The quantum yield for triplet isomerization of 11-cis, $\Phi^{T}_{iso}(11\text{-cis}\rightarrow) = 1.0 \pm 0.2$, is independent of the sensitizer triplet energy. The corresponding yield for all-trans, $\Phi^{T}_{iso}(\text{trans}\rightarrow) = 0.15 \pm 0.05$, derived from the relative isomerization efficiencies of 11-cis and all-trans, is substantially higher than the currently accepted values, but it agrees qualitatively with the cis-content in the photostationary states. The quantum yield of direct photoisomerization of 11-cis at 254 nm, $\Phi^{d}_{iso}(11\text{-cis}\rightarrow) = 0.42 \pm 0.05$,[71a] could indicate a wavelength dependence as previous measurements with excitation around 350 nm have given values around 0.25. The measured quantum yields suggest that the singlet contributions to the direct photoisomerization of all-trans and 11-cis are negligible. Additional experiments are needed to clarify this point. Photoisomerization of all-trans by direct excitation produces a thermally unstable isomer with $\lambda_{max} = 302$ nm. This isomer rearranges to 13-cis and we identify it with 11,13-dicis. On the basis of previous spectroscopic measurements and the present photoisomerization experiments a picture of the retinal triplet states as different mixtures of triplet species seems to be the best model. Within such a model the spectroscopic differences between triplet states obtained from different isomers and the sensitizer energy dependent changes in the primary product ratios can be explained by assuming the composition of the mixtures of triplet species to be dependent upon the starting isomer as well as the sensitizer triplet energy for energies below the vertical triplet energy of retinal.

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Lifetimes of Oxocarbenium Ions in Aqueous Solution from Common Ion Inhibition of the Solvolysis of α-Azido Ethers by Added Azide Ion[1]

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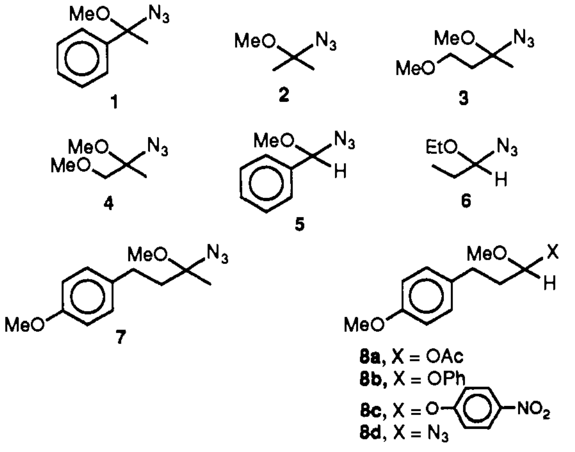
Abstract: Rate constants for hydration of the oxocarbenium ions derived from a series of carbonyl compounds have been determined from common ion inhibition of the solvolysis of the corresponding α-azido ethers by trapping of the oxocarbenium ion intermediate with added azide ion, assuming $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}: acetophenone, $k_{HOH} = 5 \times 10^7$; acetone, 1×10^9; 4-methoxybutanone, 2×10^9; methoxyacetone, 4×10^9; benzaldehyde, 2×10^9; propionaldehyde, 2×10^{10} s^{-1}. Substitution on the reacting carbon atom affects log k_{HOH} 0.4 as much as log K_{eq}. Resonance effects are much larger than polar effects of substituents on k_{HOH}, compared with K_{eq}; this represents imbalance in the expression of these effects in the transition state. Use of these substituent effects to estimate the lifetime of glycosyl and methoxymethyl oxocarbenium ions gives values of $k_{HOH} \sim 10^{12}$ s^{-1} for the glycosyl cation and 10^{12}–10^{15} s^{-1} for the methoxymethyl cation. It is concluded that the glycosyl cation has a short but significant lifetime in aqueous solution and that there is little or no barrier for hydration of the methoxymethyl cation. The effects of substituents on the rate constants for addition to oxocarbenium ions are smaller than those for addition to the corresponding carbonyl compounds. The decrease in reactivity toward water of protonated acetone compared with the corresponding oxocarbenium ion by $\sim 10^5$ suggests that the proton occupies an intermediate position between the carbonyl group and water. The dependence of log k_{ROH} on pK_{ROH} for the addition of alcohols to oxocarbenium ions derived from derivatives of butanone and propionaldehyde in aqueous alcohol mixtures follows slopes of 0.5 and 0.1, respectively.

In recent years, the common belief that hydrolysis and substitution reactions of all acetals proceed through an oxocarbenium ion intermediate[2] has been called into question.[3,4] In particular, this mechanism will not be followed if the putative oxocarbenium ion intermediate has a lifetime that is shorter than a bond vibration ($\sim 10^{-13}$ s), because such an intermediate has no barrier to collapse.[5] Rate constants for hydration of the oxocarbenium ions derived from substituted acetophenone dimethyl acetals in the range $k_{HOH} = 7 \times 10^6$–4×10^8 s^{-1} were estimated from diffusion-controlled trapping of the intermediate with sulfite dianion[3] and very similar values were obtained from extrapolations of directly measured rate constants in strong acids.[6] A crude extrapolation of a linear free energy relationship between k_{HOH} for

Chart I



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[1] Supported in part by grants from the National Institutes of Health (GM 20888) and the National Science Foundation (PCM 8117816, DMB-87-15832).

[2] Cordes, E. H. *Prog. Phys. Org. Chem.* **1967**, *4*, 1–44. Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603.

[3] Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238–8248.

[4] (a) Craze, G-A.; Kirby, A. J.; Osborne, R. *J. Chem. Soc., Perkin Trans. II* **1978**, 357–368. (b) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789–6798.

[5] Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169. Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345–375.

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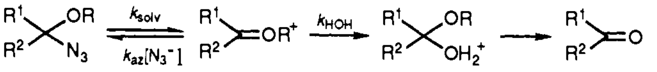
Scheme I



oxocarbenium ions and rate constants for the attack of sulfite dianion on the corresponding carbonyl compounds gave values of k_{HOH} for oxocarbenium ions derived from benzaldehydes and aliphatic aldehydes of $\sim 10^{10}$–10^{11} s^{-1}.[3] The methoxymethyl cation was predicted to react with water with $k_{HOH} \sim 10^{15}$ s^{-1}, so that this species may not exist as an intermediate, and the much slower hydrolysis of methyl β-D-glucopyranoside compared with formaldehyde dimethyl acetal suggested that glycosyl cations might not have a significant lifetime in aqueous solution.

In this paper we report the lifetimes of a series of oxocarbenium ions in aqueous solution that were determined from common ion inhibition of the solvolysis of the corresponding α-azido ethers. We reported previously[7] that the rate constant for the reaction of a propionaldehyde-derived oxocarbenium ion, determined by this method, is ≥ 2–5×10^{10} s^{-1}, which agrees surprisingly well with the predicted value.[3]

The unimolecular solvolysis in aqueous solution of the α-azido ethers **1**–**6** (Chart I) proceeds through ionization of the substrate to give an oxocarbenium ion (k_{solv}, Scheme I), which may be captured by azide ion to regenerate the starting material ($k_{az}[N_3^-]$) or react with water to give the protonated hemiacetal (k_{HOH}), which breaks down to give the corresponding carbonyl compound. When the latter step is fast, the observed rate constant for this mechanism is given by eq 1. Competition between reaction with water and with azide ion, which results in common ion inhibition,

$$k_{obsd} = k_{solv}k_{HOH}/(k_{HOH} + k_{az}[N_3^-]) \qquad (1)$$

gives the ratio k_{az}/k_{HOH}. The value of k_{HOH} was obtained from this ratio and a value of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-controlled reaction of azide ion with the oxocarbenium ion.[3,8-10] The ratio k_{az}/k_{HOH} is obtained from the ratio of the slope and intercept of a plot of $1/k_{obsd}$ against $[N_3^-]$,[11] according to eq 2. Equilibrium constants for the formation of the free

$$1/k_{obsd} = 1/k_{solv} + \{k_{az}/(k_{solv}k_{HOH})\}[N_3^-] \qquad (2)$$

oxocarbenium ions from the starting α-azido ethers can be calculated from $K_{eq} = k_{solv}/k_{az}$.

Results

Figure 1 shows that k_{obsd} for the solvolysis of the butanone derivative **3**, determined from the protonation of a phenolate anion indicator by the acid produced during solvolysis, decreases by 90% as the concentration of added azide ion is increased in the range 0–2.0 M. Values of k_{solv} and k_{az}/k_{HOH} were obtained from a linear reciprocal plot of the data according to eq 2 (inset) and were used to calculate the curve through the data of the main figure. Values of k_{az}/k_{HOH} for **2**, **4**, and **5** were determined by the same method. The rate constant for solvolysis of the acetone derivative **2** was found to decrease 8-fold when the concentration of azide ion is increased from zero to 2.0 M (not shown). Solvolysis of the methoxyacetone derivative **4** shows 55% inhibition of k_{obsd} at 1.0 M azide (Figure 2). Solvolysis of the benzaldehyde derivative **5** in 10 mM CAPS[12] buffer (pH ≈ 10.3), followed spectrophotometrically by the appearance of benzaldehyde, is also inhibited by azide ion; there is no effect of 0.01 M NaOH (Figure 2).

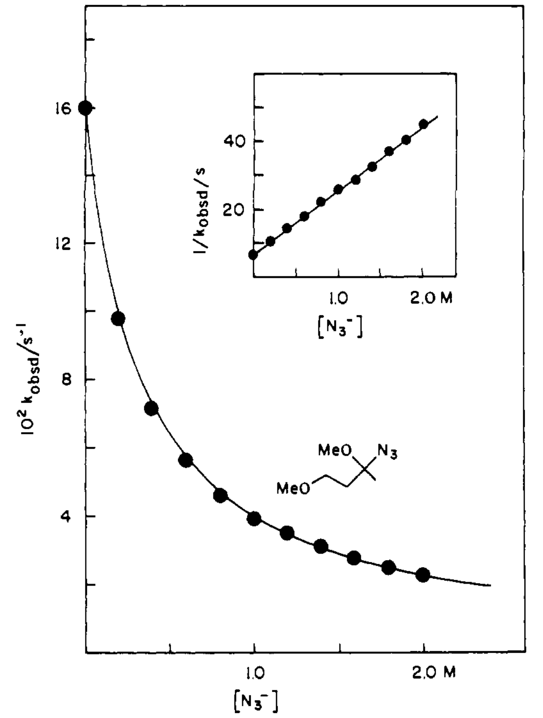


Figure 1. The dependence of k_{obsd} on the concentration of azide ion for the solvolysis of 3-azido-1,3-dimethoxybutane (**3**) in water at 25 °C and ionic strength 2.0 ($NaClO_4$). The inset shows the linear plot of the data, according to eq 2 of the text. The curve through the data of the main figure was calculated from eq 1 and values of k_{solv} and k_{az}/k_{HOH} were obtained by least-squares analysis from the linear plot.

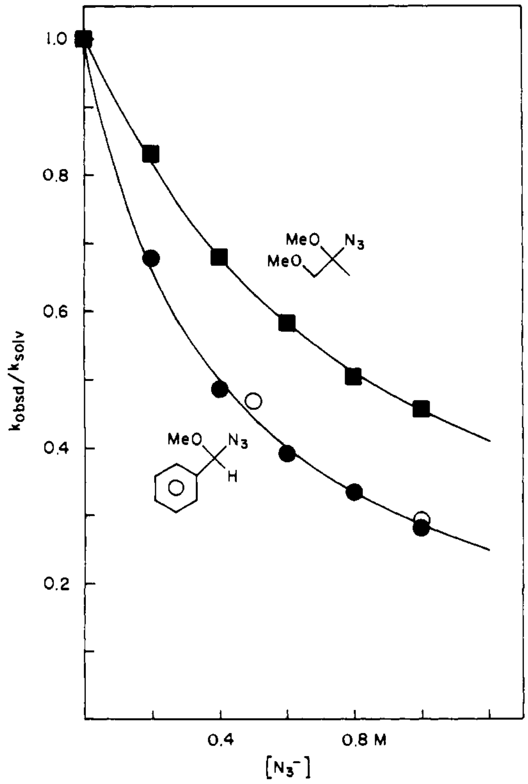


Figure 2. The dependence of k_{obsd}/k_{solv} on the concentration of azide ion for the solvolysis of 2-azido-1,2-dimethoxypropane (**4**) (■) and azidomethoxyphenylmethane (**5**) (●, ○) in water at 25 °C and ionic strength 2.0 ($NaClO_4$). The reactions of **5** were buffered with 10 mM CAPS, 50% free base (●), or 0.01 M NaOH (○). The curves through the data were calculated from eq 1 and values of k_{solv} and k_{az}/k_{HOH} obtained by least-squares analysis from linear plots of the data according to eq 2.

Solvolysis of the acetophenone derivative **1** in 50:50 (v:v) acetonitrile:water with 10 mM CAPS buffer, 50% free base, was

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(6) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031-7036.

