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Spontaneous Cleavage of *gem*-Diazides: A Comparison of the Effects of α-Azido and Other Electron-Donating Groups on the Kinetic and Thermodynamic Stability of Benzyl and Alkyl Carbocations in Aqueous Solution

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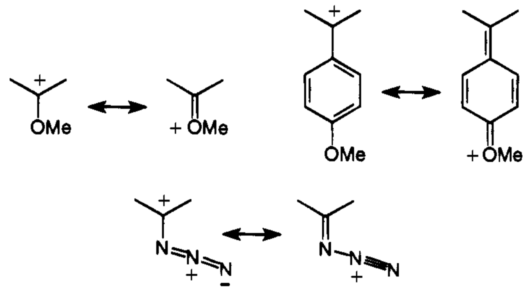
Abstract: The solvolysis reactions of ring-substituted benzylic and 1-propyl *gem*-diazides in water proceed by a stepwise mechanism through α-azido carbocation intermediates, which are captured by water to give the corresponding aldehyde as the sole detectable product. Rate constant ratios k_{az}/k_s (M^{-1}) for partitioning of these carbocations between reaction with azide ion and reaction with water, determined by analysis of azide common ion inhibition of the solvolysis reaction, decrease from 8600 M^{-1} for the relatively stable carbocation $4\text{-MeOC}_6H_4CH(N_3)^+$ to 2 M^{-1} for the highly unstable $CH_3CH_2CH(N_3)^+$. Rate constants k_s (s^{-1}) for reaction of these carbocations with solvent water, and equilibrium constants $K_{az} = k_{solv}/k_{az}$ (M) for their formation from the corresponding neutral azide ion adducts (*gem*-diazides), were calculated from the experimental values of k_{az}/k_s (M^{-1}) and k_{solv} (s^{-1}) for solvolysis of the *gem*-diazides, respectively, using $k_{az} = 5 \times 10^9\ M^{-1}\ s^{-1}$ for the diffusion-limited reaction of azide ion with α-substituted benzyl carbocations. The polar and resonance Hammett reaction constants are $\rho^n = \rho^R = -3.8$ for the equilibrium formation of the α-azidobenzyl carbocations from the *gem*-diazides and $\rho^n = 1.6$ and $\rho^R = 2.6$ for their capture by water, respectively. These are slightly larger than the corresponding Hammett constants for the reactions of α-methoxy-α-methylbenzyl carbocations [$XC_6H_4CCH_3(OMe)^+$], but considerably smaller than those for the reactions of α-methylbenzyl carbocations [$XC_6H_4CH(CH_3)^+$]. This shows that the magnitudes of electron donation from an α-N_3 and an α-MeO group to the cationic benzylic carbon are similar, and that they are much larger than the magnitude of electron donation from an α-methyl group. An α-N_3 group provides *ca.* 4 kcal/mol less stabilization of the 1-propyl carbocation than does an α-EtO group, relative to the neutral azide ion adducts. There is no simple relationship between rate and equilibrium constants for the formation and reaction of carbocations stabilized by α-EtO, α-N_3, and α-(4-$MeOC_6H_4$) groups. The α-EtO group provides the greatest thermodynamic stabilization of the 1-propyl carbocation, but this is not expressed as a larger activation barrier for the nucleophilic addition of solvent; rather, the α-EtO-substituted carbocation is also the most reactive toward solvent. Possible explanations for the breakdown of these rate−equilibrium relationships are discussed.

We would like to understand the effects of electron-donating substituents on the thermodynamic stability and kinetic reactivity of simple carbocations in aqueous solution (Scheme 1). Carbocations stabilized by an α-azido group have been implicated as intermediates of the Schmidt and related rearrangement reactions,[2−4] while *ab initio* calculations predict that an α-azido group is more effective than an α-hydroxy group, but less effective than an α-amino group, at stabilizing the methyl carbocation, relative to the hydride ion adducts.[5] These calculations prompted us to carry out experiments which led to the generation of the α-azidobenzyl carbocations **H-2** and **4-MeO-2** as intermediates in the spontaneous cleavage reactions of the corresponding ring-substituted benzyl *gem*-diazides **X-1** and to the determination of the equilibrium constants for formation of these two α-azido-stabilized carbocations from the neutral substrates and of rate constants for their reaction with solvent.[6,7]

Scheme 1



In this paper we report (1) the details of the experiments described earlier in preliminary form, together with additional data for the spontaneous cleavage of an extended series of **X-1** and of the simple alkyl *gem*-diazide **3** to give the α-azido-stabilized carbocations **X-2** and **4**, (2) equilibrium constants for cleavage of **X-1** to give **X-2** and rate constants for the addition of solvent water to the α-azidobenzyl carbocations, and (3) the equilibrium constant for cleavage of **3** to give **4** and the rate

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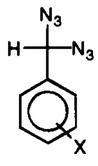
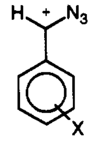
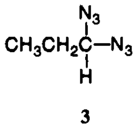
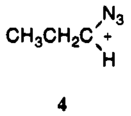
constant for the addition of solvent water to the simple α-azidoalkyl carbocation **4**.


X-1


X-2


$CH_3CH_2C(N_3)(H)-N_3$

3


$CH_3CH_2C^+(N_3)H$

4

The equilibrium constants for cleavage of **X-1** to give the α-azido carbocations **X-2** are similar to those for cleavage of the corresponding α-azido ethers to give α-alkoxy carbocations, which is consistent with the earlier conclusion from theoretical[3,5] and experimental[2,4] work that the α-azido group, like α-alkoxy, is a powerful electron donor. A comparison of the effects of the α-azido, α-alkoxy, and α-(4-methoxyphenyl) substituents on the equilibrium constants for formation of simple carbocations from the corresponding neutral azide ion adducts with those on the rate constants for reaction of these electrophiles with solvent water shows that there is no simple relationship between the thermodynamic stability and kinetic reactivity of carbocations stabilized by a single strongly electron-donating substituent. The α-alkoxy and α-azido substituents provide the greatest and least, respectively, thermodynamic stabilization of a primary alkyl carbocation relative to the neutral azide ion adducts, but the smallest kinetic barrier is that for addition of water to the α-alkoxy-substituted carbocation, and the largest is for addition to the α-(4-methoxyphenyl)-substituted carbocation. These data reveal the complex nature of the relationship between the kinetic barriers and the thermodynamic driving force for nucleophilic addition to simple resonance-stabilized carbocations, and they provide insight into the interactions which give rise to the small kinetic barriers to these reactions.

Experimental Section

Materials. Inorganic salts and organic chemicals used for chemical syntheses were reagent grade and were used without further purification. Thiosemicarbazide was recrystallized from water. Methanol was HPLC grade from Fisher, and dichloromethane was spectroscopic grade from Aldrich. Sodium azide was from Fluka. The water used for kinetic studies was distilled and then passed through a Milli-Q water purification system.

