7900 *J. Am. Chem. Soc.* **1989**, *111*, 7900-7909

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 In both cases the reaction mixtures were incubated at 25 °C and aliquots were withdrawn at various times for analysis by HPLC.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 All reactions were run at 25 °C and aliquots were withdrawn at various times for analysis by HPLC.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 ^1H 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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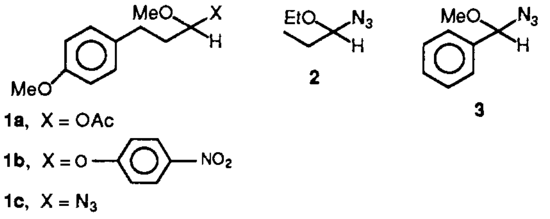
Abstract: The propionaldehyde acetal derivatives 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane, 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane, and 1-azido-1-ethoxypropane undergo concerted bimolecular substitution reactions with anionic nucleophiles. The products are unstable adducts that 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 $\sim 10^{-15}$ 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



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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.

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vibration ($\sim 10^{-13}$ s), so that concerted substitution reactions should be enforced.[5,6] In accord with this prediction, methoxymethyl (formaldehyde) derivatives were shown to undergo concerted bimolecular substitution reactions with nucleophiles.[7,8]

We reported previously[4,9] that the aqueous solvolysis of the propionaldehyde derivatives **1c** and **2** (Chart I) proceeds through very short-lived oxocarbenium ion intermediates, with rate constants for reaction with water of $k_{HOH} \geq 2 \times 10^{10}$ s^{-1}. This means that these oxocarbenium ions do not have a long enough lifetime to diffuse up to nucleophilic reagents in dilute solutions. Therefore, the nucleophilic substitution reactions of acetal derivatives of simple aldehydes are expected to proceed chiefly through a stepwise or concerted preassociation mechanism, in which the nucleophile is present at the time that bond breaking occurs.[5,6]

We report here that the substitution reactions of the propionaldehyde acetal derivatives **1a**, **1b**, and **2** with most nucleophilic reagents in aqueous solution are indeed bimolecular and describe evidence that the concerted mechanism is enforced by the absence of a barrier to collapse of the oxocarbenium ion in the presence of strong nucleophiles. We also report the surprising result that the acetal derivative of benzaldehyde, **3**, which forms an oxocarbenium ion that is diffusionally equilibrated in aqueous solution ($k_{HOH} = 2 \times 10^9$ s^{-1}),[4] undergoes facile S_N2 displacement reactions that are also enforced concerted. Interestingly, there is a significant concurrent S_N1 pathway for the substitution reactions in this system, because the oxocarbenium ion has a lifetime in the presence of solvent but not in the presence of a strong nucleophile. The reaction with water is slow enough for trapping of the oxocarbenium ion by added solutes to compete with trapping by solvent water.

Thus, according to a recently proposed nomenclature for reaction mechanisms,[10] these compounds can react by a $D_N + A_N$ mechanism, in which dissociation occurs to give an oxocarbenium intermediate that can diffuse through the solvent and react with solvent or other nucleophilic reagents, and by an A_ND_N mechanism, in which nucleophilic attack and expulsion of the leaving group occur in a single concerted reaction.

Glycosyl cations are expected to be even more reactive toward water than the oxocarbenium ions derived from propionaldehyde derivatives,[4] so that concerted bimolecular reactions of good nucleophiles with glycosyl derivatives should also be enforced by the absence of a significant lifetime of glycosyl cations in their presence.

Experimental Section

Materials. Sodium hydride, benzyl bromide, anhydrous tetrahydrofuran (THF),[11] and Gold Label trifluoroethanol (99+%) were purchased from Aldrich. Sodium azide was purchased from Fluka. 4-Nitrophenol and semicarbazide hydrochloride were recrystallized. 1-Chloro-1-methoxy-3-(4-methoxyphenyl)propane, 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane, 1-azido-1-ethoxypropane, and azidomethoxyphenylmethane were synthesized as described in the preceding paper.[4] Water was glass distilled. All other chemicals were of reagent grade and were used without further purification, apart from drying when necessary.

Synthesis. ^{1}H NMR spectra at 300 MHz and ^{13}C spectra at 75 MHz were recorded in $CDCl_3$ on a Varian XL-300 spectrometer and chemical shifts are reported as δ ppm downfield of an internal tetramethylsilane standard at 0 ppm. Mass spectra were recorded on a Hewlett-Packard 5985B spectrometer. Infrared spectra were recorded on a Perkin-Elmer 683 spectrophotometer. Column chromatography was carried out with Merck Kieselgel 60 (70–230 mesh) and Fisher certified solvents.