(7) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 3677-3679.

(8) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689-4691.

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

(10) McClelland, R. A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* **1986**, *108*, 7023-7027. McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913-6914. McClelland, R. A.; Banait, N.; Steenken, S. Unpublished experiments.

(11) k_{solv} is the observed rate constant for solvolysis of the α-azido ether in the absence of azide or other added salts except $NaClO_4$.

(12) Abbreviations: CAPS, 3-(*N*-cyclohexylamino)propanesulfonic acid; MES, 2-(*N*-morpholino)ethanesulfonic acid; CHES, 2-(*N*-cyclohexylamino)ethanesulfonic acid; TFE, 2,2,2-trifluoroethanol; THF, tetrahydrofuran; EDTA, ethylenediaminetetraacetic acid.

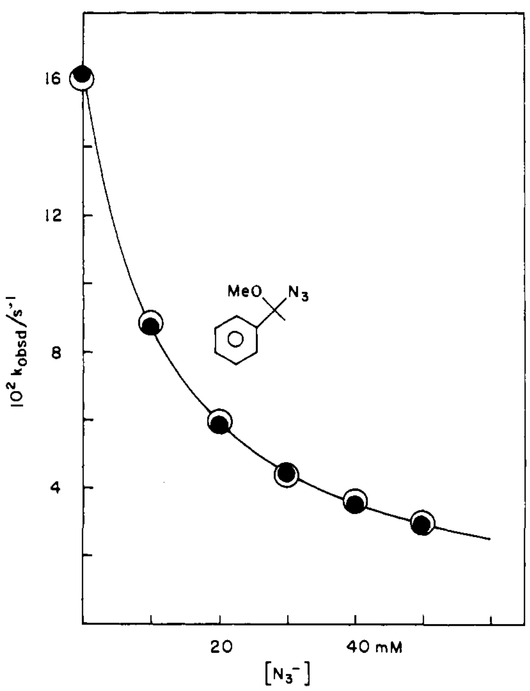


Figure 3. The dependence of k_{obsd} on the concentration of azide ion for the solvolysis of 1-azido-1-methoxy-1-phenylethane (**1**) in 50:50 (v:v) acetonitrile:water at 25 °C and ionic strength 0.5 (NaClO$_4$). The reactions were buffered with CAPS, 50% free base, at 10 mM (●) or 20 mM (○). The curve through the data was calculated from eq 1 and values of k_{solv} and k_{az}/k_S obtained by least-squares analysis from linear plots of the data according to eq 2.[13,14]

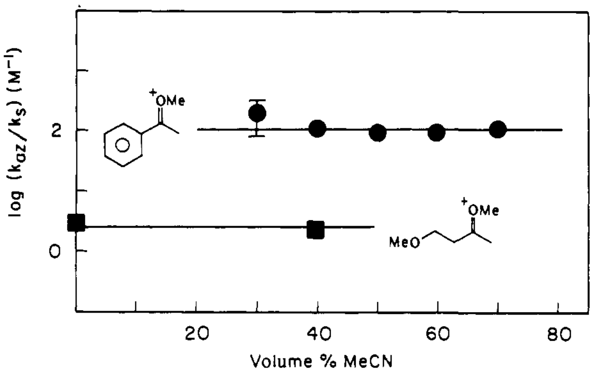


Figure 4. Variation of the partitioning ratio, k_{az}/k_S, with solvent composition in mixed acetonitrile:water solvents at 25 °C for the oxocarbenium ions derived from 1-azido-1-methoxy-1-phenylethane (**1**) (●) and 3-azido-1,3-dimethoxybutane (**3**) (■). The reactions of **1** were buffered with 10 mM CAPS, 50% free base, and were at ionic strength 0.5 or 1.0 (NaClO$_4$). The reactions of **3** were at ionic strength 1.0 or 2.0 (NaClO$_4$).

followed spectrophotometrically by the appearance of acetophenone; identical rate constants were obtained when the buffer concentration was increased to 20 mM (Figure 3). Figure 4 shows that the partitioning ratio k_{az}/k_S[13,14] does not change significantly with solvent composition from 30:70 (v:v) to 70:30 (v:v) acetonitrile:water for **1** and does not differ significantly between water and 40:60 (v:v) acetonitrile:water for **3**; the zero slope of the correlation shows that the change in solvent composition has the same effect on k_S and k_{az}. It has also been shown that the ratio k_{az}/k_S does not change significantly in the range 0–60% acetonitrile–water for reactions of triarylcarbenium ions.[10] Therefore, the value of k_{az}/k_{HOH} for **1** was obtained by extrapolation to pure water (in which the rate constants are too large to measure by conventional methods).

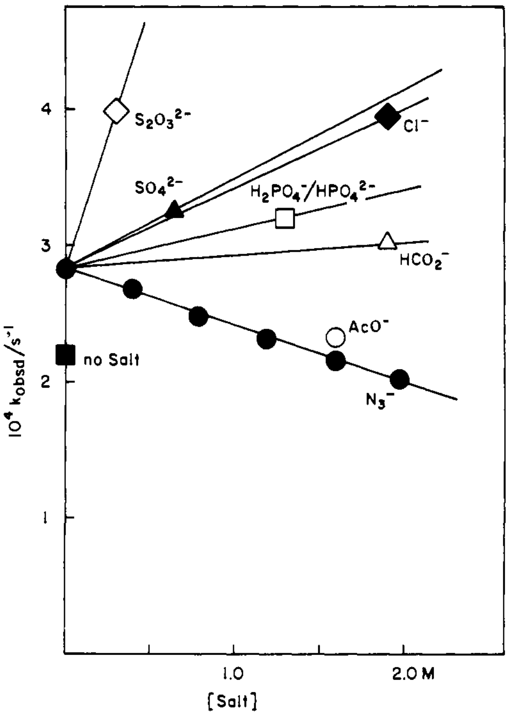
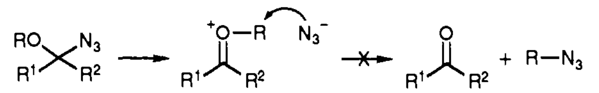


Figure 5. The dependence of k_{obsd} on the concentration of added salts for the reaction of 1-azido-1-ethoxypropane (**6**) in water at 25 °C and ionic strength 2.0 (NaClO$_4$). The line drawn through the points for azide was calculated from eq 1 and values of k_{solv} and k_{az}/k_{HOH} obtained by least-squares analysis from a linear plot of the data according to eq 2.

Scheme II



The following show that the partitioning ratios for **1**–**5**, obtained as described above, represent true rate constant ratios, k_{az}/k_{HOH}, for the reactions of the oxocarbenium ion intermediates with azide and water.

(1) Solvolysis gave good first-order kinetics in all cases. Therefore, there is no significant inhibition of solvolysis by the small concentration of azide ion that is produced during the reaction.

(2) Specific salt effects on k_{solv} for **3** at ionic strength 2.0 are small: 2.0 M bromide, iodide, or thiosulfate caused no change in k_{obsd}, and 2.0 M chloride caused only a 20% decrease. The total replacement of perchlorate at ionic strength 0.2 by chloride or bromide caused a 25% decrease in k_{obsd} for the solvolysis of **1** in 50:50 (v:v) acetonitrile:water; the decrease for 0.2 M iodide was 10%. The inhibition data for this compound were usually obtained with ≤50 mM azide, which represents replacement of only 5–10% of the perchlorate by azide. Specific salt effects on the solvolysis of **5** could not be evaluated, because this compound undergoes bimolecular substitution with good nucleophiles.[15] However, the excellent fit of all the data for the solvolysis of **1**–**5** to eq 1 suggests that the simple reaction mechanism of Scheme I is followed.

(3) The good fit of the experimental data to eq 1 and 2 shows that general base catalysis by added azide ion of the addition of water to the oxocarbenium ions, or dealkylation of these intermediates by azide (Scheme II), is not significant. The values of k_{HOH} (Table II) are therefore reliable rate constants for the addition of water to the oxocarbenium ion intermediates, subject only to the uncertainty in the diffusion-limited rate constant for their reaction with azide ion, which we estimate to be ≤2-fold.

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[13] k_S is the rate constant for reaction of the oxocarbenium ion with bulk mixed solvent.

[14] For the experiments in mixed solvents the k_{HOH} term in eq 1 and 2 is replaced by k_S.

[15] Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.*, following paper in this issue.

Table I. Effects of Salts on the Hydrolysis of Acetal Derivatives[a]

salt	concn, M	ionic strength	**8a** 10^3k_{obsd}, s^{-1}	**8c** 10_4k_{obsd},[b] s^{-1}	**6** 10^4k_{obsd}, s^{-1}	**5** 10^2k_{obsd}, s^{-1}
no salt	0	0	1.96	1.52	2.19[c]	1.20
$NaClO_4$	0.25	0.25	2.03			
	0.5	0.5	2.16			
	1.0	1.0	1.90			
	2.0	2.0	2.08	1.56	2.84[d]	2.18
$NaHCO_2$	1.0	1.0	2.60			
	1.0	2.0[e]		1.65		
	1.9	2.0[e]			3.05	
	2.0	2.0				2.05
$NaCH_3CO_2$	1.0	1.0	2.21			
	1.0	2.0[e]		1.52		
	1.6	2.0[e]			2.33	
	2.0	2.0				1.12
$NaCH_3CH_2CO_2$	1.0	2.0[e]		1.37		
	2.0	2.0				1.15

[a] In aqueous solution at 25 °C, unless otherwise noted. [b] At 41 °C. [c] Buffered with 0.1 M acetate, 80% free base. [d] Concentrations were 1.9–1.98 M. [e] Ionic strength maintained with $NaClO_4$.

The solvolysis of the propionaldehyde derivative **6** was followed spectrophotometrically by trapping of the propionaldehyde product with thiosemicarbazide. Figure 5 shows that k_{obsd} for the solvolysis of this compound at ionic strength 2.0 is decreased 30% by the addition of 2.0 M azide. A plot of the data according to eq 2 (not shown) gave a satisfactory correlation, from which a value for k_{az}/k_{HOH} was obtained. Several salts cause an increase in k_{obsd} for the solvolysis of **6** (Figure 5), because this compound undergoes bimolecular substitution with good nucleophiles.[15] However, decreases in k_{obsd} similar to that in the presence of azide ion were found when the ionic strength was decreased to zero and in the presence of acetate ion (Figure 5 and Table I). The following strongly suggest that the decrease in k_{obsd} for the solvolysis of **6** in the presence of azide ion represents largely common ion inhibition, rather than a specific salt effect on k_{solv}.

(1) There is no significant change in k_{obsd} for the solvolysis of **8d**, which gives a less stable intermediate, when azide is substituted for perchlorate ion at ionic strength 1.0.[7]

(2) The excellent fit of the azide inhibition data for **1**, **2**, **3**, **4**, and **5** to eq 1 suggests that the decreases in rate are caused by trapping of the oxocarbenium ion intermediate, rather than by a specific salt effect resulting from the removal of perchlorate ion.

(3) A decrease in k_{obsd} with decreasing ionic strength might be expected, because solvolysis of the α-azido ethers involves rate-limiting diffusional separation of an ion pair that is formed from an uncharged reactant. There is a decrease in k_{obsd} of 45% for the solvolysis of **5**, but no effect on **8a** and **8c**, when the concentration of sodium perchlorate was decreased from 2.0 M to zero (Table I).[16]

(4) Formate has little or no effect, while acetate and propionate at the same concentration cause a decrease of ~50% in k_{obsd} for the solvolysis of **5** (Table I). This suggests that there is an unfavorable interaction of the nonpolar side chains of acetate and propionate with the developing charge in the transition state for ionization of the substrate that could also decrease k_{obsd} for **6**. Similar effects have been observed for the solvolysis of **8c** (Table I) and of *p*-(dimethylamino)benzoyl fluoride, which proceeds through an acylium ion intermediate.[17]

Table II gives the partitioning ratios, k_{az}/k_{HOH}, for the reactions of the oxocarbenium ions derived from **1**–**6** with azide and water. These have been combined with the diffusion-limited rate constant of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1},[3,8-10] to give rate constants for the reaction of the oxocarbenium ions with water, k_{HOH}. Table II also gives the observed values of k_{solv}. A value of $k_{solv} = 60 \pm 50$ s^{-1} for the solvolysis of **1** in water was obtained by extrapolation of the observed values of k_{solv} in acetonitrile–water mixtures. The magnitude of this rate constant provides an explanation for the failure of an earlier attempt to trap the oxocarbenium ion derived from acetophenone dimethyl acetal with azide ion.[3] The values of k_{solv} have been combined with $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}, to give equilibrium constants for the formation of the free oxocarbenium ions from the starting α-azido ethers, $K_{eq} = k_{solv}/k_{az}$.

The following justify the assumption that the reaction of azide ion with the oxocarbenium ions studied here is diffusion controlled.