Synthesis. ^1H NMR spectra at 200 MHz were recorded on a Varian Gemini spectrometer at the University of Kentucky. Chemical shifts are reported downfield from an internal tetramethylsilane standard at 0 ppm.

Ring-substituted diazidophenylmethanes were prepared from the corresponding benzaldehydes using the following general procedure.[8] The ring-substituted benzaldehyde (16 mmol) was dissolved in dichloromethane (10 mL) containing 0.06 equiv of $SnCl_2 \cdot 2H_2O$, with stirring under argon. The mixture was cooled to 0 °C, and azidotrimethylsilane (2.5 equiv) was added over a period of 2 h. The solution was warmed to room temperature and stirred for 20 h, except for 4-nitrobenzaldehyde which was stirred for 72 h. The reaction mixture was then passed down a small column of basic alumina, eluting with dichloromethane. Purification by column chromatography on silica gel, eluting with 5% or 25% ethyl ether in hexanes, gave the diazides as clear oils. Similarly, 1,1-diazidopropane was prepared from propionaldehyde,[8] except that the aldehyde (30 mmol) was used neat and the mixture was stirred at room temperature for 48 h. The reaction mixture was then poured into cold water and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the diazide (36%) which was used without further purification. **CAUTION! These compounds are explosive.**[9]

Spectral data (^1H NMR and IR) obtained for the following *gem*-diazides were in agreement with those from the literature:[8] 1,1-diazidopropane, diazido(4-methoxyphenyl)methane, diazido(4-methylphenyl)methane, diazidophenylmethane, and diazido(4-nitrophenyl)methane. Spectral data for the new *gem*-diazides prepared in this work are given below.

Diazido[4-(methylthio)phenyl]methane was obtained in a yield of 73%: IR (liquid film) 2110 cm^{-1} (N_3); ^1H NMR δ 7.35, 7.28 (4H, A_2B_2, $J = 9$ Hz, Ar), 5.71 (1H, s, $CH(N_3)_2$), 2.50 (3H, s, CH_3).

Diazido(4-fluorophenyl)methane was obtained in a yield of 61%: IR (liquid film) 2110 cm^{-1} (N_3); ^1H NMR δ 7.43 (2H, m, Ar), 7.12 (2H, m, Ar), 5.73, (1H, s, $CH(N_3)_2$).

Diazido(3-methoxyphenyl)methane was obtained in a yield of 92%: IR (liquid film) 2100 cm^{-1} (N_3); ^1H NMR δ 7.26 (1H, Ar), 6.91 (3H, m, Ar), 5.64 (1H, s, $CH(N_3)_2$), 3.76 (3H, s, CH_3).

Diazido(3-fluorophenyl)methane was obtained in a yield of 71%: IR (liquid film) 2100 cm^{-1} (N_3); ^1H NMR δ 7.41 (1H, m, Ar), 7.16 (3H, m, Ar), 5.73 (1H, s, $CH(N_3)_2$).

HPLC Analyses. The products of solvolysis of the ring-substituted diazidophenylmethanes were analyzed by HPLC as described in previous work,[10,11] except that peak detection was by a Waters 996 diode array detector. They were identified as the corresponding benzaldehydes by comparison of their UV spectra and HPLC retention times with those of authentic materials.

Kinetic Studies. Unless noted otherwise, rate constants for reaction of the ring-substituted diazidophenylmethanes were determined in water containing 1% acetonitrile at 25 °C and a constant ionic strength of 2.0, maintained with $NaClO_4$.

The rapid reactions of diazido(4-methoxyphenyl)methane in the absence of added azide ion were followed by monitoring the appearance of 4-methoxybenzaldehyde at 286 nm using the SX.17MV stopped flow device from Applied Photophysics. The aqueous solution at ionic strength 2.0 ($NaClO_4$) and a solution of substrate in acetonitrile were placed into separate thermostated mixing syringes. These solutions were mixed in a ratio of 25:1 to give a final reaction mixture of 4% acetonitrile/water containing 2×10^{-5} M substrate. First-order rate constants were obtained from the fit of the absorbance data to a single exponential function, using the software supplied with the instrument.

Other reactions of diazidophenylmethanes were initiated by making a 100-fold dilution of a solution of substrate in acetonitrile into the reaction mixture to give a final substrate concentration of 2×10^{-5} to 1×10^{-4} M and were followed spectrophotometrically by monitoring the appearance of the ring-substituted benzaldehyde product at the following wavelengths: X = 4-MeS, 310 nm; 4-Me, 263 nm; 4-F, 246 nm; 4-H, 244 nm; 3-MeO, 251 nm; 3-F, 287 nm. In some cases, reactions in the presence of azide ion were monitored at a longer wavelength, in order to reduce the background absorbance due to azide ion: X = 4-MeO, 295 nm; 4-Me, 280 nm; 4-F, 275 nm; 4-H, 280 nm; 3-MeO, 310 nm. The reactions of diazido(4-nitrophenyl)methane (7×10^{-5} M) were followed by monitoring the disappearance of the substrate by HPLC, with peak detection at 263 nm and 1-[4-(dimethylamino)phenyl]-2,2,2-trifluoroethanol as an internal injection standard.

In the absence of added azide ion, the reactions of diazido(4-methoxyphenyl)methane and diazido[4-(methylthio)phenyl]methane did not exhibit clean first-order kinetics. These deviations from first-order kinetics were ascribed to the onset of common ion inhibition with accumulation of the azide ion leaving group. Rate constants for reaction of these substrates in the absence of added azide ion were therefore determined in the presence of 3 mM $HClO_4$, which served to protonate the azide ion leaving group and render it unreactive. There is no significant specific acid catalysis of the cleavage of these two substrates by 3 mM $HClO_4$, because identical rate constants were observed for reaction in the presence of 3 and 5 mM $HClO_4$.

Pseudo-first-order rate constants, k_{obsd} (s^{-1}), were determined as the slopes of semilogarithmic plots of reaction progress against time, which were linear for at least three half-times.

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Table 1. Rate and Equilibrium Constants for the Formation and Reaction of Ring-Substituted α-Azidobenzyl Carbocations in Aqueous Solution (Scheme 2)[a]

ring substituent X	k_{solv}[b] (s^{-1})	$K_{az} = k_{solv}/k_{az}$[c] (M)	k_{az}/k_s[d] (M^{-1})	k_s[e] (s^{-1})
4-MeO	0.62[f,g]	1.2×10^{-10}	8600	5.8×10^{5}
4-MeS	8.0×10^{-2}[g]	1.6×10^{-11}	3600	1.4×10^{6}
4-Me	6.6×10^{-3}	1.3×10^{-12}	450	1.1×10^{7}
4-F	7.5×10^{-4}	1.5×10^{-13}	170	2.9×10^{7}
H	3.9×10^{-4}	7.8×10^{-14}	86	5.8×10^{7}
3-MeO	1.9×10^{-4}	3.8×10^{-14}	78	6.4×10^{7}
3-F	2.1×10^{-5}	4.2×10^{-15}	16	3.1×10^{8}
4-NO_2	4.9×10^{-7} (4.0×10^{-6})[h]	9.8×10^{-17}	6 (4)[h]	8.6×10^{8}