1-Methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane (1b). 4-Nitrophenol (2.32 g, 16.7 mmol) in dry THF (20 mL) was added dropwise to a stirred solution of oil-free sodium hydride (670 mg of a 60% dispersion, 16.7 mmol) in dry THF (20 mL) under argon at 0 °C. Freshly prepared 1-chloro-1-methoxy-3-(4-methoxyphenyl)propane (1 g, 4.7 mmol) in dry THF (15 mL) was added, the mixture was allowed to warm to room temperature, and THF (30 mL) was added. The mixture was heated under gentle reflux for 21 h and filtered; the solid was washed with ether. The combined extracts were evaporated and the residue was dissolved in ether (150 mL), washed with $NaHCO_3$ (6 × 50 mL) and with water (50 mL), dried ($MgSO_4$), and evaporated to give a brown oil (1.27 g). This was purified by column chromatography on silica gel (50 g), eluting with 19/1 chloroform/ethyl acetate, to give **1b** (750 mg, 50%) as an oil: IR (liquid film) 1520 (NO_2), 1350 cm^{-1} (NO_2); ^{1}H NMR δ 8.15 (2 H, d, J = 10 Hz, Ar), 7.10 (2 H, d, J = 8 Hz, Ar), 7.04 (2 H, d, J = 10 Hz, Ar), 6.84 (2 H, d, J = 8 Hz, Ar), 5.26 (1 H, t, J = 6 Hz, CH), 3.78 (3 H, s, $ArOCH_3$), 3.38 (3 H, s, OCH_3), 2.71 (2 H, m, $ArCH_2$), 2.17 (2 H, m, CH_2); ^{13}C NMR δ 162.4, 158.2, 142.5, 132.8, 129.5, 126.0, 116.7, 114.2 (Ar), 102.3 (CH), 55.4 ($ArOCH_3$), 52.6 (OCH_3), 34.4 (CH_2), 29.8 ($ArCH_2$); MS, m/z 317 (1.5%, M$^+$), 121 (100).

Kinetic Methods. Rate constants for the solvolysis of 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane at 25 °C and ionic strength 1.0, maintained with $NaClO_4$, were determined spectrophotometrically at 287 nm by following the protonation of phenolate anion by the acid that is formed during solvolysis. Reaction volumes of 4 mL containing 5 μL of 0.22 M phenol (90% phenolate anion) in 4 cm path length quartz cuvettes were used. Reactions were initiated by injection of $\sim$25 μL of a solution of substrate in acetonitrile to give a final concentration of 0.05–0.1 mM (the concentration of phenolate anion was always at least as large as that of the substrate). For runs in solutions containing sodium azide, reaction volumes of 2.5 mL containing 10 μL of the phenol solution in 1 cm path length cuvettes were used, with substrate concentrations at 0.1–0.3 mM. Periodic control experiments in which the phenolate indicator was titrated spectrophotometrically with hydrochloric acid, in the presence and absence of azide ion, showed that the absorbance change at 287 nm is linear with added acid in the range of the substrate concentrations used. The first-order rate constants, k_{obsd}, were obtained from the slopes of semilogarithmic plots of $(A_t - A_\infty)$ against time, which were linear for 2–3 half times. Second-order rate constants, k_N, for the reactions of added nucleophiles with the substrate were determined by the same method from the observed rate constants in solutions of 1.0 M nucleophile.

Rate constants for the solvolysis of 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane at 41 °C and ionic strength 2.0, maintained with $NaClO_4$, were determined spectrophotometrically by following the release of 4-nitrophenoxide ion at 405 nm. Reactions in a volume of 3 mL containing 20 μL of 1 M NaOH were initiated by injecting 25 μL of a solution of substrate in acetonitrile to give a final concentration of 0.01 mM. Identical rate constants were obtained when 25 μL of NaOH was used. First-order rate constants, k_{obsd}, were determined from the slopes of semilogarithmic plots of $(A_\infty - A_t)$ against time, which were linear for at least 3 half times. Second-order rate constants, k_N, for the reactions of added nucleophiles with the substrate were determined by the same method from the slopes of linear plots of k_{obsd} against [nucleophile], usually with at least five data points.

First-order rate constants, k_{obsd}, for the solvolysis of 1-azido-1-ethoxypropane at 25 °C and ionic strength 2.0, maintained with $NaClO_4$, were determined spectrophotometrically by trapping of the propionaldehyde formed with thiosemicarbazide, as described previously.[4] Second-order rate constants, k_N, for the reactions of added nucleophiles with the substrate were determined by the same method from the slopes of linear plots of k_{obsd} against [nucleophile], with 2–6 data points.

The rate constants for solvolysis of azidomethoxyphenylmethane were determined spectrophotometrically by the appearance of benzaldehyde, as described previously.[4] Second-order rate constants, k_N, for the reactions of added nucleophiles with the substrate were determined from the slopes of linear plots of k_{obsd} against nucleophile concentration, with 2–6 data points.

Product Studies in the Presence of Azide Ion. The products from the solvolysis of 1-acetoxy-1-methoxy-3-(4-methoxyphenyl)propane at 25 °C

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(3) We have extended the correlation between the rate constants for attack of water on oxocarbenium ions and for attack of sulfite dianion on the corresponding carbonyl compounds and find that the extrapolated value of k_{HOH} for the methoxymethyl cation is 5×10^{12}–10^{15} s^{-1}.[4] This agrees surprisingly well with the value of $k_{HOH} \approx 10^{12}$ s^{-1} calculated from the effect of alkyl substituents on oxocarbenium ion stability,[4] and $k_{HOH} \geq 10^{12}$ s^{-1} obtained by extrapolation of a linear free energy relationship between known values of k_{HOH} and the equilibrium constants for formation of the oxocarbenium ions from the corresponding α-azido ethers.[4] If the methoxymethyl cation does exist in aqueous solution, then its lifetime is very short indeed.

(4) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.*, previous paper in this issue.

(5) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169.

(6) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345–375.

(7) Craze, G.-A.; Kirby, A. J.; Osborne, R. *J. Chem. Soc., Perkin Trans. 2* **1978**, 357–368.

(8) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789–6798.