(1) The ratio k_{az}/k_{HOH} shows a large dependence on the structure of the oxocarbenium ion, and ranges from 0.22 to 100 M^{-1}. These selectivities are much smaller than that of $k_{az}/k_{HOH} \approx 10^6$ M^{-1} for the reactions of azide ion and water with stable carbocations.[18] They are consistent with a single diffusion-limited rate constant for the reaction of the oxocarbenium ions with azide, but increasing rate constants with decreasing carbocation stability for the reaction with water.[8,9,19]

(2) The oxocarbenium ions derived from substituted acetophenone dimethyl acetals react with sulfite dianion and water with values of k_{sul}/k_{HOH} = 13–700 M^{-1},[3] which are much smaller than the ratio $k_{sul}/k_{HOH} \approx 10^8$ M^{-1} for the reaction of sulfite and water with stable triarylmethyl carbocations.[20] They are consistent with a single diffusion-limited rate constant for the reaction of sulfite, but not water, with the oxocarbenium ions, and this is supported by several other pieces of evidence.[3] The ratio $k_{az}/k_{HOH} = 100$ M^{-1} for the oxocarbenium ion derived from **1** may be combined with $k_{sul}/k_{HOH} = 53$ M^{-1} for the same ion,[3] to give $k_{az}/k_{sul} \approx 2$. This ratio suggests that the reactions of both azide and sulfite are diffusion controlled, but that there is a small steric or statistical effect that decreases the reactivity of sulfite by a factor of 2.

(3) Several lines of evidence suggest that the reaction of azide ion with substituted 1-phenylethyl carbocations, with values of k_{az}/k_S in 1:1 (v:v) trifluoroethanol:water of up to 115 M^{-1}, is diffusion controlled[8,9] and diffusion-limited rate constants of 4–7 $\times 10^9$ M^{-1} s^{-1} have been measured directly for the reaction of azide with carbocations in water or predominantly aqueous solutions.[10]

Table III gives dimensionless rate constant ratios, k_{ROH}/k_{TFE}, for the solvolysis of **8a** and **8b** in mixtures of ROH:TFE:H_2O containing 50% H_2O (v:v), which were determined from product analysis by HPLC as described in the Experimental Section. The reaction of **8a** with alcohols gives mixed acetal products, while the reaction with water gives 3-(4-methoxyphenyl)propionaldehyde. Product ratios for the acid-catalyzed reaction of **8b** in 10:40:50 (v:v:v) ROH:TFE:H_2O were determined during the first 10–20% of reaction and were constant within the experimental error during this period. The products were identical with those formed in the solvolysis of **8a**. Analysis by HPLC of the products from solvolysis of **8a** and **8b** in 1:1 (M:M) EtOH:TFE gave rate constant ratios of k_{EtOH}/k_{TFE} = 2.8 and 3.0, respectively, which agree with the values in ROH:TFE:H_2O.

Rate constant ratios, k_{ROH}/k_{TFE}, for the solvolysis of **7** in ROH:TFE:H_2O containing 50% H_2O (v:v) were determined similarly and are also given in Table III. Solvolysis of **7** in 50:50 (v:v) TFE:H_2O gave k_{HOH}/k_{TFE} = 3.0 and solvolysis in 1:1 (M:M) EtOH:TFE gave k_{EtOH}/k_{TFE} = 11; the latter value is ~2-fold larger than the value in ROH:TFE:H_2O.

Discussion

Lifetimes of Oxocarbenium Ions. The rate constants in Table II of $k_{HOH} = 2 \times 10^{10}$ and 2×10^9 s^{-1} for addition of water to the oxocarbenium ions formed from derivatives of propionaldehyde, **6**, and benzaldehyde, **5**, respectively, agree more closely than might have been expected with a large extrapolation of the rate constants for hydration of substituted acetophenone oxocarbenium ions in a correlation with rate constants for the addition of sulfite dianion to the corresponding carbonyl compounds.[3] The rate constant of

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(16) A 40% decrease in k_{obsd} for the solvolysis of **1** in 50:50 (v:v) acetonitrile:water was found when the concentration of sodium perchlorate was changed from 0.2 M to zero; a 60% decrease in k_{obsd} was found for **3** with a change from 2.0 M to zero [$NaClO_4$] in water.

(17) Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 3160–3161.

(18) Bunton, C. A.; Huang, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 3536–3544. Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348–354. Ritchie, C. D.; Hofelich, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7039–7044.

(19) Ta-Shma, R.; Rappoport, Z. *Tetrahedron Lett.* **1982**, *23*, 781–784; *J. Am. Chem. Soc.* **1983**, *105*, 6082–6095.

(20) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239–2250.

Table II. Rate and Equilibrium Constants and Partioning Ratios for the Hydrolysis of α-Azido Ethers and Acetals.[a]

compd	k_{solv},[b] s^{-1}	k_{az}/k_{HOH},[c] M^{-1}	k_{HOH},[d] s^{-1}	K_{eq},[e] M	K'_{eq}[f]
1	60 ± 50[g]	100[h]	5×10^7	1.2×10^{-8}	5×10^{-4}
2	0.77	3.9	1×10^9	1.5×10^{-10}	2×10^{-4}
3	0.16	3.0	2×10^9	3.2×10^{-11}	
4	1.30×10^{-3}	1.3	4×10^9	2.6×10^{-13}	
5	2.18×10^{-2}	2.6	2×10^9	4.4×10^{-12}	2×10^{-6}
6	2.84×10^{-4}	0.22	2×10^{10}[i]	5.7×10^{-14}	4×10^{-9}
$CH_2(OCH_3)_2$			10^{13}[j]		10^{-16}
glucose-OMe			10^{12}[j]		10^{-18}

[a] In aqueous solution at 25 °C and ionic strength 2.0 ($NaClO_4$), unless otherwise noted. First-order rate constants, k_{obsd}, for the solvolysis of **2**, **3**, and **4** were determined by monitoring the protonation of a phenoxide ion indicator by the acid produced during solvolysis. Reactions of **1** and **5** were carried out in the presence of 10 mM CAPS buffer, 50% free base, and the appearance of acetophenone or benzaldehyde was followed spectrophotometrically. The solvolysis of **6** was followed spectrophotometrically in the presence of buffers by trapping the propionaldehyde formed with thiosemicarbazide. [b] Observed rate constant for solvolysis in the absence of azide or other added salts, except $NaClO_4$. [c] Calculated as the ratio of the slope and intercept of a plot of ≥6 values of $1/k_{obsd}$ against $[N_3^-]$. [d] Calculated from k_{az}/k_{HOH} and a value of $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-controlled reaction of azide ion with the oxocarbenium ion intermediate. [e] Calculated from $K_{eq} = k_{solv}/k_{az}$ and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}. [f] For $R_2C(OR')_2 + H^+ \rightarrow R_2COR'^+ + HOR'$, from $k_{H^+}/k_{R'OH}$. Values of k_{H^+} are from ref 3 (**1**); 25 (**2**; $10k_{H^+}$ in 49.6% dioxane, from the observed solvent effect for other acetals); 27 (**5**); 28 (**6**); 26 ($CH_2(OCH_3)_2$); and Cocker, D.; Sinnott, M. L., *J. Chem. Soc.*, *Perkin Trans. II* **1975**, 1391–1400 (glucose-OMe). Values of k_{MeOH} (M^{-1} s^{-1}) are $3/55 = 0.06k_{HOH}$ for **1** and $k_{EtOH} = 2/55 = 0.04k_{HOH}$ for **2** and **5** (Table III); $k_{R'OH} = 0.02k_{HOH}$ for the other compounds. [g] Extrapolated from a plot of log k_{solv} against vol % MeCN for solvolysis of **1** in MeCN:H_2O mixtures at ionic strength 0.5 or 1.0 ($NaClO_4$). [h] At ionic strength 0.5 ($NaClO_4$), extrapolated from the variation of this ratio with solvent composition in MeCN:H_2O mixtures, see Figure 4. [i] A 30% decrease in k_{solv} was observed at 2.0 M azide, see text. [j] Estimated value (see text).

Table III. Rate Constant Ratios, k_{ROH}/k_{TFE}, for the Reactions of **8a**, **8b**, and **7** in ROH:TFE:H_2O Containing 50% H_2O (v:v)[a]

		8a, vol % ROH =			**7**, vol % ROH =		
ROH	pK_{ROH}[b]	5	10	20	5	10	20
CH_3OH	15.5	3.6	4.0 3.0 ± 0.5[c]	4.5	8.1	5.8 4.8[d]	3.2
CH_3CH_2OH	16.0	2.9	2.9 2.8 ± 0.5[c]	3.2	5.4	4.4 3.7[e]	2.4
$CH_2{=}CHCH_2OH$	15.5	2.7	3.0 3.4 ± 0.6[c]	3.3	4.4	3.9	2.1
$CH_3OCH_2CH_2OH$	14.8	1.8	1.8 1.6 ± 0.3[c]	1.9	1.4	1.2	0.70
$ClCH_2CH_2OH$	14.3	1.9	1.9	2.1	1.4	1.3	0.78
$NCCH_2CH_2OH$	14.0[f]	1.9	1.7 1.4 ± 0.3[c]	1.7	0.53	0.40	0.30
Cl_2CHCH_2OH	12.9	1.4	1.4 1.6 ± 0.3[c]	1.3	<0.4[g]	<0.2[g]	<0.2[g]
CF_3CH_2OH	12.4	1.0	1.0	1.0	1.0	1.0	1.0
H_2O	15.7	2.5 ± 0.5[h]	3.0 ± 0.5[h]	3.0 ± 0.5[h]	2.4[i]	2.1[i]	1.5[i]

[a] In the presence of various buffers and determined by product analysis with HPLC, as described in the Experimental Section. Reactions of **8a** and **8b** were at 25 °C and ionic strength 0.5 ($NaClO_4$). Reactions of **7** were at 22 ± 2 °C and ionic strength 0.5 ($NaClO_4$), unless otherwise noted. The solvolysis mixture consisted of 50% H_2O, $(50-x)$% TFE, and x% ROH (v:v:v). [b] Unless otherwise noted, the pK_{ROH} values are from: Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 1050–1053; **1960**, *82*, 795–798. [c] Rate constant ratios for the acid-catalyzed reaction of **8b** at 25 °C and ionic strength 0.5 ($NaClO_4$). [d] Value in the absence of salt, except 50 mM CHES buffer, 20% free base. [e] Value at ionic strength 0.5, maintained with KNO_3 or KOAc. [f] Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205–1209. [g] No 2,2-dichloroethanol adduct was detected. [h] Average value from all experiments with the various alcohols and determined by conversion of the aldehyde to its semicarbazone, as described in the Experimental Section. [i] Average value from all experiments with the various alcohols.

5×10^7 s^{-1} for hydration of the oxocarbenium ion derived from the acetophenone derivative **1** is smaller than the previously reported value[3] of 9.5×10^7 s^{-1} because of the 2-fold greater efficiency of azide compared with sulfite ion as a diffusion-controlled trapping reagent, presumably because of a more favorable steric or statistical effect. The previously reported rate constants for substituted acetophenone oxocarbenium ions should therefore be reduced by a factor of 2. The acetone oxocarbenium ion derived from **2** undergoes hydration with $k_{HOH} = 1 \times 10^9$ s^{-1}.

Comparison of the lifetimes for the oxocarbenium ions derived from the acetophenone and benzaldehyde derivatives, **1** and **5**, and the acetone and propionaldehyde derivatives, **2** and **6**, shows that substitution of a hydrogen atom by a methyl group stabilizes the oxocarbenium ion toward hydration by a factor of 20–40. Substitution of a phenyl substituent for a hydrogen atom stabilizes the oxocarbenium ion by a factor of ~400, from comparison of the acetophenone and propionaldehyde derivatives **1** and **6** (this comparison neglects the slightly larger stabilization that might be expected for an ethyl compared with a methyl substituent), and substitution of phenyl for methyl stabilizes the oxocarbenium ion by 10–20-fold, from comparison of the acetophenone and acetone derivatives, **1** and **2**, and the benzaldehyde and propionaldehyde derivatives, **5** and **6**. The close agreement of these two comparisons shows that there is no large deviation from additivity for these substituent effects, in spite of the large rate constant of $k_{HOH} = 2 \times 10^{10}$ s^{-1} for the propionaldehyde oxocarbenium ion. The addition of a methoxy group to the α-carbon atom destabilizes the acetone oxocarbenium ion by only a factor of 4, from comparison of **2** and **4**. A methoxy group in the β-position destabilizes the acetone oxocarbenium ion by a factor of 2, from comparison of **2** and **3**, which is consistent with the expected fall-off factor of ~2 for a polar substituent.[21] Electron withdrawal by the 4-methoxyphenyl group in the β-position of **8** is sufficiently destabilizing that only a lower limit could be set on the lifetime of the substituted propionaldehyde oxocarbenium ion derived from **8**;[7] this is in contrast to the stabilizing effect from conjugation with the phenyl groups that are attached directly to the oxocarbenium ions derived from **1** and **5**.