[a] Solutions contained 1% acetonitrile. At 25 °C and $I = 2.0$ ($NaClO_4$), unless noted otherwise. [b] Pseudo-first-order rate constant for stepwise solvolysis of **X-1**. [c] Equilibrium constant for formation of **X-2** from **X-1**, calculated using $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[10,19,20] [d] Rate constant ratios for partitioning of **X-2** between reaction with azide ion and reaction with water, determined by analysis of azide common ion inhibition of the solvolysis of **X-1**. [e] Pseudo-first-order rate constant for reaction of **X-2** with a solvent of water, calculated from k_{az}/k_s (M^{-1}) and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[10,19,20] [f] Estimated from $k_{solv} = 0.50$ s^{-1} in 4% acetonitrile/water (see Results). [g] Determined in the presence of 3 mM $HClO_4$, in order to prevent the onset of common ion inhibition by accumulated azide ion leaving group (see Experimental Section). The rate constant was unaffected by an increase to 5 mM $HClO_4$. [h] At 40 °C.

The reactions of 1,1-diazidopropane (5 mM) in water containing 1% acetonitrile at 40 °C and a constant ionic strength of 2.0, maintained with $NaClO_4$, were followed spectrophotometrically by monitoring the rapid conversion of the propionaldehyde product to its thiosemicarbazone.[12] Reactions were initiated by making a 100-fold dilution of a solution of substrate in acetonitrile into the reaction mixture that contained thiosemicarbazide (30 mM) buffered at pH 6 with 50 mM 2-(*N*-morpholino)ethanesulfonic acid (MES, $[BH^+]/[B] = 1.0$). The initial velocity of the reaction was determined by monitoring the change in absorbance ($A - A_o$) at 290 nm over a period of 6 h (3–5% reaction), using the reaction mixture without substrate as a blank reference. There was no change in the initial velocity when the concentration of thiosemicarbazide was increased to 50 mM, which shows that solvolysis of 1,1-diazidopropane to give propionaldehyde is rate-determining for the overall reaction. The total change in absorbance for complete reaction of the substrate ($A_\infty - A_o$) was determined by making a 5-fold dilution of the reaction mixture into a fresh portion of the reaction solution followed by heating at 70 °C until a stable end point was reached (*ca.* 24 h). The total change in absorbance was in acceptable agreement (±10%) with that observed for conversion of authentic propionaldehyde to its thiosemicarbazone under similar reaction conditions. Pseudo-first-order rate constants, k_{obsd} (s^{-1}), were obtained from the slopes of linear plots of $(A - A_o)/(A_\infty - A_o)$ against time which covered the first 3–5% of the reaction.

Results

The solvolysis reactions of ring-substituted diazidophenylmethanes **X-1** in water at 25 °C and $I = 2.0$ ($NaClO_4$) gave the corresponding ring-substituted benzaldehydes as the sole detectable products (>99% yield). First-order rate constants for these reactions in the absence of added azide ion, k_{solv} (s^{-1}), determined by monitoring the appearance of the corresponding benzaldehyde by UV spectroscopy or the disappearance of the substrate by HPLC, are reported in Table 1. The value of $k_{solv} = 0.62$ s^{-1} for reaction of **4-MeO-1** in water was estimated from $k_{solv} = 0.50$ s^{-1} in 4% acetonitrile/water, determined by stopped flow spectroscopy, and the 1.24-fold larger value of k_{solv} for **4-MeS-1** in 1% acetonitrile/water than in 4% acetonitrile/water.

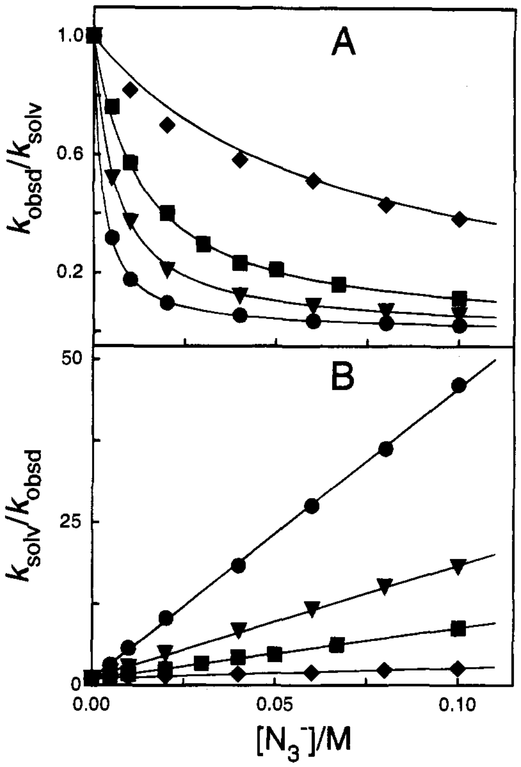
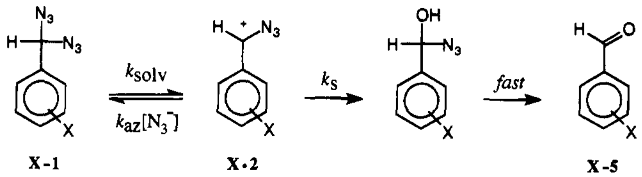


Figure 1. (A) Dependence of k_{obsd}/k_{solv} on the concentration of added sodium azide for the solvolysis of ring-substituted benzyl *gem*-diazides **X-1** in water at 25 °C and $I = 2.0$ ($NaClO_4$). Key: (●), X = 4-Me; (▼), X = 4-F; (■), X = 3-MeO; (◆), X = 3-F. (B) Linear reciprocal plots of the data from (A), according to eq 1 of the text. Key: (●), X = 4-Me; (▼), X = 4-F; (■), X = 3-MeO; (◆), X = 3-F.

Scheme 2



The effects of increasing concentrations of added sodium azide on k_{obsd} (s^{-1}) for reaction of **X-1** are given in Table S1 of the supplementary material. Figure 1A shows the dependence of the normalized rate constant ratio k_{obsd}/k_{solv} for selected **X-1** on the concentration of added azide ion, where k_{obsd} is the observed rate constant at a given concentration of azide ion and k_{solv} is the rate constant for reaction in the absence of azide ion (Table 1). This strong azide common ion inhibition shows that the reactions of **X-1** proceed by a stepwise mechanism through the diffusionally-equilibrated α-azidobenzyl carbocations **X-2** that can be trapped by azide ion or by water (Scheme 2). Figure 1B shows linear replots of the data from Figure 1A, according to eq 1 derived for the mechanism shown in Scheme 2. The slopes of these plots of k_{az}/k_s (M^{-1}, Scheme 2) are reported in Table 1.

$$\frac{k_{solv}}{k_{obsd}} = 1 + \left(\frac{k_{az}}{k_s}\right)[N_3^-] \qquad (1)$$