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

(10) Commission on Physical-Organic Chemistry, IUPAC. *J. Pure Appl. Chem.* **1989**, *61*, 23–56.

(11) Abbreviations: THF, tetrahydrofuran; TFE, 2,2,2-trifluoroethanol; MOPS, 3-(*N*-morpholino)propanesulfonic acid.

(12) The rate constant for hydrolysis of the α-azido ether at 25 °C and 1.0 M NaN_3 is 1.24×10^{-5} s^{-1}.[9]

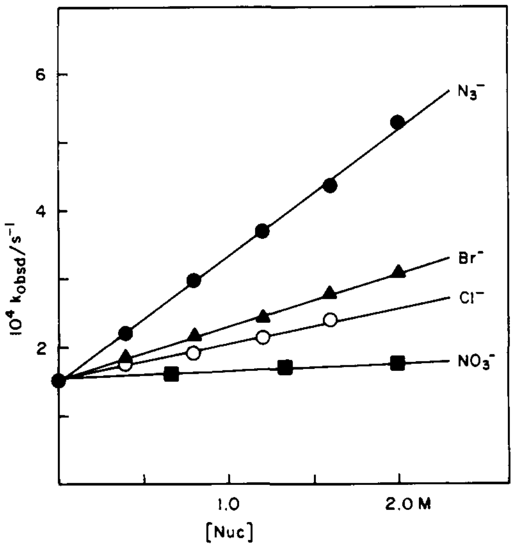


Figure 1. The dependence of k_{obsd} on the concentration of anionic nucleophiles for reactions of 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane (**1b**) in water at 41 °C and ionic strength 2.0 ($NaClO_4$).

in 1.0 M aqueous sodium azide were analyzed by HPLC under the conditions described previously[4] with peak detection at 270 nm. MOPS buffer[11] (10 μL, pH 7.8) was added to 2.5 mL of 1.0 M NaN_3 to give a final concentration of 3 mM. To this was added 10–50 μL of semicarbazide (pH 7.8) to give a final concentration of 4–20 mM. The solution was incubated at 25 °C and the reaction was initiated by the addition of 10 μL of a solution of substrate in acetonitrile to give a final concentration of 0.1 mM. After the reaction was complete the products were analyzed by HPLC. Two peaks were observed. These were identified as the semicarbazone and the α-azido ether by comparison with the products obtained in an identical experiment conducted in the absence of NaN_3 in 1.0 M $NaClO_4$. The products were stable for several half-lives and the product ratios were found to be independent of the concentration of semicarbazide in the concentration range used. Product ratios were calculated directly from the observed peak areas; it was shown that the semicarbazone and the α-azido ether have identical extinction coefficients within the experimental error.

Preparation and Solvolysis of Benzyl Azide. Benzyl azide was prepared by stirring benzyl bromide in a solution of trifluoroethanol saturated with sodium azide at room temperature in the dark for 7 days. NMR indicated quantitative conversion to the azide. The product was isolated by filtration and evaporation and was used without further purification. Analysis by HPLC with peak detection at 270 nm showed two peaks, corresponding to benzyl azide and an unidentified impurity with a shorter retention time, with a ratio of areas of ~3.5:1. The latter was stable to the solvolysis conditions. The solvolysis of benzyl azide in 0, 1.0 and 2.0 M thiocyanate at ionic strength 2.0 maintained with $NaClO_4$ was carried out as follows. A solution of substrate in acetonitrile (100 μL) was dissolved in 10 mL of reaction solution to give a final concentration of 1 mM. To this was added 25 μL of a solution of 4-chlorobenzaldehyde in acetonitrile to give a final concentration of 0.015 mM. This served as an injection standard for HPLC. The solution was incubated in the dark at 25 °C and aliquots were withdrawn at intervals. These were analyzed by HPLC with peak detection at 270 nm. The reactions were followed for about 1 half time and the pseudo-first-order rate constants were determined from a semilogarithmic plot of the normalized benzyl azide peak area against time.

Results

Figure 1 shows that k_{obsd} for the pH-independent disappearance of the propionaldehyde derivative **1b**, determined spectrophotometrically from the appearance of 4-nitrophenoxide ion, increases linearly upon the addition of nucleophiles at constant ionic strength, maintained with sodium perchlorate. Azide ion causes an increase of greater than 3-fold in k_{obsd} at 2.0 M, while weaker nucleophiles have lesser effects. In the presence of >0.4 M sodium thiosulfate or >1.6 M sodium chloride, lag phases arising from insolubility of the substrate were observed; these data were not used for the determination of rate constants. The disappearance of **1a** was followed spectrophotometrically from the protonation of a phenolate anion indicator by the acid produced during solvolysis (see Experimental Section); rate constants were determined at 0 and 1.0 M nucleophile. The second-order rate constants, k_N, for the reactions of nucleophiles with **1a**, **1b**, **2**, and **3** are summarized in Table I.