These effects of substituents and the effects of substituents on the equilibrium constants for formation of the oxocarbenium ions from the azide adducts are summarized in Table IV.

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(21) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975; p 99.

Table IV. Effects of Substituents on Rate and Equilibrium Constants for Reactions of Oxocarbenium Ions[a]

substituent	comparison	effect of substituent k_{HOH}	effect of substituent K^b
H → CH_3	**5** → **1**	−40*x*	−2700*x*
	6 → **2**[c]	−20*x*	−2600*x*
H → Ph	**6** → **1**[c]	−400*x*	-2×10^5x
CH_3 → Ph	**2** → **1**	−20*x*	−80*x*
	6 → **5**[c]	−10*x*	−80*x*
CH_3 → CH_3OCH_2	**2** → **4**	+4*x*	+600*x*

[a] From the data in Table II. [b] For formation of the azido ether from the oxocarbenium ion. [c] For **6** the substituent on the oxygen and reacting carbon atoms is ethyl, instead of methyl.

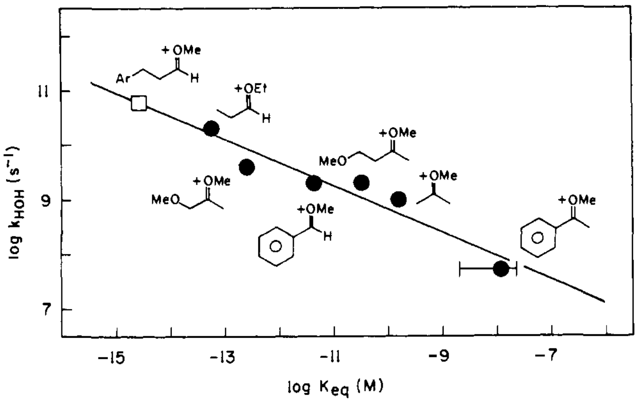
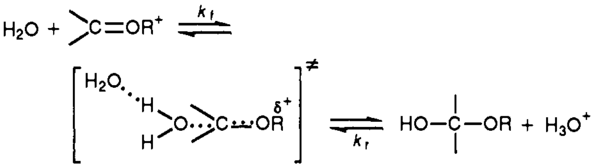


Figure 6. Correlation between rate constants for the reaction of oxocarbenium ions with water (k_{HOH}) and equilibrium constants for their formation from the corresponding α-azido ethers (K_{eq}), at 25 °C and ionic strength 2.0 ($NaClO_4$): (●) data from Table II; (□) predicted value of k_{HOH} for this oxocarbenium ion based on $K_{eq} = k_{solv}/k_{az}$ for **8d** with values of $k_{solv} = 1.35 \times 10^{-5}$ s^{-1} at 25 °C and ionic strength 1.0 ($NaClO_4$),[7] and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}. The line has a slope of −0.4.

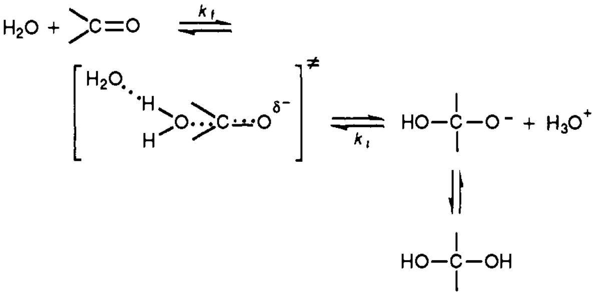
Although the rate constants for hydration of these oxocarbenium ions are large, they are below the diffusion-controlled limit and show no indication of leveling off with increasing reactivity because of an approach to this limit. The value of $k_{HOH} = 2 \times 10^{10}$ s^{-1} for hydration of the cation formed from **6** corresponds to a second-order rate constant of 4×10^8 M^{-1} s^{-1} for the reaction with water. This is below the diffusion-controlled limit, but it indicates that this compound is at the borderline where diffusional processes are just beginning to become significant for reaction with the solvent. The slightly less stable cation formed from **8d** reacts with solvent so rapidly that it shows little or no trapping by 1 M azide ion.[7]

Changes and Imbalances in Structure–Reactivity Relationships. The oxocarbenium ions show a decrease in selectivity compared with addition reactions of the much less reactive carbonyl compounds. Figure 6 shows a correlation of log k_{HOH} with log K_{eq} for formation of the oxocarbenium ion (Table II) with a slope of −0.4. In the addition direction this corresponds to a slope of $\partial \log k/\partial \log K = 0.4$ for addition to oxocarbenium ions, which is much smaller than the corresponding slope of 0.7 for the addition of hydroxide ion to substituted carbonyl compounds.[22] However, the difference in the rate constants for the acid-catalyzed addition of water to CH_3CHO and $(CH_3)_2CO$ is 17-fold, which does not differ significantly from the factor of 20-fold for the corresponding oxocarbenium ions.[23] Evidently, the partial protonation of the substrate that occurs in the transition state of the general acid catalyzed hydration of carbonyl compounds[24] decreases their selectivity almost to that of the oxocarbenium ion.

The overall slope of $\partial \log k/\partial \log K = 0.4$ does not give a complete picture of the effect on rate and equilibrium constants of substituents with widely varying structure. The effects of different substituents on the rate and equilibrium constants for hydration of oxocarbenium ions and the corresponding carbonyl compounds are summarized in Table V. Both reactions involve attack at sp^2 carbon by water and the removal of a proton by a solvent molecule (eq 3 and 4). The effects of substituents on the reverse reactions of the oxocarbenium ions, Δ log k_r, were estimated from their effects on the rate constants for acid-catalyzed hydrolysis of the corresponding diethyl acetals.[25-28] This estimation is not exact for absolute rate constants, but it should be a good approximation for the effects of substituents on the rate constants. Substituent effects on the equilibrium constants were obtained from Δ log *K* = Δ log k_f − Δ log k_r. Some of the values of Δ log k_r were obtained from rate constants determined in 49.6% dioxane–water, but there is no significant difference between the effects of substituents on several reactions that were examined in this solvent and in water.[25-28] Rate and equilibrium constants for the hydration of carbonyl compounds were determined in aqueous solution.[22-24,29-32]



(3)



(4)

The effects of a methyl, a phenyl, and an electron-withdrawing CH_3OCH_2 group on the reactions are quite different. In general, the much larger effect of substituents on the rate constants, k_f, for addition to >C=O compared with >C=OR$^+$ reflects the increase in selectivity that is brought about by the decrease of ~10^{14} in the reactivity of >C=O compared with >C=OR$^+$. For example, the effect of substitution of a methyl group for a hydrogen atom on k_f is 0.004 as large as on k_r for addition to >C=OR$^+$, while the same ratio is 800 for addition to >C=O. The fraction of the substituent effect that is expressed in the transition state compared with the product is 0.27 for >C=OR$^+$ and 0.91 for >C=O. This indicates that the transition state is early for addition to >C=OR$^+$ and late for addition to >C=O.

The fact that replacement of a methyl by a phenyl substituent decreases the rate and the equilibrium constants for addition to both compounds shows that the resonance effect of the phenyl group is larger than its electron-withdrawing polar effect. The difference in the effects on k_f/k_r of 0.2 for >C=OR$^+$ and 25 for >C=O also indicates early and late transition states for the two reactions, respectively, but the differences are much smaller than

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(22) Hine, J.; Green, L. R.; Meng, P. C., Jr.; Thiagarajan, V. *J. Org. Chem.* **1976**, *41*, 3343–3349.

(23) Greenzaid, P.; Luz, Z.; Samuel, D. *Trans. Faraday Soc.* **1968**, *64*, 2780–2786.

(24) (a) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444–5459. (b) Sørensen, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4675–4690.

(25) Kreevoy, M. M.; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 5590–5595.

(26) Salomaa, P. *Suomen Kemis. B* **1960**, *33*, 11–16.

(27) Dunlap, R. B.; Ghanim, G. A.; Cordes, E. H. *J. Phys. Chem.* **1969**, *73*, 1898–1901.

(28) Kresge, A. J.; Weeks, D. P. *J. Am. Chem. Soc.* **1984**, *106*, 7140–7143.

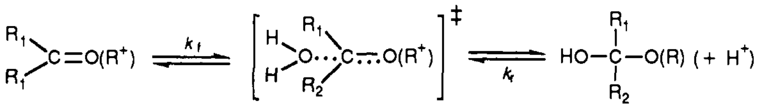
(29) Lewis, C. A., Jr.; Wolfenden, R. *Biochemistry* **1977**, *16*, 4886–4890.

(30) Greenzaid, P.; Luz, Z.; Samuel, D. *J. Am. Chem. Soc.* **1967**, *89*, 749–756.

(31) McClelland, R. A.; Coe, M. *J. Am. Chem. Soc.* **1983**, *105*, 2718–2725.

(32) Kanchuger, M. S.; Byers, L. D. *J. Am. Chem. Soc.* **1979**, *101*, 3005–3010. Burkey, T. J.; Fahey, R. C. *J. Org. Chem.* **1985**, *50*, 1304–1306.

Table V. Comparison of the Effects of Substituents on Reactions of Oxocarbenium Ions and Carbonyl Compounds



ΔR_1	compd	Δ log k_f	Δ log K	Δ log k_r	$\Delta k_f/\Delta k_r$	fraction in ‡
H→CH_3	>C=OR^+	-1.3, -1.6	-5.3	3.8[a]	0.004	0.27
	>C=O[b]	-3.2, -≥2.5	-3.5, -2.8	0.3	800	0.91
CH_3→Ph	>C=OR^+	-1.0, -1.3	-3.1	1.9[a]	0.2	0.37
	>C=O[c]	-1.7	-2.0	0.3	25	0.85
(H) CH_3OCH_2→CH_3	>C=OR^+	-0.6	-2.4, -3.1	1.8, 2.5[d]	0.03	0.22
	>C=O[e]	-2	-1.4	-0.6	*f*	*f*

[a] From k_{H^+} for the hydrolysis of $CH_2(OEt)_2$, $CH_3CH(OEt)_2$, $(CH_3)_2C(OEt)_2$, and $PhCH(OEt)_2$ in water and 49.6% dioxane–water.[25-28] [b] From the rate and equilibrium constants for reactions of HCHO, CH_3CHO, and $(CH_3)_2CO$ in water.[23,24,29,30] [c] From rate and equilibrium constants for reactions of CH_3CHO[24] and PhCHO in water. Values for PhCHO of $k_f = 1.1 \times 10^{-4}$ and $k_r = 0.019$ s^{-1} were obtained from a short extrapolation of Hammett correlations measured by McClelland.[31] [d] From k_{H^+} for the hydrolysis of $(CH_3)_2C(OEt)_2$, $HOCH_2(CH_3)C(OEt)_2$, $CH_3CH(OEt)_2$, and $HOCH_2CH(OEt)_2$ in 49.6% dioxane–water.[25] [e] From values of K_{hyd} for CH_3CHO, $HOCH_2CHO$, $(CH_3)_2C{=}O$, and $CH_3OCH_2COCH_3$;[24,29,32] and values of $k_{HOH} \leq 2 \times 10^{-5}$ s^{-1} for $(CH_3)_2CO$ and 0.185 s^{-1} for $(CH_3OCH_2)_2CO$,[22,23] from (Δ log k)/2. [f] The effect of the substituent is larger for k_f than for K and is in the same direction for k_f; see text.

for methyl substitution. This result and the fact that 0.37 of the resonance effect of the phenyl group, compared with 0.27 of the effect of the methyl group, is expressed in the transition state relative to the overall equilibrium, show that the loss of resonance stabilization by the phenyl group is expressed much more in the transition state than the effect of the methyl group. This value is also much larger than the fraction of 0.22 for the effect of the CH_3OCH_2 (or $HOCH_2$) group on the transition state compared with the product.

These differences represent *imbalance* between the effects of resonance stabilization and other substituent effects. Very similar behavior has been observed previously for addition to substituted 1-phenylethyl carbocations and to triarylmethyl and diarylmethyl carbocations.[9,33] In the reverse direction this imbalance represents a delay in the development of resonance stabilization as the cation is formed. This is consistent with the requirement for geometric change and rehybridization in order for resonance stabilization to occur.[34-36]

This imbalance may be illustrated as follows: Suppose that there would be 12 kcal of resonance stabilization in the product and 6 kcal in the transition state, if the transition state were held in a planar structure that permits optimum delocalization. In fact, it is not in the planar structure, so that the geometry is not optimal for sp^2 hybridization and only a fraction of the potential stabilization is observed, perhaps 3 kcal. Thus, the development of resonance stabilization represents a fraction of a fraction and is not linear with reaction progress.[35,36]

The effect of substitution of phenyl for methyl is 85% manifested in the transition state compared with the product for attack on >C=O; this is not significantly different from the fraction of 0.91 for the methyl group. Thus, there is little or no imbalance in a late transition state for the addition reaction because most of the resonance stabilization has already been lost.