The solvolysis of 1,1-diazidopropane (**3**) in water at 40 °C and $I = 2.0$ ($NaClO_4$) was followed spectrophotometrically by monitoring the rapid conversion of the propionaldehyde product to its thiosemicarbazone.[12] The observed rate constant for solvolysis in the absence of added azide ion is $k_{solv} = 1.7 \times 10^{-6}$ s^{-1}. A value of $k_{solv} = 2 \times 10^{-7}$ s^{-1} for reaction of **3** at 25

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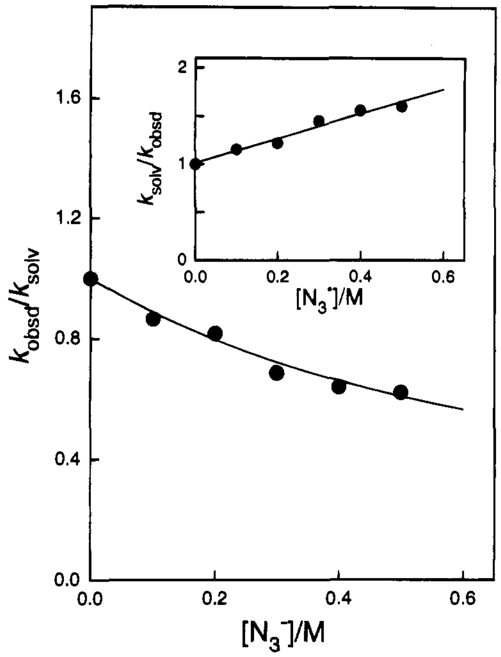

Figure 2. Dependence of k_{obsd}/k_{solv} on the concentration of added sodium azide for the solvolysis of 1,1-diazidopropane (**3**) in water at 40 °C and $I = 2.0$ ($NaClO_4$). Inset: Linear reciprocal plot of the data from the main figure, according to eq 1 of the text.

°C was estimated from the 8-fold larger value of k_{solv} for 4-NO_2-**1** at 40 °C than at 25 °C (Table 1).

The effect of increasing concentrations of added sodium azide on k_{obsd} (s^{-1}) for reaction of **3** is given in Table S2 of the supplementary material and is illustrated in Figure 2. The slope of the linear replot of these data according to eq 1 (inset, Figure 2) gives $k_{az}/k_s = 1.3$ M^{-1} for partitioning of the α-azido-1-propyl carbocation (**4**) at 40 °C. A value of $k_{az}/k_s = 2$ M^{-1} for partitioning of **4** at 25 °C was estimated from the 1.5-fold smaller value of k_{az}/k_s for partitioning of 4-NO_2-**2** at 40 °C than at 25 °C (Table 1).

Discussion

Reaction Mechanism and Lifetimes of Reaction Intermediates. Pseudo-first-order rate constants, k_{solv} (s^{-1}), for the solvolyses of X-**1** were determined by monitoring the appearance of the corresponding ring-substituted benzaldehydes X-**5** by UV spectroscopy (see Experimental Section). There was no detectable lag in the formation of X-**5**, which shows that there is no accumulation of the intermediate azidohydrins (Scheme 2), whose reactivities are therefore much greater than those of the parent *gem*-diazides. In no case was there detectable formation of the ring-substituted benzonitrile or formanilide products of Schmidt-type rearrangement of X-**2** with loss of nitrogen.[13] This shows that the pseudo-first-order rate constants for reaction of the α-azidobenzyl carbocations (iminodiazonium ions) X-**2** with solvent water, k_s (Scheme 2), are much larger than those for Schmidt-type rearrangement. A change in solvent to "dry" acetonitrile leads to a large decrease in k_s (s^{-1}) for the reaction of 4-MeO-**2** and a dramatic change in the product distribution to mostly 4-methoxybenzonitrile (86%) and 4-methoxyformanilide (2%), resulting from Schmidt-type rearrangement of 4-MeO-**2**.[13]

There is a 10^6-fold increase in k_{solv} for X-**1** as the ring substituent X is changed from 4-NO_2 to 4-MeO (Table 1), which is consistent with a large development of positive charge at the benzylic carbon in the rate-determining transition state for solvolysis. The strong common ion inhibition of the solvolysis of X-**1** by added azide ion (Figure 1) provides classic evidence for a stepwise $D_N + A_N$ (S_N1)[14,15] mechanism, with rate-determining cleavage of X-**1** to form the diffusionally-equilibrated carbocation reaction intermediates X-**2** which can be trapped by azide ion or by solvent (Scheme 2).

The capture of the liberated reaction intermediates X-**2** by added azide ion leads to a reduction in their steady-state concentration and hence in k_{obsd} for solvolysis of the starting X-**1**. The contact ion pair intermediates X-**2**·N_3^- are too short-lived to undergo significant trapping by azide ion. Therefore, the leaving group anion will react only with the free carbocation, and it cannot have a large effect on the contribution to the observed rate constant of a pathway involving direct capture of the ion pair intermediate by solvent.[12,16-18] The 1700-fold decrease in k_{obsd} for solvolysis of 4-MeO-**1** as the concentration of azide ion is increased from 0 to 0.2 M (Table S1) shows that >99.94% and <0.06%, respectively, of the solvolysis reaction proceeds through the diffusionally-equilibrated carbocation 4-MeO-**2** that can be trapped by azide ion and through the contact ion pair 4-MeO-**2**·N_3^- that reacts directly with solvent.[16] Similarly, the good fit to eq 1, derived for the mechanism shown in Scheme 2, of the kinetic data for solvolysis of other X-**1** in the presence of increasing concentrations of azide ion shows that these reactions also proceed through liberated carbocation reaction intermediates and that there is no detectable formation of product by direct solvent capture of the contact ion pair intermediates X-**2**·N_3^-.

The large reduction in the magnitude of azide common ion inhibition of the solvolysis of X-**1** as the ring substituent X is changed from electron-donating to electron-withdrawing (Figure 1) corresponds to sharp decreases in the selectivity of the carbocation intermediates X-**2** toward azide ion, k_{az}/k_s (M^{-1}, Table 1), with their increasing instability. These data provide strong evidence that k_{az} (M^{-1} s^{-1}) is limited by the rate of diffusional encounter of azide ion and X-**2**, which is independent of carbocation reactivity, so that the entire change in the selectivity k_{az}/k_s is due to a change in k_s for the activation-limited addition of solvent to X-**2**.[10,11] The reaction of azide ion with several α-substituted 4-methoxybenzyl carbocations in 98:2 2,2,2-trifluoroethanol/water,[19a] and with ring-substituted benzhydryl and trityl carbocations in 1:2 acetonitrile/water,[19b,c] has been shown by direct measurement to be diffusion limited, with $k_{az} = (5-7) \times 10^9$ M^{-1} s^{-1}. Therefore, absolute rate constants k_s (s^{-1}) for capture of X-**2** by water, and equilibrium constants $K_{az} = k_{solv}/k_{az}$ (M) for formation of X-**2** from X-**1**, were obtained from the rate constant ratios k_{az}/k_s (M^{-1}, Table 1) for partitioning of X-**2** and the rate constants k_{solv} (s^{-1}, Table 1) for solvolysis of X-**1**, respectively, using $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[10,19,20]

