R\text{-}Nu} = 1.17$ 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-N$_3$** remained constant as [N_3^-] was increased from 0.00 [100% yield of **MeO-1-OSolv**] to 0.30 M [97% yield of **MeO-1-N$_3$**]. This shows that these products have the same extinction coefficient at $\lambda_{max} = 276$ 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 semilogarithmic 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-OCH$_2$CF$_3$** (A_{ROTFE}), and **MeO-1-N$_3$** (A_{RN3}). The ratio of the yields of the products of the reactions of **MeO-1-Ts** in 50/50 (v/v) TFE/H$_2$O at $I = 0.5$ (NaClO$_4$) was determined directly from the ratio of the HPLC peak areas for the products using eq 5 because **MeO-1-OSolv** and **MeO-1-N$_3$** have the same extinction coefficient at $\lambda_{max} = 276$ nm (see above).

$$f_S = \frac{(A_{ROTs})/1.17}{(A_{ROTs})/1.17 + \sum A_{RNu}} \tag{4}$$

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

At ca. 2 half-times for the reaction of **MeO-1-[α-^{13}C]Ts** the remaining substrate and the products were extracted into either ether or toluene. The organic layer was washed with water, dried over MgSO$_4$, and then removed using a rotary evaporator. The resulting sample was dissolved in 0.6 mL of $CDCl_3$ for ^{13}C 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-[α-^{13}C]OH** at 63.83 ppm; **MeO-1-[β-^{13}C]OH** at 38.24 ppm; **MeO-1-[α-^{13}C]OCH_2CF_3** at 73.87 ppm; **MeO-1-[β-^{13}C]-OCH_2CF_3** at 35.23 ppm; **MeO-1-[α-^{13}C]N_3** at 52.69 ppm; **MeO-1-[β-^{13}C]N_3** at 34.19 ppm.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Derivation of the relationship between the observed product selectivity $(k_{az}/k_s)_{obs}$ and the rate constants from Scheme 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) More O'Ferrall, R. *Adv. Phy. Org. Chem.* **2010**, *44*, 19−122.

(2) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4549−4555.

(3) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 2057−2062.

(4) Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 11434−11445.

(5) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888−7900.

(6) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 9507−9512.

(7) Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 9798−9805.

(8) Lancelot, C. J.; Cram, D. J.; Schleyer, P. v. R. *Carbonium Ions* **1972**, *3*, 1347−1483.

(9) Protti, S.; Dondi, D.; Mella, M.; Fagnoni, M.; Albini, A. *Eur. J. Org. Chem.* **2011**, *17*, 3229−3237.

(10) Manet, I.; Monti, S.; Grabner, G.; Protti, S.; Dondi, D.; Dichiarante, V.; Fagnoni, M.; Albini, A. *Chem.—Eur. J.* **2008**, *14*, 1029−1039.

(11) Fujio, M.; Funatsu, K.; Goto, M.; Seki, Y.; Mishima, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1091−1095.

(12) Olah, G. A.; Comisarow, M. B.; Namanworth, E.; Ramsey, B. *J. Am. Chem. Soc.* **1967**, *89*, 5259−5265.

(13) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361−1372.

(14) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373−1383.

(15) McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823−6858.

(16) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 4238−4240.

(17) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 6349−6356.

(18) Toteva, M. M.; Moran, M.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8814−8819.

(19) Koskikallio, J. *Acta Chem. Scand.* **1969**, *23*, 1477−1489.

(20) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511−527.

(21) Seki, Y.; Fujio, M.; Mishima, M.; Tsuno, Y. *Mem. Fac. Sci., Kyushu Univ., Ser. C* **1980**, *12*, 197−208.

(22) Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455−1465.