The electron-withdrawing CH_3O or HO group in the α-position destabilizes >C=OR^+ by a polar effect. Its effect on the rate constant is only 0.22 as large as on the equilibrium constant. This polar effect is probably the most reliable measure of reaction progress because it is a direct measure of the change in charge distribution in the transition state; it confirms the early transition state for the addition reaction. The relatively small effect of the substitution of CH_3OCH_2 for CH_3 on rate compared with equilibrium constants may also account for the negative deviation of log k for $(CH_3OCH_2)_2C{=}O$ in a correlation of log k with log K_{eq} for the addition of hydroxide ion to a series of carbonyl compounds with aromatic and alkyl substituents.[22] There is a similar, although smaller, negative deviation of the rate constant for reaction of the oxocarbenium ion derived from a methoxyacetone derivative in Figure 6.

The effect of this polar substituent on the rate constant for hydration of the >C=O group is larger than on the equilibrium constant. The reason for this is that the transition state is late and the immediate product of the reaction is the anion, because a proton is removed by water acting as a general base[24] (eq 4). There is a smaller effect on the equilibrium constant because the final product of the reaction is the uncharged hydrate. This development of charge in the transition state probably does not have a large effect on the substituent effects of methyl and phenyl groups because the methyl group has almost no "inductive" effect[37] and the predominant effect of the phenyl group is to stabilize the reactants by resonance.

The effects of substituents are generally one-half to two-thirds as large on the equilibrium constants for addition to >C=O as for addition to >C=OR^+. The larger stabilization by a methyl group of >C=OR^+ compared with >C=O provides evidence that the stabilization involves hyperconjugation, because there is no inductive effect[37] and the steric effect of the methyl group is similar or identical in the two reactions.

Substitution of phenyl for methyl increases the rate and equilibrium constants for oxocarbenium ion formation from acetals, but not ketals;[3,25,27,28] however, it causes approximately the same decrease of ~10 fold in k_{HOH} for reaction with the cations derived from **2** and **1** and from **6** and **5** (Table II). The effects of methyl and phenyl substituents on log K for formation of the azide adducts from >C=OR^+ are 0.64 and 0.61 of those for formation of the hydrates or acetals (Tables II and V); the effect of the CH_3OCH_2 substituent, however, is the same for the two reactions. The reason for this difference is not known; conceivably it represents hyperconjugation of the methyl group with the C–N bond of the azide adduct.

The large differences, or imbalances, in the effects of different classes of substituents on the rate constants for formation and for hydration of an oxocarbenium ion suggest that the direction of acid-catalyzed cleavage of an ether that can give two different oxocarbenium ions as products[38] is not likely to give a reliable estimate of the relative reactivity of the two ions toward water, unless there is a closely similar balance of polar, resonance, and steric effects in the two products.

Hydrolysis of Acetals. The rate constant of $k_{HOH} = 2 \times 10^9$ s^{-1} for hydration of the oxocarbenium ion formed from benzaldehyde derivatives provides strong experimental support for the suggestion that diffusional separation of the benzaldehyde oxo-

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(33) McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966–3972. Diffenbach, R. A.; Sand, K.; Taft, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 4747–4749.

(34) Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907–3911.

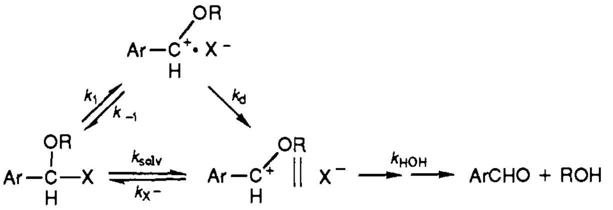
(35) Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897–1903.

(36) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948–7960.

(37) Reference 21, p 98.

(38) Cocker, D.; Jukes, L. E.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. II* **1973**, 190–194.

carbenium ion and the leaving group can be kinetically significant in the hydrolysis of benzaldehyde derivatives that proceed through this intermediate. This is especially likely for an anionic leaving group that is a good nucleophile (eq 5).[3] If water reacts with a rate constant of 2×10^9 s^{-1}, then leaving groups that are stronger nucleophiles will react with values of k_{-1} that are larger than k_d for diffusional separation so that k_d will become rate limiting.

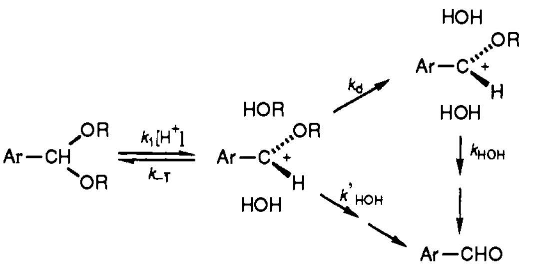


(5)

With still stronger nucleophiles there may be no significant chemical barrier for the recombination step, so that the intimate ion pair will not have a significant lifetime and cannot be an intermediate. The first stable intermediate will then be an ion pair in which the leaving group is not in an optimal position to react; the "solvent-separated" ion pair that is shown in the k_{solv} pathway of eq 5 is one example of such an intermediate.

A rate-determining diffusional step to form separated ions or molecules is supported by values of $\beta_{lg} = -1.0$ for the pH-independent hydrolysis of *p*-(dimethylamino)benzaldehyde *O,S*-acetals;[39] similar values of β_{lg} or large values of ρ for the leaving group that correspond to complete ionization in the rate-limiting transition state have been observed for a number of related reactions.[3,40,41] The ratio of the rate constants for the attack of PhS$^-$ and PhSH on the benzaldehyde oxocarbenium ion of $k_{PhS^-}/k_{PhSH} = 40$ can be calculated from the ratio of the rate constants for the pH-independent and acid-catalyzed cleavage of benzaldehyde *O*-ethyl *S*-phenyl acetal and the pK_a of PhSH.[39] This ratio increases rapidly to $k_{PhS^-}/k_{PhSH} \geq 10^{2.9}$ and $\geq 10^{5.9}$ for the *p*-methoxy- and *p*-(dimethylamino)benzaldehyde derivatives, respectively, which is the expected behavior if k_{PhS^-} is diffusion limited and k_{PhSH} is activation limited. The ratio $k_{PhS^-}/k_{PhSH} = 40$ for reaction with the benzaldehyde oxocarbenium ion and an assumed value of $k_{RS^-} = 5 \times 10^9$ M^{-1} s^{-1} gives $k_{RSH} = 1.25 \times 10^8$ M^{-1} s^{-1} and a ratio of $k_{HOH}/k_{PhSH} = 16$ M. Thus, PhSH is 3 times more reactive than water when the reagents are compared at equal concentrations. The failure to observe an uncatalyzed addition reaction of RSH and acetaldehyde in water is consistent with a similar ratio of k_{HOH}/k_{RSH}.[42]

The rate constant of $k_{HOH} = 2 \times 10^9$ s^{-1} for hydration of the benzaldehyde oxocarbenium ion in water also provides a quantitative basis for the prediction that C–O bond cleavage is not entirely rate limiting for the acid-catalyzed hydrolysis of some substituted benzaldehyde acetals under certain conditions.[39] When the rate constants for return of the oxocarbenium ion to reactants, k_{-1} in eq 6, and for its hydration in the presence of ROH, k'_{HOH}, are similar to k_d for diffusional separation of ROH from the oxocarbenium ion, bond breaking is not completely rate limiting.



(6)

The reaction will then proceed partly or entirely with rate-limiting diffusional separation of ROH (k_d) or by a preassociation mechanism, in which hydration occurs before the leaving group has diffused away (k'_{HOH}).[3]

The values of $k_{HOH} = 2 \times 10^9$ s^{-1} for the benzaldehyde oxocarbenium ion and $\rho = 1.6$ for the hydration of substituted acetophenone oxocarbenium ions[3] give an estimated rate constant of $\sim 4 \times 10^{10}$ s^{-1} for hydration of the oxocarbenium ion formed from *p*-nitrobenzaldehyde acetals. This indicates that k_{-1} is very fast and will compete with k_d and k'_{HOH}. The following evidence shows that the rate-limiting transition state for hydrolysis of this acetal has a large amount of C–O bond cleavage and closely resembles the transition state that is expected when k_d or k'_{HOH} is partly rate limiting; however, it does not provide rigorous proof that these steps are rate limiting:

(1) Cordes et al. have reported that the α-secondary deuterium effect for hydrolysis of benzaldehyde diethyl acetals increases sharply with electron-withdrawing substituents on the ring up to $k_H/k_D = 1.15$ for *p*-nitrobenzaldehyde acetal.[43] This is consistent with essentially complete cleavage of the C–O bond in the rate-limiting transition state, and the rate constant for hydrolysis of this acetal shows a negative deviation from the Hammett correlation followed by other benzaldehyde acetals[27] that is consistent with a change in rate-limiting step for this compound.

(2) Capon and Page found that a cyclic acetal of *p*-nitrobenzaldehyde undergoes much less isomerization concurrently with hydrolysis than do the corresponding acetals with less electron-withdrawing substituents.[44] The isomerization requires rotation of the oxocarbenium ion, so that this result shows that the carbocation exists but that k_{HOH} is very similar to the rate constant for rotation at sp^2 carbon.

(3) Young et al. found that the α-secondary isotope effect of $k_H/k_D = 1.06$ for the hydrolysis of benzaldehyde dimethyl acetal in 20% dioxane increases to $k_H/k_D = 1.15$ in 70% dioxane.[45] There is also a decrease in ρ from −2.6 to −4.0 and, in particular, in ρ^r from −0.9 to −2.0 for the hydrolysis of benzaldehyde acetals in 70% dioxane compared with water.[45] These values are close to the values of $\rho = -3.6$ and $\rho^r = -2.2$ for the formation of oxocarbenium ions at equilibrium from substituted acetophenone acetals.[3] The decreased dielectric constant in 70% dioxane may destabilize the oxocarbenium ion and increase k_{-1}, while the smaller concentration of water will decrease k'_{HOH} so that it becomes more rate limiting.

(4) Jensen and Yamaguchi observed limiting solvent deuterium isotope effects of $k_{D^+}/k_{H^+} = 3.3$ and no general acid catalysis for the hydrolysis of diethyl acetals of *m*-chlorobenzaldehyde and *m*-nitrobenzaldehyde; this is consistent with either k_d or k'_{HOH} as the rate-limiting step.[46]

Methoxymethyl and Glycosyl Oxocarbenium Ions. The lifetime of the methoxymethyl oxocarbenium ion may be estimated in three ways:

(1) Figure 7 shows a correlation of log k for the hydration of oxocarbenium ions and for the addition of sulfite dianion to the corresponding carbonyl compound. This correlation includes new rate constants that are reported here and rate constants that appear to be most reliable for sulfite addition.[47] The new data give a slope of 1.2, which is slightly smaller than that of the earlier correlation,[3] and a long extrapolation predicts a rate constant of approximately 5×10^{12} to 10^{15} s^{-1} for the methoxymethyl cation;

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(39) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476–1488.

(40) Sinnott, M. L. *J. Chem. Soc., Perkin Trans. II* **1973**, 180. Lönnberg, H.; Pohjola, V. *Acta Chem. Scand.* **1976**, *A30*, 669–670. Tarnus, C.; Schuber, F. *Bioorg. Chem.* **1987**, *15*, 31–42.

(41) Craze, G.-A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. II* **1978**, 354–356.

(42) Lienhard, G. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966**, *88*, 3982–3995.

(43) Bull, H. G.; Koehler, K.; Pletcher, T. C.; Ortiz, J. J.; Cordes, E. H. *J. Am. Chem. Soc.* **1971**, *93*, 3002–3011.

(44) Capon, B.; Page, M. I. *J. Chem. Soc. D, Chem. Commun.* **1970**, 1443–1444.

(45) Young, P. R.; Bogseth, R. C.; Rietz, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 6268–6271.

(46) Jensen, J. L.; Yamaguchi, K. S. *J. Org. Chem.* **1984**, *49*, 2613–2615.

(47) Rate constants for the addition of sulfite dianion to substituted acetophenones, isobutyraldehyde, and formaldehyde are from the following, respectively: Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288–3294. Green, L. R.; Hine, J. *J. Org. Chem.* **1974**, *39*, 3896–3901. Sørensen, P. E.; Andersen, V. S. *Acta Chem. Scand.* **1970**, *24*, 1301–1306. The rate constant for the addition of sulfite dianion to benzaldehyde was calculated from the data of: Kokesh, F. C.; Hall, R. E. *J. Org. Chem.* **1975**, *40*, 1632–1636.