The equilibrium constant for formation of 4-MeO-**2** is 18-fold smaller than that for formation of the corresponding oxocarbenium ion 4-$MeOC_6H_4CH(OMe)^+$,[6,7] but it is 10^8-fold larger than that for formation of the 4-methoxybenzyl carboca-

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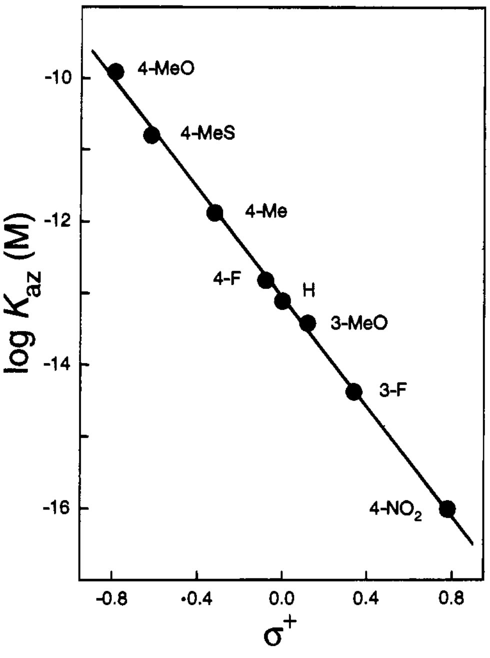
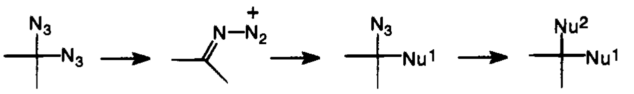


Figure 3. Hammett $\varrho^+\sigma^+$ correlation of equilibrium constants K_{az} (M) for formation of ring-substituted α-azidobenzyl carbocations X-**2** from the corresponding neutral azide ion adducts X-**1**.[22]

Scheme 3



tion,[7] from the respective neutral azide ion adducts. This shows that, relative to the neutral azide ion adducts, an α-azido group provides a substantial stabilization of 10.8 kcal/mol of the 4-methoxybenzyl carbocation, which is only slightly smaller than the stabilization of 12.5 kcal/mol provided by an α-methoxy group.

We also note that azide ion acts as both a moderately good leaving group and a powerful carbocation-stabilizing functional group in nucleophilic substitution reactions. These properties could be exploited in the development of synthetically useful transformations of *gem*-diazides to give bisnucleophile adducts (Scheme 3). We have described the use of benzylic *gem*-diazide precursors in the synthesis of mixed acetals and thioacetals in an earlier communication.[21] The large selectivity of such α-azido carbocations toward nucleophilic reagents determined here suggests that it may also be possible to trap these species with carbanionic nucleophiles, resulting in the assembly of new carbon−carbon bonds.

Structure−Reactivity Relationships. The good Hammett correlation of log K_{az} (M) for formation of X-**2** from the neutral azide ion adducts X-**1** with σ^+ substituent constants[22] ($\varrho^+ = -3.8$, Figure 3) requires that these data likewise show a good fit to eq 2, developed by Young and Jencks,[23] with $\varrho^n = \varrho^R = -3.8$, where σ^n are polar substituent constants[22] and ϱ^n and ϱ^R are the Hammett reaction constants which measure the sensitivity of rate or equilibrium constants to changes in polar and resonance substituents. Table 2 gives the Hammett reaction constants determined in this and earlier work for the reactions shown in Scheme 4. The Hammett reaction constants for the equilibrium formation of ring-substituted α-azidobenzyl carbocations N$_3$(H)-**7** (or X-**2**) from the corresponding azide ion adducts N$_3$(H)-**6**-N$_3$ (or X-**1**, $\varrho^n = \varrho^R = -3.8$) are substantially smaller than those for formation of ring-substituted α-methylbenzyl carbocations CH$_3$(H)-**7** in the acid-catalyzed cleavage of 1-arylethanols CH$_3$(H)-**6**-OH ($\varrho^n = -7.6$, $\varrho^R = -9.3$).[10] However, they are comparable to those for formation of ring-substituted α-methoxy-α-methylbenzyl carbocations MeO(CH$_3$)-**7** in the acid-catalyzed cleavage of acetophenone dimethyl acetals MeO(CH$_3$)-**6**-OMe ($\varrho^n = -3.6$, $\varrho^R = -2.2$).[24]

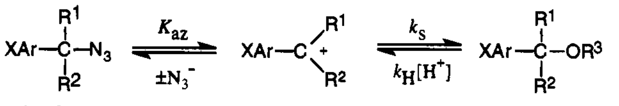
Table 2. Hammett Reaction Constants for Formation of α-Substituted Benzyl Carbocations from the Corresponding Azide Ion Adducts or Alcohols and for their Reaction with Water (Scheme 4)

R^1, R^2	k_s (s^{-1})	$1/K_R = k_H/k_s$ (M^{-1})	$K_{az} = k_{solv}/k_{az}$ (M)
N$_3$, H[a]	$\varrho^n = 1.6$		$\varrho^n = -3.8$
	$\varrho^R = 2.6$		$\varrho^R = -3.8$
	$r^+ = 1.6$		$r^+ = 1.0$
MeO, CH$_3$[b]	$\varrho^n = 1.6$	$\varrho^n = -3.6$	
	$\varrho^R = 1.6$	$\varrho^R = -2.2$	
	$r^+ = 1.0$	$r^+ = 0.6$	
CH$_3$, H[c]	$\varrho^n = 2.7$	$\varrho^n = -7.6$	
	$\varrho^R = 4.9$	$\varrho^R = -9.3$	
	$r^+ = 1.8$	$r^+ = 1.2$	

[a] Data from Table 1 of this work (in aqueous solution). [b] R^3 = Me. Data from ref 24 (in aqueous solution). [c] R^3 = H. Data from ref 10 (in 50:50 (v/v) trifluoroethanol/water).

$$\log(k/k_0) = \varrho^n\sigma^n + \varrho^R(\sigma^+ - \sigma^n) \tag{2}$$

Scheme 4



R^1(R^2)-6-N$_3$ **R^1(R^2)-7** **R^1(R^2)-6-OR^3**

These Hammett reaction constants provide a measure of changes in the interactions between the ring substituents and the benzylic carbon on moving from the neutral reactants to the cationic products. The relative magnitudes of the polar reaction constants, ϱ^n, show that the thermodynamic stability of CH$_3$(H)-**7** is the most sensitive to changes in polar substituents, while the stabilities of N$_3$(H)-**7** and MeO(CH$_3$)-**7** show similar, but smaller, sensitivities to these substituents. These data are consistent with a large reduction in the effective positive charge at the benzylic portion of R^1(R^2)-**7**, by delocalization of charge onto the electron-donating α-azido group in N$_3$(H)-**7** and α-methoxy group in MeO(CH$_3$)-**7**. The similar values of ϱ^n for the formation of N$_3$(H)-**7** ($\varrho^n = -3.8$) and MeO(CH$_3$)-**7** ($\varrho^n = -3.6$) suggest that the positive charge delocalized onto the α-azido group of N$_3$(H)-**7** is close to the sum of the charges at the α-methoxy and α-methyl groups of MeO(CH$_3$)-**7**. The value of $\varrho^R = -2.2$ for the equilibrium formation of MeO(CH$_3$)-**7** is smaller than that for the comparable reactions of N$_3$(H)-**7** ($\varrho^R = -3.8$). We do not understand why the reactions of these two carbocations are correlated by similar values of ϱ^n, but substantially different values of ϱ^R.