Table I. Second-Order Rate Constants for the Reaction of Acetal Derivatives with Nucleophiles in Aqueous Solution[a]

nucleophile	$n(\mathrm{MeI})$[b]	**1a** $10^4 k_N$,[c] $M^{-1}\ s^{-1}$	**1b** $10^5 k_N$,[d] $M^{-1}\ s^{-1}$	**2** $10^5 k_N$,[e] $M^{-1}\ s^{-1}$	**3** $10^3 k_N$,[e] $M^{-1}\ s^{-1}$
H_2O[f]	−0.27	0.34	0.28	0.51	0.39
Cl^-	4.37	8	5	6	≤1.0[g]
Br^-	5.79	10	7.5	8.7	3.4
I^-	7.42	14	11	15	14
N_3^-	5.78	15	19		
SCN^-	6.70	9	8.3	17	46
$S_2O_3^{2-}$	8.95		13	38	52
NO_3^-	1.5		0.9		
SO_4^{2-}	3.5			6	

[a] Determined as described in the Experimental Section. [b] See ref 13. [c] At 25 °C and ionic strength 1.0 ($NaClO_4$). [d] At 41 °C and ionic strength 2.0 ($NaClO_4$). [e] At 25 °C and ionic strength 2.0 ($NaClO_4$). [f] The second-order rate constants for water are $k_{solv}/55.6$, where k_{solv} is the observed rate constant for solvolysis in the presence of $NaClO_4$ at the ionic strengths indicated. [g] No increase in k_{obsd} was found at 2.0 M chloride; the upper limit is calculated assuming that a 10% increase would have been detected.

Linear increases in k_{obsd} with increasing nucleophile concentration were also observed for the disappearance of the propionaldehyde derivative **2**. The reaction was followed spectrophotometrically by trapping the product aldehyde as its thiosemicarbazone. Thiocyanate and iodide at 1.9 M cause 2-fold increases in k_{obsd}, while 2.0 M azide causes a 30% decrease in k_{obsd} that is attributed to common ion inhibition.[4]

Large increases in k_{obsd} upon the addition of nucleophiles were observed for the disappearance of the benzaldehyde derivative **3**, determined spectrophotometrically from the appearance of benzaldehyde. Increases of 2-fold in k_{obsd} were found in the presence of 2.0 M iodide or 0.53 M thiosulfate, while for 2.0 M thiocyanate the increase was 5-fold. The plot of k_{obsd} against nucleophile concentration for the reaction of **3** with thiocyanate showed slight downward curvature, with a negative deviation of ~10% at 2.0 M; the second-order rate constant for the reaction was obtained from the linear part of the plot. Chloride ion at 2.0 M gives no change in k_{obsd} for this compound; azide causes common ion inhibition, with a 4-fold decrease in k_{obsd} at 1.0 M.[4]

The substitution of sodium perchlorate for sodium bromide, iodide, or thiosulfate at ionic strength 2.0 gives no change in k_{obsd} for the solvolysis of the butanone derivative 3-azido-1,3-dimethoxybutane; 2.0 M azide causes a 7-fold decrease in k_{obsd} for this compound, which is attributed to common ion inhibition.[4]

The products from the solvolysis of **2** and **3** were determined to be the corresponding aldehydes by ultraviolet spectroscopy of the aldehyde or its thiosemicarbazone. The solvolysis of **1a** gave only the aldehyde for all reactions except those run in the presence of azide, in which the corresponding α-azido ether was also formed.[9] This product is much more stable than the acylal[12] and does not lead to any kinetic complications. At 1.0 M azide the yield of the α-azido ether was 48%,[9] determined by HPLC analysis as described in the Experimental Section. The products from the solvolysis of **1b** were not analyzed, but it is likely that the α-azido ether (**1c**) is formed in the presence of azide because at 25 °C the rate constants for solvolysis of **1b** and **1c** are similar.

The rate constant for the disappearance of benzyl azide in aqueous 2.0 M $NaClO_4$ was determined by HPLC, from the decrease in the peak area for benzyl azide, to be $\sim 2 \times 10^{-6}\ s^{-1}$. In the presence of 1.0 or 2.0 M NaSCN rate constants identical with this, within the experimental error, were obtained. This probably means that the observed reaction is not solvolysis, because if there were a reaction with water, then a second-order reaction with thiocyanate would be expected to increase k_{obsd}. The absence of a rate increase gives an upper limit for the second-order rate constant for the reaction of benzyl azide with thiocyanate of <3

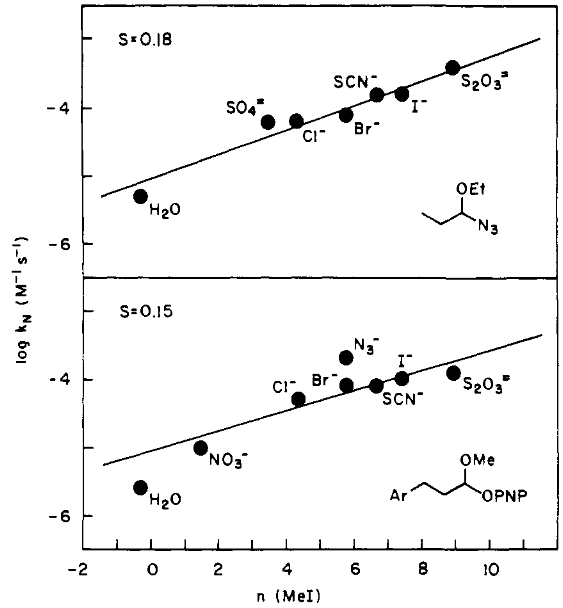


Figure 2. Swain–Scott correlations of log k_N against the *n* (MeI) value for the nucleophile[13] for the reactions of 1-azido-1-ethoxypropane (**2**) at 25 °C (upper plot) and 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane (**1b**) at 41 °C (lower plot), in water at ionic strength 2.0 ($NaClO_4$).

$\times 10^{-7}$ M^{-1} s^{-1}, assuming that a 25% increase in k_{obsd} would have been detected.