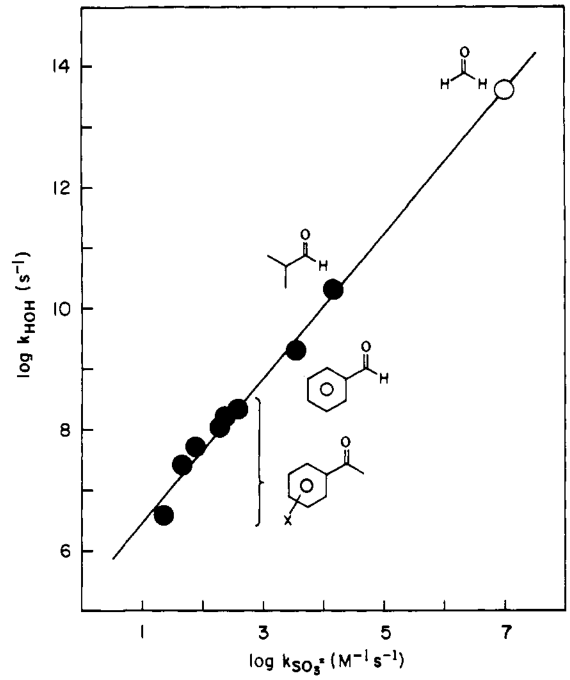


Figure 7. Correlation between rate constants for the reaction of water with oxocarbenium ions and for the attack of sulfite dianion on the corresponding carbonyl compounds. The line has a slope of 1.2. Values of k_{HOH} for the oxocarbenium ions derived from substituted acetophenones are from ref 3, corrected for the difference in their reactivity toward sulfite and azide (~2-fold). The value of $k_{HOH} = 2 \times 10^{10}$ s^{-1} for the oxocarbenium ion derived from **6** is an estimate for the ion derived from isobutyraldehyde. The rate constants for the addition of sulfite dianion to the carbonyl compounds are from the literature.[47] The open circle for formaldehyde is an estimated value of k_{HOH} for the methoxymethyl cation.

the point in the figure corresponds to 5×10^{13} s^{-1}.

(2) Correction of the rate constant of 2–5 × 10^{10} s^{-1} for hydration of the oxocarbenium ions derived from propionaldehyde derivatives by a factor of 20–40, for stabilization by a methyl group, gives a rate constant of roughly 10^{12} s^{-1} for the methoxymethyl cation. This assumes additivity of both steric and hyperconjugative effects of methyl groups. Such additivity is observed for S_N2 substitution on methyl, ethyl, and isopropyl compounds, which involves both bond making and bond breaking,[48] but substitution of CH_3 for H on the extremely unstable $CH_3OCH_2^+$ cation may well provide more stabilization than substitution of CH_3 for H on $CH_3O(CH_3)CH^+$; $k_{HOH} = 10^{12}$ s^{-1} would then be an underestimate.

(3) A lower limit for k_{HOH} can be obtained from an extrapolation of the correlation shown in Figure 6. A value of $k_{solv} = 10^{-8}$ s^{-1} for $CH_3OCH_2N_3$ was estimated from $k_{solv} = 1.5 \times 10^{-5}$ s^{-1} for **8d**,[7] and a calculated ratio of 6.6×10^{-4} for the k_{solv} values of $CH_3OCH_2O(4\text{-}NO_2Ph)$[4a,41,49] and **8c** (Table I), assuming the same ratio for 4-nitrophenolate and azide leaving groups. Estimation of K_{eq} from k_{solv} and extrapolation of the line in Figure 6 then gives a rate constant of $k_{HOH} = 10^{12}$ s^{-1} for the methoxymethyl cation. However, this estimate is only a lower limit because it *assumes* that the solvolysis of $CH_3OCH_2N_3$ proceeds through a cationic intermediate with diffusion-controlled separation of the ion pair. If the solvolysis of $CH_3OCH_2N_3$ proceeds through concerted displacement by water,[4] any stepwise reaction will be slower, the estimated value of K_{eq} is too large, and k_{HOH} will be larger.

The fact that the rate constant for reaction with water falls well *below* Swain–Scott correlations for the concerted second-order reactions of (methoxymethoxy)-2,4-dinitrobenzene and *N*-(methoxymethyl)-*N*,*N*-dimethylanilinium ions provides no support for the hypothesis that the reaction with water proceeds by a different, stepwise mechanism;[4] however, it does not exclude this possibility.

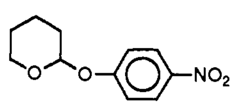
We conclude that the lifetime of the methoxymethyl cation in hydroxylic solvents is "borderline"; if it does exist, its lifetime is on the order of 10^{12} s^{-1}. It certainly does not exist as a discrete intermediate when it is in contact with stronger nucleophilic reagents than water, which is consistent with the previous conclusion that the concerted reactions of these reagents with nucleophiles are enforced because stepwise reactions are not possible.[4]

The lifetime of a typical glycosyl oxocarbenium ion may be estimated in two ways:

(1) The expected lifetime may be estimated by correcting the value of $k_{HOH} = 2 \times 10^{10}$ s^{-1} for the propionaldehyde oxocarbenium ion for destabilization of the cation by the electron-withdrawing effect of the hydroxyl groups of the sugar. It was assumed that an α-HO group increases k_{HOH} by the same factor of 4 as the α-MeO group of **4** compared with **2** (Table IV), there is destabilization by interaction with positive charge on both the oxygen and the anomeric carbon atoms of the glycoside, and the fall-off factor is 0.5 for an intervening carbon atom.[21] The expected increase in k_{HOH} is then $4 \times (0.5 \times 4)^3$ = 32-fold. This gives a rate constant of approximately 6×10^{11} s^{-1} for hydration of a glycosyl cation.

(2) If the reaction is stepwise, the value of k_{HOH} may be estimated from an extrapolation of the correlation in Figure 6, as described above for the methoxymethyl cation. The rate constant for solvolysis of 2,4-dinitrophenyl glucoside in water at 25 °C is 0.05 of that for the corresponding methoxymethyl compound, extrapolated to 25 °C.[4a,50] Assuming the same ratio for the azide derivatives gives $k_{solv} = 5 \times 10^{-10}$ s^{-1}, which can be used to calculate K_{eq}. This gives $k_{HOH} = 5 \times 10^{12}$ s^{-1} from extrapolation of the data in Figure 6. However, the slope of the correlation in Figure 6 is determined mainly by the effect on k_{HOH} of substitution at the reacting carbon atom by alkyl or aryl groups; the addition of polar substituents has a much smaller effect on k_{HOH} than on K_{eq}. For example, the addition of a CH_3O substituent to **2** to give **4** causes a 600-fold decrease in k_{solv} and K_{eq} but only a 4-fold increase in k_{HOH} (Table IV). There is a similar imbalance of polar and resonance effects on k_{HOH} and K_{eq} for addition to substituted 1-phenylethyl carbenium ions,[9] as described above. Therefore, the value of $k_{HOH} = 5 \times 10^{12}$ s^{-1} is probably an overestimate.

It has been widely believed that rate constants for the hydrolysis of pyranosides are decreased as a consequence of the formation of an unstable cyclic oxocarbenium ion in the half-chair conformation.[51,52] However, the slighly *larger* value of $k_{solv} = 3.7 \times 10^{-4}$ s^{-1} for the solvolysis of **9** at 39 °C[41] compared with $k_{solv} = 1.5 \times 10^{-4}$ s^{-1} for **8c** at 41 °C (Table I) suggests that the formation of a cyclic oxocarbenium ion in a 6-membered ring, per se, does not involve a large development of strain in the transition state. This is consistent with the identical heats of hydrogenation of −28.6 kcal mol^{-1} for *cis*-2-butene and cyclohexene.[53] Interactions between C2–C3 and C4–C5 hydroxyl groups may decrease the rate of formation of a glycosyl cation,[54] but it is not clear that such interactions would have a large effect on k_{HOH} for this ion.



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[48] Hine, J. S. *Physical-Organic Chemistry*, 2nd ed.; McGraw Hill: New York, 1962; p 176.

[49] The ratio of rate constants for *p*-nitrophenyl and 3,4-dinitrophenyl derivatives was taken from k_{solv} for 2-aryloxytetrahydropyrans.

[50] Bennet, A. J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 7287–7294.

[51] Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience: New York, 1965; p 420.

[52] Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1–122.

[53] Reference 48, p 19.

[54] Capon, B.; Overend, W. G. *Advances in Carbohydrate Chemistry*; Wolfrom, M. L., Tipson, R. S., Eds.; Academic Press: New York, 1960; Vol. 15, pp 11–51.

These considerations suggest that the glycosyl oxocarbenium ion does have a short but significant lifetime in aqueous solution, with a value of k_{HOH} on the order of 10^{12} s^{-1}.

This lifetime is too short to allow complete diffusional equilibration with dilute solutes or even with solvent molecules. Thus, the acid-catalyzed anomerization of methyl-β-D-glucopyranoside in CD_3OD gives >98% incorporation of CD_3OD into the α product but no detectable exchange of CD_3OD into the remaining β compound.[55] This shows that the intermediate oxocarbenium ion collapses to products faster than the leaving CH_3OD can exchange with CD_3OD. On the other hand, the solvolysis of sugars with more nucleophilic leaving groups gives products with both inversion and retention, although inversion usually predominates.[56,57] This may be explained by the absence of a significant lifetime for the oxocarbenium ion in the presence of a stronger nucleophile. The intimate ion pair therefore cannot exist as an intermediate if the nucleophilic atom is properly positioned for reaction, as described above (eq 5). The first stable intermediate for a significant fraction of the reaction will then be a solvent-separated ion pair, which can react with solvent on either the α or β face.

Bennet and Sinnott have carried out an extensive investigation of isotope effects for the cleavage of glucopyranosides and have observed small or no increases in the rate of solvolysis of glucopyranoside derivatives in the presence of added nucleophiles in water.[50] The results show that the transition state for these reactions has a large amount of carbocation character and are consistent with a unimolecular reaction for solvolysis; however, they do not prove that the reaction proceeds through an oxocarbenium ion intermediate.

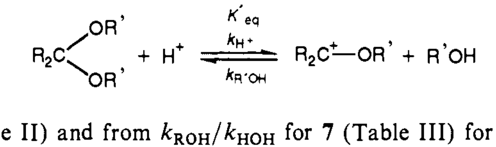
The conclusion that the stability of a glycosyl cation is similar to or larger than that of the methoxymethyl cation is the opposite of an earlier conclusion,[3,56] which was based on the 20-fold faster solvolysis of the 2,4-dinitrophenyl methoxymethyl compared with the corresponding glucosyl compound that was noted above and the faster acid-catalyzed cleavage of $H_2C(OMe)_2$ compared with methyl β-D-glucopyranoside, by a factor of 10^3. The difference may arise from a concerted reaction mechanism for the methoxymethyl derivatives, so that the reaction rate is not a measure of carbocation stability, or from the above-mentioned discrepancy between the effects of polar substituents on the rate of formation and on the stability of carbocations. The hydroxyl substituents are expected to have a much larger effect on the rate of formation of the glycosyl cation than on its rate of reaction with water.

An examination of the products from the solvolysis of a series of α- and β-D-glucosyl derivatives in 1:1 CF_3CH_2OH:EtOH (M:M) showed that different product ratios were obtained with different leaving groups, inversion is favored over retention, and the selectivity for EtOH compared with TFE is large (up to ~20-fold) for the reactions that occur with both inversion and retention.[56] These results show that although some product formation occurs before the leaving group diffuses away into the bulk solvent, there can still be a large selectivity toward the incoming nucleophile. Internal return may account for the high selectivity of some, but not all of these reactions. This appears to be a true "borderline" reaction, in which an intermediate oxocarbenium ion has a very short lifetime that depends on the nucleophilicity and the orientation of surrounding solvent molecules.

If the oxocarbenium ion is formed in the presence of trifluoroethanol it will generally not react with it because of the relatively low nucleophilic reactivity of trifluoroethanol. Furthermore, the strong electron-withdrawing effect of the CF_3 group, which is larger than that of OH, will tend to orient the molecule in an unreactive position relative to the cation.[58]

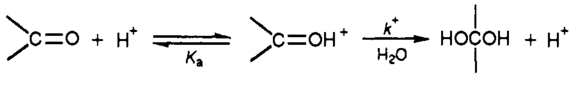
These conclusions are consistent with the large decrease, or even a reversal, of the selectivity for ethanol over trifluoroethanol in the reaction that occurs with retention when fluoride ion is the leaving group.[56] The transition state for departure of the basic fluoride ion may be stabilized by hydrogen bonding to the relatively acidic trifluoroethanol molecule and the fluoride ion may catalyze nucleophilic attack by the trifluoroethanol molecule in a solvent-separated ion pair, which must be the first stable product of bond breaking to F^- (eq 5).[56,59] An even larger reversal of selectivity is observed in the presence of phenol, a still more acidic nucleophile, which reacts ~20-fold faster with retention than inversion when fluoride ion is the leaving group.[56]

Equilibrium Constants for the Formation of Oxocarbenium Ions from Acetals. The rate constants for acid-catalyzed hydrolysis of acetals and for the addition of methanol or ethanol to the oxocarbenium ions were used to estimate the equilibrium constants for oxocarbenium ion formation in aqueous solution, according to eq 7. The values of k_{MeOH} and k_{EtOH} were estimated from k_{HOH} (Table II) and from k_{ROH}/k_{HOH} for **7** (Table III) for the less reactive acetals **1**, **2**, and **5**; k_{ROH}/k_{HOH} was taken as 0.02 M^{-1} for **6** and the putative oxocarbenium ions formed from acetals of formaldehyde and glucose. The estimated values of K'_{eq} are shown in Table II and span a range of ~10^{17}. At pH 7 the apparent equilibrium constant for the formation of the glucose oxocarbenium ion is ~10^{-27} M.