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(20) The reactivity of azide ion toward ring-substituted triarylmethyl carbocations in 1:2 acetonitrile/water does not drop below the diffusion limit of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} until their selectivity exceeds $k_{az}/k_s \approx 3 \times 10^4$ M^{-1}.[19b] The largest selectivity observed in this work, $k_{az}/k_s = 8600$ M^{-1} for 4-MeO-**2**, is *ca.* 3-fold smaller than this limit, so that for all the carbocations studied here it is reasonable to assume that azide ion reacts at the diffusion limit, with $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}.

(21) Jagannadham, V.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 8465−8466.

(22) Substituent constants are taken from the following: Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975; pp 55−78.

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(24) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238−8248.

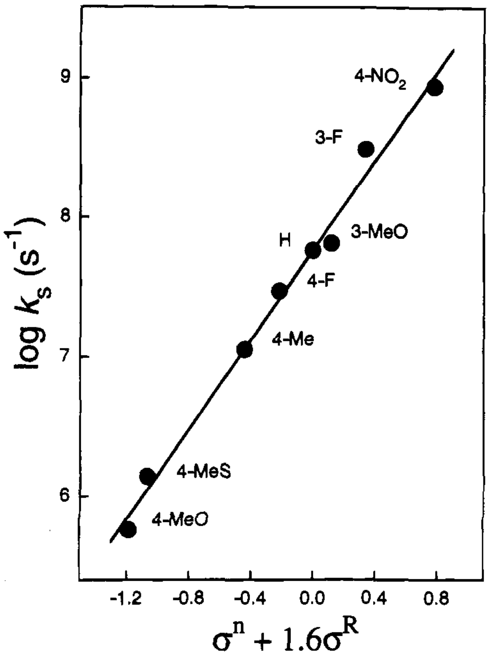


Figure 4. Fit to the Yukawa–Tsuno equation (eq 3, $r^+ = 1.6$) of log k_s (s^{-1}) for reaction of ring-substituted α-azidobenzyl carbocations **X-2** with solvent water, where σ^n are polar substituent constants and $\sigma^R = \sigma^+ - \sigma^n$ are resonance substituent constants.[22]

The values of log k_s (s^{-1}) for the reaction of solvent water with N_3(H)-**7** were fit to eq 2 by first determining $\varrho^n = 1.6$ as the slope of a plot of log k_s against σ^n ($= \sigma^m$)[22] for reaction of the *meta*-substituted and unsubstituted N_3(H)-**7** and then determining $\varrho^R = 2.6$ as the slope of a plot of log $k_s - \varrho^n\sigma^n$ against $\sigma^+ - \sigma^n$ for reaction of the *para*-substituted N_3(H)-**7**.[10] Figure 4 is a convenient alternative illustration of these correlations in the form of the Yukawa-Tsuno equation, eq 3,[25] where $r^+ =$

$$\log k_s = \varrho^n[(\sigma^n + r^+(\sigma^+ - \sigma^n)] + C \qquad (3)$$

$\varrho^R/\varrho^n = 1.6$. The Hammett reaction constants for the reaction of solvent water with N_3(H)-**7** (this work) and with MeO(CH_3)-**7**,[24] along with those for the reaction of water with CH_3(H)-**7** in 50:50 (v/v) 2,2,2-trifluoroethanol/water,[10] are given in Table 2. The large Hammett reaction constants for the addition of solvent to CH_3(H)-**7** ($\varrho^n = 2.7$, $\varrho^R = 4.9$) and the smaller, but similar, reaction constants for the addition of solvent to N_3(H)-**7** ($\varrho^n = 1.6$, $\varrho^R = 2.6$) and MeO(CH_3)-**7** ($\varrho^n = \varrho^R = 1.6$) are consistent with the above conclusion that electron donation from the α-azido and α-methoxy groups leads to similar reductions in the magnitude of the interactions between the aromatic ring substituents and the positive charge at $R^1(R^2)$-**7**.

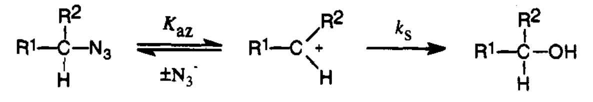
The value of $r^+ = \varrho^R/\varrho^n = 1.6$ for the addition of water to N_3(H)-**7** is larger than $r^+ = 1.0$ for the reference ionization reaction of cumyl chlorides, but it is similar to $r^+ = 1.8$ for the addition of water to CH_3(H)-**7** (Table 2). The difference between the polar and resonance reaction constants ($\varrho^R > \varrho^n$) for the latter series of carbocations reflects an imbalance between the large fractional change in resonance interactions and the smaller fractional change in polar interactions between the ring substituent and the benzylic carbon on moving from the carbocation to the transition state for nucleophile addition,[10] and such imbalances have been noted in several other comparisons of resonance and polar substituent effects on the reactivity of carbocations.[10,12,24,26,27] It is therefore likely that the large value of $r^+ = 1.6$ for the addition of solvent to N_3(H)-**7** also reflects an imbalance between the fractional expression of resonance and polar substituent effects at the transition state. We were not able to determine the normalized Hammett reaction constants for K_R that would be needed to quantify this imbalance.

Table 3. Effects of Strongly Electron-Donating α-Substituents on the Rate and Equilibrium Constants for Formation and Reaction of Simple Alkyl Carbocations in Aqueous Solution (Scheme 5)[a]

R^1	R^2	$K_{az} = k_{solv}/k_{az}$[b] (M)	k_s[c] (s^{-1})
N_3	CH_3CH_2	4×10^{-17}[d]	3×10^{9}[e]
EtO	CH_3CH_2	6×10^{-14}[f]	2×10^{10}[f]
4-$MeOC_6H_4$	CH_3	5×10^{-16}[g]	1×10^{8}[h]

[a] At 25 °C and $I = 2.0$ ($NaClO_4$), unless noted otherwise. [b] Equilibrium constant for formation of the carbocation from the neutral azide ion adduct, calculated using $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[10,19,20] [c] Pseudo-first-order rate constant for reaction of the carbocation with a solvent of water, calculated from k_{az}/k_s (M^{-1}) and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[10,19,20] [d] Calculated using $k_{solv} = 2 \times 10^{-7}$ s^{-1} at 25 °C (see Results). [e] Calculated using $k_{az}/k_s = 2.0$ M^{-1} at 25 °C (see Results). [f] Data from ref 12. [g] Calculated using $k_{solv} = 1.3 \times 10^{-7}$ s^{-1} in 50:50 (v/v) 2,2,2-trifluoroethanol/water[7] and the 20-fold larger value of k_{solv} for **H-1** in water than in 50:50 (v/v) 2,2,2-trifluoroethanol/water.[37] [h] Calculated using data from ref 10 at $I = 1.0$ ($NaClO_4$).