Discussion

The strongest evidence that the reactions of the propionaldehyde derivatives **1a**, **1b**, and **2** with anionic nucleophiles are bimolecular is the linear increase in the pseudo-first-order rate constants, k_{obsd}, caused by the addition of nucleophiles (Figure 1), and the increase in the second-order rate constants for these reactions, k_N, with increasing reactivity of the nucleophile in known S_N2 substitution reactions. For **1a**, the fraction of the azide adduct formed (48%) is close to that expected from the observed rate increase (1.8-fold) in the presence of azide[9] (Table I), which means that there is no detectable trapping by azide of any intermediate that would otherwise react with water. Similarly, the increases in k_{obsd} for the disappearance of the benzaldehyde derivative **3**, caused by the addition of bromide, iodide, thiocyanate, and thiosulfate ions, provide evidence for bimolecular reactions of these nucleophiles. There is no detectable reaction of **3** with chloride ion. There are no detectable bimolecular reactions of bromide, iodide, or thiosulfate with the more hindered butanone derivative, 3-azido-1,3-dimethoxybutane.[4]

Structure–Reactivity Relationships. Effect of Alkoxy and Alkyl Groups. Swain–Scott correlations of log k_N for the reactions of **1b** and **2**, with the nucleophilic constants (*n*) for reactions of methyl iodide in methanol[13,14] are shown in Figure 2. The *s* values of 0.15 and 0.18, respectively, show that the sensitivity to the nucleophilicity of the attacking nucleophile is small, on the order of one-fifth that for attack on a methyl halide. The data for **1a** are less certain, but are consistent with an *s* value of ~0.1 ± 0.05.[15] Slopes of $s = 0.18$ and 0.25 were obtained for the reactions of **1b** and **2**, respectively, from correlations of a smaller number of points with nucleophilic constants for the reactions of methyl bromide in water[16] (not shown).

Bimolecular substitution reactions of (methoxymethoxy)-2,4-dinitrobenzene[7] and the *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion[8] are characterized by similar *s* values of 0.2–0.3, and the plot of log k_N for the reactions of **1b** against log k_N for the latter compound (Figure 3) is consistent with a linear correlation with a slope of 0.7. Least-squares analysis of the data, excluding the point for water, gives a slope of 0.8. This indicates that there is slightly less interaction with the attacking nucleophile in the transition states for the bimolecular reactions of **1a**, **1b**, and **2** than in the substitution reactions of methoxymethyl derivatives.

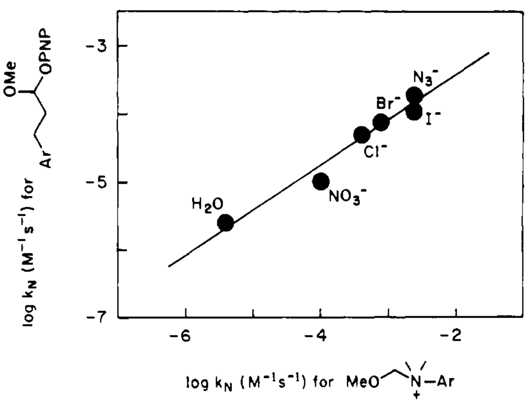
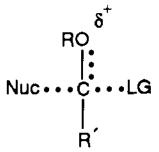


Figure 3. Comparison of nucleophilic reactivities toward 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane (**1b**) in water at 41 °C and ionic strength 2.0 ($NaClO_4$) and the *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion in water at 25 °C and ionic strength 1.0 ($NaClO_4$).[8] The line has a slope of 0.7.

These results are consistent with a transition state, **4**, in which there is electron donation from the RO group to the central carbon atom. The increase in bonding with the RO group is accompanied by a decreased interaction with the nucleophile and leaving group, compared with the transition state for substitution at the methyl group.



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The net effect of this electron donation from RO in **4** is to stabilize the transition state. This is evident in the increase of $>10^5$ for the rate of substitution by SCN^- on **3** compared with benzyl azide. Similar rate increases have been observed for nucleophilic reactions with methoxymethyl derivatives.[7,8,17]

We would describe this transition state as loose, or "exploded", because of the relatively weak interaction with the nucleophile and leaving group. This agrees with the results of molecular orbital analysis by Kost and Aviram.[18] However, a model proposed by Shaik describes transition states of this kind in different terms.[19]

The following are also consistent with a large amount of carbocation character in the transition state for nucleophilic substitution on acetal derivatives:

Azide is only 4-fold more reactive than chloride toward **1b**, while the estimated reactivity of 1-ethoxy-1-chloroethane in water is ~10^{10}-fold greater than that of **2**,[20] in which azide is the leaving group. This means that the transition state for this class of compounds is early with respect to bond-making to the nucleophile, but late with respect to bond-breaking to the leaving group.

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(13) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319–326. A value of $n = -0.27$ is used for water.[14]

(14) Dietze, P. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4549–4555.

(15) A plot of the logarithm of the ratio of the second-order rate constants for the reactions of nucleophiles with **1a** and **1b** against the *n* values for methyl iodide[13] has a slope that is not detectably different from zero, so that the sensitivity to the incoming nucleophile is the same for **1a** and **1b**.

(16) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141–147.