(7)

Protonated Acetone. An upper limit of the rate constant k^+ for the addition of water to protonated acetone (eq 8) can be obtained from the observed rate constant for the acid-catalyzed hydration of acetone, $k_{H^+} = k^+/K_a$, and the acid dissociation constant of protonated acetone, K_a. The observed rate constant[23] of $k_{H^+} = 16.5$ M^{-1} s^{-1} and the value[60] of $pK_a = -3.06$ give a rate constant for the hydration of protonated acetone of $k^+ \leq 2 \times 10^4$ s^{-1}. This rate constant is an upper limit because the acid-catalyzed hydration of formaldehyde and acetaldehyde, and presumably acetone, proceeds by concerted general acid catalysis and the rate constant for H⁺ fits the Brønsted correlation for catalysis by other general acids; the reaction with protonation in an initial equilibrium step is too slow to be observed.[24] Previous estimates of limiting values of k_{HOH} for addition to protonated CH_3CHO and $HCHO$[24] are uncertain because of the difficulty in estimating the pK_a values of these species, which have not been determined.



(8)

This upper limit for k^+ is much smaller than the rate constant of $k_{HOH} = 1 \times 10^9$ s^{-1} for hydration of the acetone oxocarbenium ion derived from **2**; the difference is a factor of ~10^5 or more. The rate constant for hydration of acetone itself[23] is $k_{HOH} \leq 2 \times 10^{-5}$ s^{-1} (the rate constants of $k_{HOH} = 10$ s^{-1} for $HCHO$[24a] and 6×10^{-3} s^{-1} for CH_3CHO[24b] suggest that this limit is close to the actual value). Thus, O-alkylation increases the rate constant for hydration of acetone by ~10^{14}, while protonation increases it by only ~10^9 or less. It is well-known that solvation of an unstable protonated intermediate can reduce its reactivity,[61] but a factor as large as 10^5 suggests that there may be a more fundamental difference between protonated and alkylated acetone.

Palm and others have suggested that the combination of a proton with a weak base, such as a carbonyl group, can give a hydrogen-bonded complex, rather than a fully protonated base,

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(55) Capon, B.; Thacker, D. *J. Chem. Soc. B* **1967**, 1010–1013.

(56) Sinnott, M. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2026–2032.

(57) Tarnus, C.; Muller, H. M.; Schuber, F. *Bioorg. Chem.* **1988**, *16*, 38–51.

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

(59) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1396–1401.

(60) Bagno, A.; Lucchini, V.; Scorrano, G. *Bull. Soc. Chim. Fr.* **1987**, 563–572.

(61) Dubois, J.-E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393–5401 and references therein.

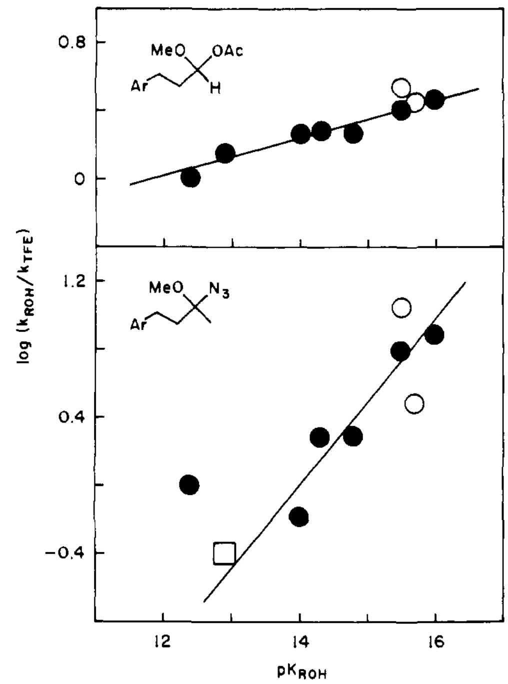
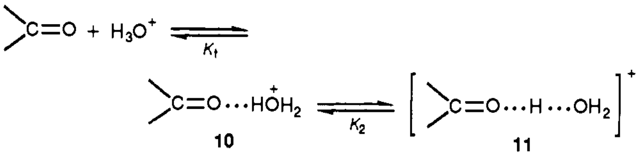


Figure 8. Brønsted plots of the rate constant ratios, k_{ROH}/k_{TFE}, for the reaction of **8a** (upper plot) and **7** (lower plot) with substituted alcohols in ROH:TFE:H_2O containing 50% H_2O (v:v); the lines have slopes of 0.11 and 0.50, respectively. The upper and lower open circles are for methanol and water, respectively. The open square is an upper limit. The data for both compounds were obtained from extrapolation of the data of Table III to a solvent containing 0% ROH.

as the product.[62] In their comprehensive examination of acetone protonation Bagno et al. obtained evidence for a perturbation of acetone in acid solution with an apparent pK_a of −1.65 that they attributed to the formation of such a hydrogen-bonded complex of the carbonyl group and the solvated proton, **10**.[60]

However, the large decrease in the rate constant for hydration of protonated compared with alkylated acetone shows that the



transition which occurs at $pK_a = -3.06$ still does not result in the formation of a full covalent bond to the carbonyl oxygen atom that is comparable to the O–CH_3 bond of the oxocarbenium ion. We suggest that the relatively weak interaction of the proton with the carbonyl group may be described by structure **11**. As the acidity of the solution increases and the concentration of water decreases, the proton moves to an intermediate position, **11**, in which it resides in a single potential well or a very rapidly equilibrating double well between the oxygen atoms of acetone and water. Similar structures may account for the small fractionation factors of the hydron in bicarboxylates[63] and extremely rapid proton transfer between molecules of low basicity that bond weakly to the proton and form strong hydrogen-bonded complexes.[64]

Reactions with Alcohols. The dependence on pK_a of the relative rate constants for the addition of substituted aliphatic alcohols to oxocarbenium ions derived from the propionaldehyde derivative **8a** and the butanone derivative **7** is shown in the upper and lower parts of Figure 8, respectively. The selectivities are extrapolated to zero concentration of the added alcohol, except for trifluoroethanol and water; they refer to reactions in 1:1 TFE:HOH (v:v). The slope of $\beta_{nuc} = 0.5$ for addition to the butanone derivative represents a large selectivity for these rapid reactions; it is comparable to the slope of −0.4 of log k against log K_{eq} for the addition of water to substituted oxocarbenium ions in Figure 6. Methanol is slightly more reactive than predicted by its pK_a, presumably because of its smaller steric requirements, and water shows a comparable negative deviation. Trifluoroethanol, which is a component of the solvent, shows a positive deviation.

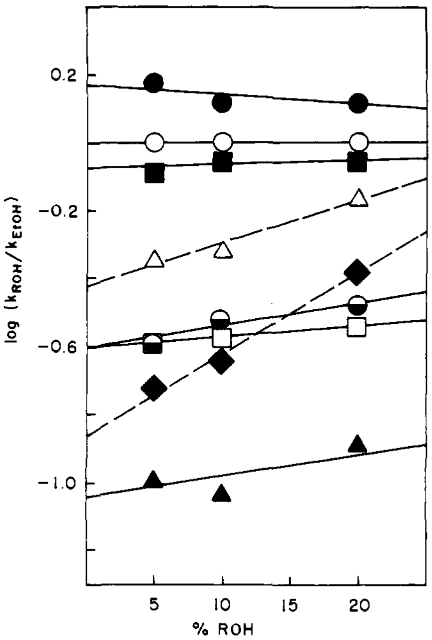


Figure 9. Variation of the rate constant ratio, k_{ROH}/k_{EtOH}, with volume percent ROH in ROH:TFE:H_2O containing 50% H_2O (v:v) for the reaction of **7** with substituted alcohols: (●) MeOH; (○) EtOH; (■) $CH_2=CHCH_2OH$; (△) H_2O; (◒) $ClCH_2CH_2OH$; (□) $MeOCH_2CH_2OH$; (◆) CF_3CH_2OH; (▲) $NCCH_2CH_2OH$. Dashed lines are drawn through the data for H_2O and TFE. For H_2O and CF_3CH_2OH, ROH = EtOH. The values of k_{ROH}/k_{EtOH} were obtained from the observed values of k_{ROH}/k_{TFE} and k_{EtOH}/k_{TFE} (Table III).

The oxocarbenium ion derived from the propionaldehyde derivative **8a** has a much smaller sensitivity to the basicity of alcohols with a slope of $\beta_{nuc} = 0.1$, as shown in the upper part of Figure 8. This difference represents a decrease in selectivity with increasing reactivity of the cation compared with the butanone cation derived from **7**; the cations derived from the acetone derivative **2** (Table II) and the propionaldehyde derivative **8d**[7] have values of $k_{HOH} = 1 \times 10^9$ and $2–5 \times 10^{10}$ s^{-1}, respectively. The decreased selectivity of the propionaldehyde derivative reflects an earlier transition state for nucleophilic attack that presumably represents a large Hammond effect. This is the behavior that is expected when the barrier becomes small and the reaction surface has a small curvature. Diffusional processes have only a small effect on these rate constants, as noted above.

Essentially the same product ratios were obtained from the acid-catalyzed solvolysis of **8b**, with phenol as the leaving group (Table III). Thus, there is no indication of an enhanced reactivity of acidic alcohols that arises from catalysis by the leaving acetate ion in the reaction of **8a**. The selectivity of the propionaldehyde derivatives toward ethanol and trifluoroethanol is the same in ROH:TFE:H_2O containing 50% (v:v) water and in 1:1 (M:M) EtOH:TFE, but the selectivity of $k_{EtOH}/k_{TFE} = 11$ in 1:1 EtOH:TFE for the ketone derivative formed from **7** is larger than the ratio $k_{EtOH}/k_{TFE} = 4$ in the partially aqueous solvent (Results and Table III).

The dependence on solvent composition of the selectivities of **7** toward different alcohols in ROH:TFE:H_2O mixtures containing 50% water (v:v) is shown in Figure 9. The selectivities are plotted as log (k_{ROH}/k_{EtOH}) and show a tendency to increase with increasing percent ROH as the alcohol becomes more acidic. There

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[62] Palm, V. A.; Haldna, Ü. L.; Talvik, A. J. *Chemistry of Carbonyl Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1966; p 439.

[63] Kreevoy, M. M.; Liang, T. M. *J. Am. Chem. Soc.* **1980**, *102*, 3315–3322.

[64] Irish, D. E.; Chen, H. *J. Phys. Chem.* **1970**, *74*, 3796–3801.

is a much larger tendency for this increase with trifluoroethanol, and a significant increase with water, which are major components of the solvent. The increase in percent ROH is accompanied by a corresponding decrease in percent TFE and the increased reactivity of the more acidic alcohols under these conditions may reflect facilitation of their reaction by the increased proton-accepting ability of the more basic alcohols in the solvent. Similar behavior has been observed previously for reaction with phenylethyl carbocations.[9,65] However, the change in the k_{TFE}/k_{HOH} ratio with increasing percent ROH is opposite to that observed in the phenylethyl system;[65] we do not have an explanation for this result.

Common Ion Inhibition. The decrease in rate that is brought about by reaction of a cationic intermediate with an excess of the leaving group in the solvent, to regenerate starting material, provides an unusually powerful, and simple, method to identify and characterize unstable intermediates. It may be useful to summarize some of the advantages and disadvantages of this technique:

(1) It provides an unequivocal method for detecting an intermediate that may be difficult to identify by other techniques, provided that the inhibition is shown not to arise from a salt effect.

(2) If reaction with the intermediate can be shown to be diffusion controlled, it provides a simple method to determine the lifetime of unstable intermediates without the use of special techniques or equipment.

(3) It permits the detection of intermediates even when the substrate undergoes second-order reactions with dilute nucleophiles in solution, because the second-order reaction of the leaving group with the substrate is degenerate. This made possible the detection of an acylium ion intermediate by common ion inhibition of the solvolysis of *p*-dimethylaminobenzoyl fluoride, for example.[17]

(4) The rate constant ratio, k_{Nu}/k_S, for the reaction of a nucleophile and solvent that is obtained from common ion inhibition measures the selectivity of only the free carbocation, whereas such ratios obtained from product analysis may include selectivities of other reactive species, such as the starting material or ion pairs.