Scheme 5



$R^1(R^2)CHN_3$ **$R^1(R^2)CH^+$** **$R^1(R^2)CHOH$**

Effects of Strongly Electron-Donating Substituents on the Stability of Simple Alkyl Carbocations. The equilibrium constant for formation of the α-azido-1-propyl carbocation (**4**) from the *gem*-diazide **3**, $K_{az} = k_{solv}/k_{az}$ (M), and the rate constant k_s (s^{-1}) for its reaction with solvent water, were calculated from k_{solv} (s^{-1}) for the ionization of **3** and k_{az}/k_s (M^{-1}) for the partitioning of **4**, respectively (see Results), and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion.[10,19,20] Table 3 gives these data for **4**, along with additional data from earlier work for the formation and reaction of other simple alkyl carbocations stabilized by the strongly electron-donating α-ethoxy[12] and α-(4-methoxyphenyl)[7] substituents (Scheme 5).

The data in Table 3 show that the α-azido-1-propyl carbocation (**4**) is 4.3 kcal/mol less stable than the α-ethoxy-1-propyl carbocation, relative to the respective neutral azide ion adducts. This is larger than the 1.7 kcal/mol difference in carbocation stability reported above, where the effects of the α-azido and α-methoxy substituents are attenuated by an additional 4-methoxyphenyl substituent. Calculations using the 6-31G* basis set predict that, in the gas phase, the α-azidomethyl carbocation is *ca.* 10 kcal/mol *more* stable than the α-hydroxymethyl carbocation, relative to the hydride ion adducts.[5] Thus, there is a crossover in the relative stabilities of these carbocations in aqueous solution, because in this medium α-hydroxy carbocations are even more stable than their α-alkoxy counterparts.[12] This crossover may be attributed to (1) the dominant effect of the larger polarizability of the α-azido than the α-hydroxy group on carbocation stability in the gas phase[5] and (2) hydrogen bonding between solvent water and the hydroxy group of

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(25) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2274–2286.

(26) Cozens, F. L.; Mathivanan, N.; McClelland, R. A.; Steenken, S. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2083–2090. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966–3972.

(27) Kandanarachchi, P.; Sinnott, M. *J. Am. Chem. Soc.* **1994**, *116*, 5601–5606.

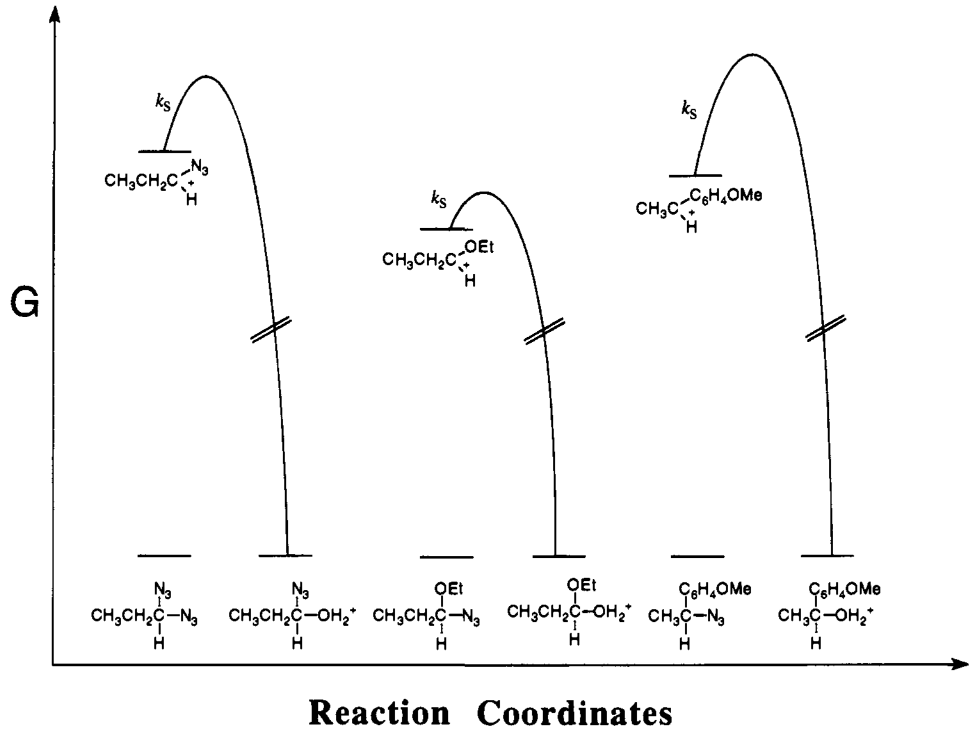

Figure 5. Reaction coordinate profiles illustrating the relative free energy changes for ionization of $R_1(R_2)CHN_3$ to give the simple alkyl carbocations $R_1(R_2)CH^+$ and the relative activation barriers for reaction of these carbocations with a solvent of water (Scheme 5 and Table 3).

α-hydroxy-substituted carbocations, which provides additional stabilization of these species in solution.[12]

Figure 5 shows a comparison of the relative activation barriers for the addition of water to $N_3(CH_3CH_2)CH^+$, $EtO(CH_3CH_2)CH^+$, and $4\text{-}MeOC_6H_4(CH_3)CH^+$ and of the thermodynamic stability of these three carbocations, relative to the respective azide ion adducts. This is a striking figure which highlights the absence of a simple relationship between the effects of these three strongly electron-donating groups on the thermodynamic and kinetic stability of simple alkyl carbocations in aqueous solution. For instance, the α-ethoxy group provides the *largest thermodynamic stabilization* of a simple primary carbocation. However, this stabilizing effect is not expressed as a relatively large activation barrier for the nucleophilic addition of solvent, but rather $EtO(CH_3CH_2)CH^+$ is also the *most reactive* of these three carbocations. Similarly, $N_3(CH_3CH_2)CH^+$, thermodynamically the most unstable carbocation, is of intermediate kinetic stability, while $4\text{-}MeOC_6H_4(CH_3)CH^+$ is of intermediate thermodynamic stability, but exhibits the lowest reactivity toward solvent.