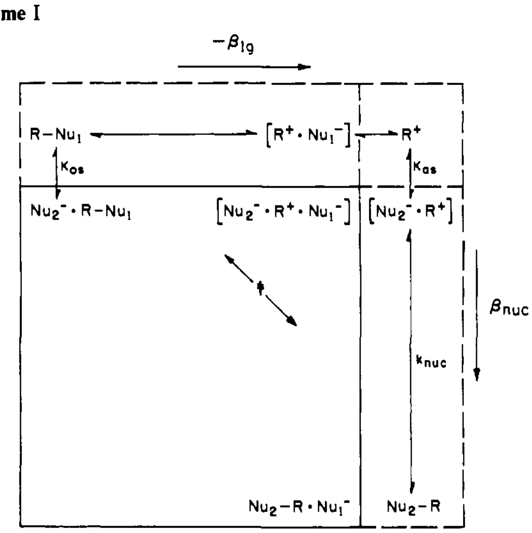
(17) Ballinger, P.; de la Mare, P. B. D.; Kohnstam, G.; Prestt, B. M. *J. Chem. Soc.* **1955**, 3641–3647.

(18) Kost, D.; Aviram, K. *J. Am. Chem. Soc.* **1986**, *108*, 2006–2013 and references therein.

(19) According to a theoretical treatment proposed by S. Shaik (*Prog. Phys. Org. Chem.* **1985**, *15*, 278–280) the transition state for reactions of this kind should not be regarded as "exploded", although there is considerable development of positive charge at the central atoms in the transition state.

(20) The estimated first-order rate constant for the hydrolysis of 1-ethoxy-1-chloroethane is 10^7 s^{-1}: Salomaa, P.; Kankaanperä, A. *Acta Chem. Scand.* **1966**, *20*, 1802–1810.

Scheme I



Azide ion exhibits a positive deviation of about 3-fold from the Swain–Scott correlations for both **1a** and **1b**, and the point for the reactions of **1b** and **2** with water shows a small negative deviation of 2- to 3-fold (Figure 2). A similar positive deviation for azide was observed for the reactions of the *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion[8] and is characteristic of substitution reactions that involve carbocation-like transition states.[8,14,21] Water shows a larger negative deviation of 6- to 10-fold in the methoxymethyl systems,[7,8] in which the reaction with water is thought to be bimolecular. However, there is no significant deviation of the rate constants for the reaction of azide or water with **1b** from the correlation with the rate constants for reactions of the *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion[8] in Figure 3. This suggests that the deviations from the Swain–Scott correlations for these reactions, at least for azide, arise from the different reactivity patterns of acetal systems compared with methyl halides.

The effect of the RO group on the structure of the transition state is in the direction that is expected for a substituent that stabilizes positive charge on the central atom. In the energy contour diagram shown in Scheme I, stabilization of the cationic structure in the upper right corner will tend to move the transition state toward this position of lower energy, perpendicular to the reaction coordinate. The increase in carbocation character corresponds to a decrease in the amount of bond-making and an increase in the amount of bond-breaking.[28]

Increased steric hindrance results in a later transition state for bond-making in some nucleophilic substitution reactions,[22] but there is no evidence of such an effect for these acetal derivatives. The lesser amount of bond-making in the transition state for the propionaldehyde compared with formaldehyde acetal derivatives may be attributed to electronic stabilization of the oxocarbenium ion when a hydrogen is replaced by an alkyl group. This lowers the energy of the carbocation species, R$^+$, in the top right-hand corner of Scheme I, and should result in a movement of the transition state perpendicular to the reaction coordinate toward the carbocation. This movement results in a decrease in β_{nuc}.

The S$_N$2 reactions of azide with the propionaldehyde derivatives **1** (and presumably **2**) are ~20-fold faster than with methoxymethyl (formaldehyde) derivatives.[23] In contrast, the S$_N$2 reactions of iodide are slower by factors of 200-fold for 1-chloropropane compared with methyl chloride and 50-fold for 2-chlorobutane compared with 1-chlorobutane.[24a] This shows that substitution of an alkyl group for one hydrogen atom in acetal systems stabilizes the carbocation-like S$_N$2 transition state. This stabilization is more than sufficient to overcome the increased steric hindrance of an alkyl substituent compared with hydrogen, which destabilizes the tighter transition state for S$_N$2 substitution of a simple aliphatic substrate.

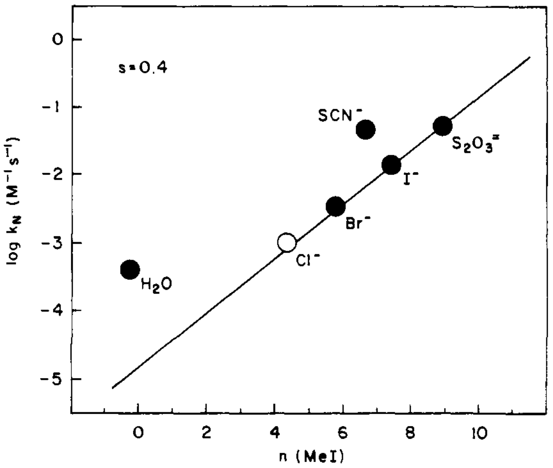


Figure 4. Swain–Scott correlation of log k_N against the *n* (MeI) value for the nucleophile[13] for the reaction of azidomethoxyphenylmethane (**3**) in water at 25 °C and ionic strength 2.0 (NaClO$_4$). The open circle for chloride is an upper limit based on the assumption that a 10% increase in k_{obsd} at 2.0 M chloride would have been detected. The point for water shows a positive deviation because solvolysis occurs through a dissociative mechanism.