(5) Rate constant ratios for the reaction of a carbocation with a nucleophile and solvent are often determined by product analysis. The common ion method is especially useful when the nucleophile or solvent adducts are unstable to the reaction conditions or when accurate product analysis is not possible.

(6) Common ion inhibition, even with a leaving group that reacts with the carbocation in a diffusion-controlled reaction, is limited to only moderately unstable carbocations. For example, a carbocation that reacts with water with a rate constant of 10^{11} s^{-1} will give a decrease in k_{obsd} for solvolysis of the azide adduct of only ~10% in the presence of 2.0 M added azide. Conversely, for very selective carbocations, there may be inhibition of the solvolysis by even the small concentration of leaving group that is released during the reaction, so that the integrated first-order rate constant decreases with the progress of the reaction. The kinetic analysis of this situation is complex, and there are special difficulties if such inhibition is extensive.[66,67]

(7) Accurate determination of the rate constant ratio k_{Nu}/k_S depends on a reliable value for k_{solv}, the rate constant for solvolysis in the absence of added common ion. This is because k_{Nu}/k_S is obtained by combination of the slope and intercept of a reciprocal plot of the inhibition data.

(8) The method may not be applicable if there are large specific salt effects of the added common ion on the rate constant k_{solv}.

Experimental Section

Materials. Commercially available materials were obtained and purified as described in the supplementary pages. 1-Methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane (**8c**) was synthesized as described in the following paper.[15] Water was glass distilled.

Synthesis. The following outlines the methods used to prepare and purify the compounds described. Full details, including ^1H NMR, ^{13}C NMR, IR, and mass spectra, are given in the supplementary pages.

The α-azido ethers (**1**–**7**) were prepared by modifications of the method of Kirchmeyer et al.[68] and were isolated by distillation (**2**–**6**) or by column chromatography on silica gel (**1** and **7**), as described in the supplementary material. (It should be noted that these compounds are potentially explosive.[68])

3-(4-Methoxyphenyl)propionaldehyde was prepared by oxidation of commercial 3-(4-methoxyphenyl)-1-propanol with pyridinium dichromate.[69] The aldehyde was isolated by conversion in situ of the remaining alcohol to its 4-nitrophenyl ester, followed by distillation.

1,1-Dimethoxy-3-(4-methoxyphenyl)propane was prepared by reaction of 3-(4-methoxyphenyl)propionaldehyde with HPLC grade methanol under reflux, using *p*-toluenesulfonic acid as a catalyst. The methanol was evaporated and the residue was dissolved in ether. This solution was washed with $NaHCO_3$, 1 M sulfite buffer, 50% dianion, and 1 M NaOH in order to remove the remaining aldehyde as its bisulfite addition compound. The acetal was purified by distillation.

1-Chloro-1-methoxy-3-(4-methoxyphenyl)propane was prepared by the action of boron trichloride on 1,1-dimethoxy-3-(4-methoxyphenyl)propane, as described by Goff et al.[70] Purification of this compound was not attempted.

2,2-Dimethoxy-4-(4-methoxyphenyl)butane, acetophenone dimethyl acetal, and 1,2,2-trimethoxypropane were prepared by reaction of the corresponding carbonyl compounds with 1 equiv of trimethyl orthoformate in HPLC grade methanol under reflux, using *p*-toluenesulfonic acid as a catalyst. The acetals were purified by distillation or by column chromatography on silica gel.

1-Acetoxy-1-methoxy-3-(4-methoxyphenyl)propane (8a) was prepared by reaction of freshly prepared 1-chloro-1-methoxy-3-(4-methoxyphenyl)propane with 1 equiv of silver acetate in acetonitrile at room temperature. The acylal was isolated by reduction in situ of the residual 3-(4-methoxyphenyl)propionaldehyde to the corresponding alcohol with $NaBH_4$, followed by column chromatography on silica gel.

1-Methoxy-3-(4-methoxyphenyl)-1-phenoxypropane (8b) was prepared by reaction of freshly prepared 1-chloro-1-methoxy-3-(4-methoxyphenyl)propane with sodium phenoxide in dry THF at room temperature. The mixed acetal was purified by column chromatography on silica gel.

Kinetic Methods. The following briefly outlines the methods used to determine rate constants for the reactions of the compounds described. Full details of all the procedures can be found in the supplementary material.

Rate constants for the reactions of 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane and 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane were determined as described in the following paper.[15]

First-order rate constants, k_{obsd}, for the reactions of 1-azido-1-ethoxypropane, at 25 °C and ionic strength 2.0 maintained with $NaClO_4$, were determined spectrophotometrically by monitoring the formation of propionaldehyde thiosemicarbazone at 290 nm. The solutions were buffered with MES or with acetate and contained 25–100 mM thiosemicarbazide. Solutions containing formate or phosphate were buffered with these. The rate constants were independent of the concentration of thiosemicarbazide.

Solvolysis of 3-azido-1,3-dimethoxybutane and 2-azido-1,2-dimethoxypropane, at 25 °C and ionic strength 2.0 maintained with $NaClO_4$, was followed spectrophotometrically at 287 nm by the protonation of a phenolate anion indicator by the acid that is formed during solvolysis. For the fast reactions of 2-azido-2-methoxypropane, the reactions were initiated by quickly adding the pre-incubated reaction solution to the cuvette which already contained the substrate and the phenolate ion indicator. For the solvolysis of 3-azido-1,3-dimethoxybutane in 40% acetonitrile in water at 25 °C and ionic strength 1.0 maintained with $NaClO_4$, solutions were made up with a solvent that was prepared by diluting a measured volume of acetonitrile to a specified final volume with water.

Rate constants for the solvolysis of azidomethoxyphenylmethane, at 25 °C and ionic strength 2.0 maintained with $NaClO_4$, were determined spectrophotometrically by following the appearance of benzaldehyde at 285 nm. The solutions were buffered with 10 mM CAPS (pH ≈ 10.3) or with 0.01 M NaOH.

The solvolysis of 1-azido-1-methoxy-1-phenylethane at 25 °C in mixed acetonitrile:water solvents and at various ionic strengths, maintained with $NaClO_4$, was followed spectrophotometrically by monitoring the appearance of acetophenone at 265–280 nm. Solutions were made up with

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(65) Ta-Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040–8050.

(66) Rappoport, Z.; Apeloig, Y.; Greenblatt, J. *J. Am. Chem. Soc.* **1980**, *102*, 3837–3848.

(67) van Ginkel, F. I. M.; Hartman, E. R.; Lodder, G.; Greenblatt, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7514–7519.

(68) Kirchmeyer, S.; Mertens, A.; Olah, G. A. *Synthesis* **1983**, 500–501.

(69) Corey, E. F.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

(70) Goff, D. A.; Harris, R. N., III; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711–4714.

solvents that were prepared by mixing specified volumes of HPLC grade acetonitrile and water and were buffered with 10 or 20 mM CAPS, 50% free base.

Solvolysis in Mixed Trifluoroethanol:Water Solvents. Full details of the procedures can be found in the supplementary material.

Reaction mixtures for the product studies in ROH:TFE:H_2O containing 50% H_2O (v:v) were prepared by mixing 1 mL of an appropriate aqueous solution at ionic strength 1.0 maintained with $NaClO_4$ with 1 mL of a mixture of trifluoroethanol and the desired alcohol ROH, to give the required volume fraction x of the alcohol in the final mixture. For 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane, 10 μL of 1 M cacodylate buffer, 80% free base was also added. For 1-methoxy-3-(4-methoxyphenyl)-1-phenoxypropane, 10–20 μL of 20 mM perchloric acid was added in place of the cacodylate buffer. In both cases the reaction mixtures were incubated at 25 °C and aliquots were withdrawn at various times for analysis by HPLC.

For solvolysis of 2-azido-2-methoxy-4-(4-methoxyphenyl)butane at 22 ± 2 °C, the aqueous solutions used were buffered with 50 or 100 mM CHES or CAPS, 20% or 50% free base at ionic strength 1.0 maintained with $NaClO_4$; the choice of buffer did not affect the product ratios. For the reaction in 10:40:50 (v:v:v) EtOH:TFE:H_2O at ionic strength 0.5 maintained with KNO_3 or KOAc, the aqueous buffer used was 100 mM CHES, 20% free base. The products were analyzed by HPLC.

Solvolysis in 1:1 (M:M) Ethanol:Trifluoroethanol. Full details of the procedures can be found in the supplementary material.

The acid-catalyzed solvolysis of 1-methoxy-3-(4-methoxyphenyl)-1-phenoxypropane in 2 mL of solvent was initiated by the addition of 10 μL of 20 mM perchloric acid. For the solvolysis of 2-azido-2-methoxy-4-(4-methoxyphenyl)butane the solutions also contained 2 mM quinuclidine or 10 mM triethylamine. All reactions were run at 25 °C and aliquots were withdrawn at various times for analysis by HPLC.

Product analysis by liquid chromatography was carried out on a Waters Associates reverse-phase octadecylsilane chromatography column (Nova-Pak C_{18} 4μ) and elution with mixtures of MeCN:H_2O. Full details of all the procedures can be found in the supplementary material.

The products of the solvolysis of 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane were analyzed after conversion in situ of the 3-(4-methoxyphenyl)propionaldehyde product to its semicarbazone. The acid-catalyzed solvolysis of 1-methoxy-3-(4-methoxyphenyl)-1-phenoxypropane yielded products that were not stable to the reaction conditions. However, the product ratios were shown to be constant within the experimental error (estimated to be ±20%) over the first 10–20% of reaction.

Calculation of Rate Constant Ratios. In all cases product ratios were the average of 4–12 HPLC analyses. Rate constant ratios, k_{ROH}/k_{TFE}, were calculated from eq 9. For water, the ROH adducts are the corresponding carbonyl compounds. Except where indicated the errors are estimated to be ±10%.

$$k_{ROH}/k_{TFE} = \{(\text{ROH adduct area}) \times [\text{TFE}]\}/\{(\text{TFE adduct area}) \times [\text{ROH}]\} \quad (9)$$

Supplementary Material Available: Full details of the methods used to prepare and purify the compounds described (including ^{1}H NMR, ^{13}C NMR, IR, and mass spectra) (17 pages). Ordering information is given on any current masthead page.

Concerted Bimolecular Substitution Reactions of Acetal Derivatives of Propionaldehyde and Benzaldehyde[1]

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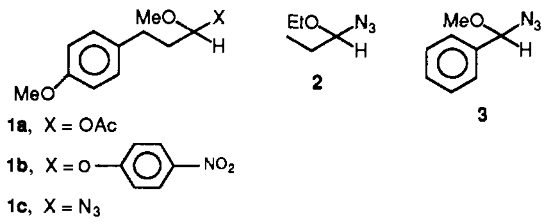
Abstract: The propionaldehyde acetal derivatives 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane, 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane, and 1-azido-1-ethoxypropane undergo concerted bimolecular substitution reactions with anionic nucleophiles. The products are unstable adducts that break down to the corresponding aldehydes. The observed rate constants follow Swain–Scott correlations with s values of 0.1–0.2, which indicate a low sensitivity to the attacking nucleophile and are consistent with an "exploded" transition state. Water shows a small negative deviation from these plots but reacts through a stepwise mechanism with a highly unstable oxocarbenium ion intermediate. Similarly, an acetal derivative of benzaldehyde, azidomethoxyphenylmethane, undergoes rapid concerted bimolecular substitution with good nucleophiles. The unexpectedly large s value of 0.4 is similar to that observed for a 4-nitrobenzyl system but, remarkably, the reactivity toward thiocyanate is >10^5-fold greater than that of benzyl azide and ~100-fold greater than that of 1-azido-1-ethoxypropane, which provides evidence for a benzylic effect. Water exhibits a positive deviation of ~30-fold from the Swain–Scott correlation for anionic nucleophiles, and hydrolysis of this compound occurs by a concurrent stepwise mechanism with a diffusionally equilibrated oxocarbenium ion intermediate. The consequences of these results for reactions of glycosyl derivatives are discussed.

Until recently, the traditional view that substitution reactions at acetal centers in aqueous solution occur solely by a stepwise process through an oxocarbenium ion intermediate has stood virtually unchallenged. However, crude extrapolation of a linear free energy relationship between the rate constants for attack of water (k_{HOH}) on the oxocarbenium intermediate derived from acetophenone dimethyl acetals and for attack of sulfite dianion on the corresponding ketones led Young and Jencks to predict that the methoxymethyl cation would have a "lifetime" in aqueous solution on the order of ~10^{-15} s.[2–4] Such intermediates cannot be said to have a significant existence in the presence of a properly oriented nucleophile because their lifetime is shorter than a bond

Chart I



1a, X = OAc

1b, X = O–C$_6$H$_4$–NO$_2$

1c, X = N$_3$

2

3

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(1) Supported in part by grants from the National Institutes of Health (GM 20888) and the National Science Foundation (PCM 8117816).

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

0002-7863/89/1511-7900$01.50/0