It is generally accepted that, subsequent to the geometric alignment that permits bond formation, encounter complexes of the methyl carbocation with nucleophilic reagents proceed directly to products, without passage over an energy maximum. A barrier to carbocation–nucleophile bond formation appears as the cationic center is stabilized by strongly electron-donating substituents. Figure 5 suggests that the height of the small kinetic barriers to the nucleophilic addition of water to simple alkyl carbocations stabilized by strongly electron-donating groups cannot result from a *constant* fractional loss of their resonance stabilization on moving to the reaction transition state, because this predicts that the barrier will increase with increasing resonance stabilization of the carbocation. Rather, these barriers are controlled by other factors which have not yet been clearly defined, so that these data present an interesting challenge to develop qualitative and quantitative models that can explain the effects of such strongly electron-donating substituents on carbocation reactivity. We are not able to provide a quantitative explanation for the differences in the activation barriers shown in Figure 5, but we suggest here several possibilities which might account for the existence of these differences.[28]

(1) Part, or all, of the barrier to these nucleophilic addition reactions may be a result of the difference between the energy gained on formation of a partial covalent bond to the nucleophile and the energy cost of weakening the resonance interactions at the cationic center on moving to the reaction transition state; the net balance between these opposing interactions being different for carbocations stabilized by different electron-donating groups.[29-31] This proposal is consistent with the observed imbalances between the relatively small fractional expression of polar substituent effects and the larger fractional expression of resonance effects in the transition state for capture of X-**2** by solvent (see above). Following the convention that polar substituent effects provide some measure of the fractional formation of a covalent bond to the nucleophile in the transition state, such imbalances then reflect the tendency of the fractional loss of resonance interactions between electron-donating substituents and the reaction center on moving from reactants to products to exceed the fractional change in covalency at this center. This may be because the movement of the reacting cationic center from a planar to a pyramidal geometry that accompanies bond formation to the nucleophile further inhibits electron delocalization to the now partly-filled and rehybridized π-orbital.[10,12,31] Thus, the fraction of the stabilizing resonance interactions that are maintained in a transition state with a fractional bond order to water of α might not be simply $1 - \alpha$. Rather, it may be a smaller fraction, because the change in geometry at the reacting center due to rehybridization leads to an additional reduction in the interactions of this center with resonance electron-donating substituents.[31]

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[29] Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219–3234.

[30] Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119–238.

[31] Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1987–1903. Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6948–6960.

The order of reactivity of the simple alkyl carbocations shown in Figure 5 suggests that resonance electron donation to a *partly-filled* and rehybridized π-orbital is most effective for an α-ethoxy group, relatively less so for an α-azido group, and least effective for a 4-methoxyphenyl group. This proposal is supported by the observation for the 4-methoxybenzyl carbocation that 10%, 34%, and 58%, respectively, of the stabilizing effects of α-methoxy, α-azido, and α-(4-methoxyphenyl) substituents on its thermodynamic stability are expressed as a decrease in k_s for the addition of water to the respective carbocations.[7,32] That is, the stabilizing effect of the α-methoxy substituent is nearly fully maintained at the reaction transition state, so that this substituent has little effect on k_s for addition of solvent, while the stabilizing effect of the α-(4-methoxyphenyl) group is largely lost at this transition state, so that the requirement for the loss of this stabilizing interaction leads to a large decrease in k_s.

We suggest, then, that these differences in the effects of electron-donating α-substituents on the barrier for nucleophile addition to carbocations represent a relatively efficient expression of resonance electron donation from an α-oxygen to the rehybridizing benzylic carbon in the transition state and the less efficient expression of extended electron donation from α-azido and α-(4-methoxyphenyl) groups. Calculations to test this proposal would be useful.

(2) The relatively small kinetic barrier for the addition of water to $EtO(CH_3CH_2)CH^+$ may be due in part to stabilization of the reaction transition state by a developing electronic geminal interaction between the incoming oxygen nucleophile and the α-ethoxy group. Calculations show that such an interaction stabilizes formaldehyde hydrate compared to the isolated hydroxyl groups at methanol by 17.4 kcal/mol.[34] There is good evidence that the loss of such geminal interactions on moving to the transition state has a large effect on the rate constants for heterolytic cleavage of neutral derivatives to form carbocations.[35] For example, the rate constant ratio k_{Cl}/k_F is 60000-fold larger for solvolysis of $MeOCH_2X$ than of $4\text{-}MeOC_6H_4CH_2X$. This can be explained by a *ca.* 6.4 kcal/mol larger geminal ground-state stabilization of $MeOCH_2F$ than of $MeOCH_2Cl$, assuming the absence of appreciable geminal interactions of these leaving groups with the 4-methoxyphenyl ring of $4\text{-}MeOC_6H_4CH_2X$.[35a,36]

It is difficult to evaluate the effect of developing electronic geminal interactions on the kinetic barrier to the addition of nucleophiles to carbocations. A product-stabilizing geminal interaction would lower the reaction barrier *if* the fractional expression of this interaction at the reaction transition state were *larger* than the fractional expression of other interactions which affect the relative stabilities of reactants and products.[29,30] Consider, for example, hypothetical carbocations **A** and **B** of equal stability *relative* to their respective alcohols **A**-OH and **B**-OH, where stabilization of carbocation **A** is due primarily to resonance electron donation, while carbocation **B** is more strongly stabilized by resonance than **A**, but this stabilizing resonance interaction is exactly offset by an electronic geminal interaction which stabilizes **B**-OH. The kinetic barrier for the addition of water to **B** will be lower than that for addition to **A** (*i.e.*, k_s will be larger for **B**), *only* if the fractional expression of the product-stabilizing geminal interaction at the transition state is *larger* than the fractional loss of the carbocation-stabilizing resonance interaction. This is an example of the application of *The principle of nonperfect synchronization*, which states that a product-stabilizing factor (*e.g.*, electronic geminal interactions) will lower the intrinsic barrier to a reaction if there is a relatively large fractional development of the interaction in the transition state.[29,30]

It is not known whether the kinetic barrier to the reaction of oxocarbenium ions such as $EtO(CH_3CH_2)CH^+$ with hydroxylic solvents is substantially reduced by the development of a stabilizing electronic geminal interaction in the transition state, because there have been no experimental or computational studies that address the efficiency of expression of electronic geminal interactions across a partial rather than a fully-formed covalent bond.

(3) The differences in the activation barriers shown in Figure 5 may be due in part to differences in steric interactions that develop between the electrophile and nucleophile on moving to the reaction transition state. These differences should not be large for the relatively uncrowded transition states for the addition of solvent to the simple alkyl carbocations $R_1(R_2)CH^+$, but even relatively small effects may be significant if they correspond to a substantial fraction of the small barriers for reaction of these unstable primary carbocations.

Conclusion. There is considerable scope for theoretical and computational studies directed toward a rationalization of the experimentally determined effects of electron-donating α-substituents on the kinetic and thermodynamic stability of simple alkyl carbocations in solution.

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Supplementary Material Available: Tables S1 and S2 containing kinetic data for the reactions of **X-1** and **3** in the presence of increasing concentrations of sodium azide (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[32] These fractions were calculated by dividing the effect of the substituent on log k_s (s^{-1}) for reaction of the carbocation with a solvent of 50:50 (v/v) 2,2,2-trifluoroethanol/water by the effect of the same substituent on log K_{az} (M) for formation of the carbocation from the neutral azide adduct, using the data from ref 7.

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