However, additional alkyl substitution has the opposite result. Bimolecular concerted reactions of anionic nucleophiles with the propionaldehyde derivative **2** are observed, but the absence of bimolecular reactions of bromide, iodide, or thiosulfate ions with the butanone derivative 3-azido-1,3-dimethoxybutane, which hydrolyzes through an oxocarbenium ion intermediate with k_{HOH} = 2 × 10^9 s^{-1},[4] is consistent with the ~60-fold slower S$_N$2 reaction of iodide with 2-chlorobutane compared with propyl chloride[24a] and the small reactivity of tertiary systems with nucleophiles. This shows that substitution of a second alkyl group for hydrogen in acetal systems causes an increase in steric crowding at the central carbon atom that is more important than stabilization of the carbocation-like transition state for S$_N$2 substitution.

Structure–Reactivity Relationships. Effect of the Phenyl Group. The Swain–Scott correlation for reactions of the benzaldehyde derivative **3** with nucleophiles (Figure 4) shows that there is a much larger sensitivity to the strength of the attacking nucleophile than for **1b** and **2**, with an approximate value of s = 0.4 in a correlation with *n* values for the reaction of methyl iodide in methanol.[13] Correlation with the *n* values for methyl bromide in water[16] gives $s \approx 0.57$ (not shown). In both correlations the point for thiocyanate shows a positive deviation of 6-fold and was not included in the correlation. The most striking feature of the two Swain–Scott correlations for the reactions of **3** is that the points for water have positive deviations of 35- and 25-fold, respectively, from the lines for the anionic nucleophiles. This is consistent with a change in the mechanism of the reaction, from bimolecular substitution with nucleophiles that are stronger than chloride ion to reaction through a different pathway, with an oxocarbenium ion intermediate, for water.

Figure 5 shows that a correlation of log k_N for reactions of **3** with anionic nucleophiles against log (k_N/k_{HOH}) for 4-nitrobenzyl mesylate in 20:80 (v:v) acetonitrile:water[24b] is consistent with a slope of 1.0. The similar *s* values of 0.15 and 0.18 for the aryloxide and azide leaving groups of **1b** and **2**, respectively, show no in-

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[21] Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383–1396.

[22] le Noble, W. J.; Asano, T. *J. Am. Chem. Soc.* **1975**, *97*, 1778–1782. le Noble, W. J.; Miller, A. R. *J. Org. Chem.* **1979**, *44*, 889–891.

[23] The second-order rate constant for the reaction of (methoxymethoxy)-2,4-dinitrobenzene with azide at 39 °C is 1.4 × 10^{-3} M^{-1} s^{-1}.[7] The second-order rate constant for the reaction of azide with **1b** at 25 °C is ~3.5 × 10^{-5} M^{-1} s^{-1}. This may be combined with the corresponding rate constant for **1a** (Table I) to give a value of $\beta_{lg} \approx -0.7$, so that the estimated rate constant for the reaction of azide with a derivative of **1** with a 2,4-dinitrophenoxide leaving group at 41 °C is 2.4 × 10^{-2} M^{-1} s^{-1}.

[24] (a) Hine, J. S. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1962; p 176. (b) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 5880–5886.

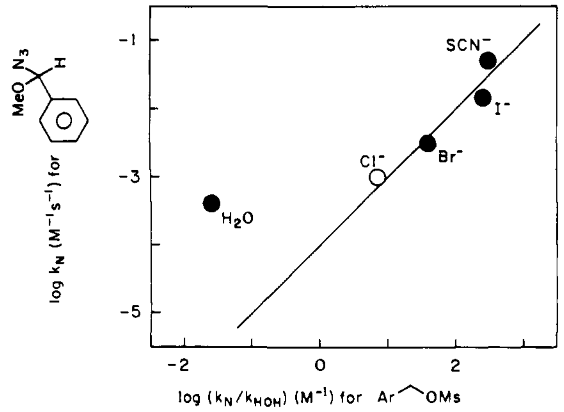
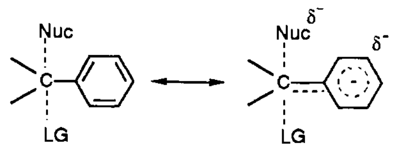


Figure 5. Comparison of nucleophilic reactivity toward azidomethoxyphenylmethane (**3**) in water at 25 °C and ionic strength 2.0 ($NaClO_4$) and nucleophilic selectivity toward 4-nitrobenzyl mesylate in 20:80 (v:v) acetonitrile:water at 25 °C and ionic strength 0.5 ($NaClO_4$).[24b] For **3** the open circle for chloride is an upper limit, based on the assumption that a 10% increase in k_{obsd} at 2.0 M chloride would have been detected, and the point for water represents a dissociative mechanism. The line has a slope of 1.0.

dication of any large effect of the leaving atom on the amount of bond formation to the incoming nucleophile in the transition state for substitution on propionaldehyde derivatives.

The introduction of the phenyl group also causes a large increase in reaction rate: the nucleophilic reactions with **3** are 100-fold faster than with **2** (Table I). This is the first example of the "benzylic effect" in acetal systems. The rate increase of 100-fold is similar to the 200-fold increase in the reactivity of iodide ion with benzyl chloride compared with propyl chloride,[24a] although it is smaller than some rate increases of ~10^3-fold.[25]

This effect of phenyl substitution may represent delocalization of electron density into the benzene ring in the transition state, as shown in **5**. This will stabilize the transition state and result in an increased interaction with the lone pair electrons of the nucleophile that accounts for the increase in s value for **3** compared with **2**. It is analogous to the effect of an α-carbonyl group, which stabilizes the transition state and results in an increased sensitivity to the nucleophile;[26] it can also be described by a molecular orbital treatment.[18] It is known that the benzylic effect requires a geometry that permits conjugation with the reaction center.[27] The relative amounts of electron withdrawal and donation presumably vary with the nature of the system.



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The phenyl group might have been expected to stabilize the cationic structure in Scheme I and cause movement of the transition state toward this structure, in the same direction as the RO substituent, but the opposite result is observed in the acetal derivatives. The difference presumably arises because the benzene ring can either accept or donate electrons. The increased interaction with nucleophiles in **3** suggests that when there is strong electron donation from the RO group to the central carbon atom, the benzene ring may act as an electron acceptor (**5**). The activating effect of such an electron acceptor is known to be larger with stronger nucleophiles.[18,29] This is consistent with the 2.3-fold increase in sensitivity to the strength of the nucleophile for the reactions of **3** compared with **2**, as shown in Figure 6. Furthermore, electron-withdrawing substituents on the benzyl group are known to increase the sensitivity of the rate to the basicity of the nucleophile, which suggests that there is more electron donation from the nucleophile in the transition state. This corresponds to a positive interaction coefficient $p_{xy'} = \partial\beta_{nuc}/\partial\sigma$.[28,30]

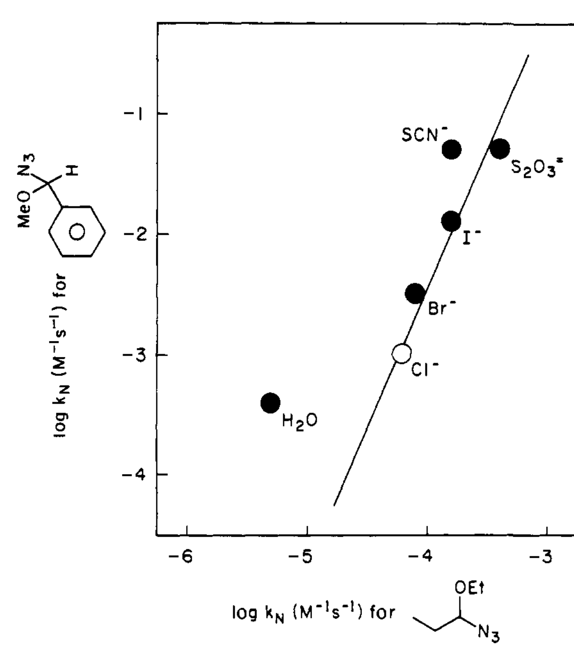
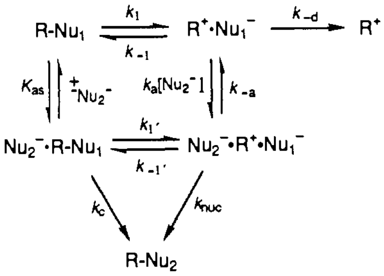


Figure 6. Comparison of nucleophilic reactivities toward azidomethoxyphenylmethane (**3**) and 1-azido-1-ethoxypropane (**2**) in water at 25 °C and ionic strength 2.0 ($NaClO_4$). The open circle for chloride is an upper limit for the former compound based on the assumption that a 10% increase in k_{obsd} at 2.0 M chloride would have been detected. The line has a slope of 2.3. The point for water shows a positive deviation because solvolysis occurs through a dissociative mechanism.

Scheme II



Mechanisms. Anionic Nucleophiles. Scheme II shows three distinct pathways by which bimolecular nucleophilic substitution can occur. Reaction by the upper pathway is a mechanism of the type proposed by Sneen[31] that involves ionization of the substrate to give an ion pair (k_1), followed by diffusion of the nucleophile up to the ion pair ($k_a[Nu_2^-]$) and collapse to products (k_{nuc}).

These mechanisms may "merge", in the sense that one may be replaced by another when there is a reversal in the relative stabilities of the transition states for the two mechanisms, but they do not represent portions of a "spectrum" of mechanisms. The different mechanisms have different compositions of the transition

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(25) Slator, A.; Twiss, D. F. *J. Chem. Soc.* **1909**, *95*, 93. Finkelstein, H. *Ber. Chem. Ges.* **1910**, *43*, 1528–1535. Conant, J. B.; Kirner, W. R. *J. Am. Chem. Soc.* **1924**, *46*, 232–252.

(26) Yousaf, T. I.; Lewis, E. S. *J. Am. Chem. Soc.* **1987**, *109*, 6137–6142 and references therein.

(27) King, J. F.; Tsang, G. T. Y. *J. Chem. Soc., Chem. Commun.* **1979**, 1131–1132. Lynas-Gray, J. I.; Stirling, J. M. *J. Chem. Soc., Chem. Commun.* **1984**, 483–484.

(28) Hughes, E. P.; Ingold, C. K.; Shapiro, U. G. *J. Chem. Soc.* **1936**, 225–236. Bunnett, J. F. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 225–235. Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511–527 and references therein.

(29) Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* **1978**, 327–328.

(30) See, for example: Hudson, R. F.; Klopman, G. *J. Chem. Soc.* **1962**, 1062–1067. Ballistreri, F. P.; Maccarone, E.; Mamo, A. *J. Org. Chem.* **1976**, *41*, 3364–3367. Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288–3294.

(31) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46–53 and references therein.

state, different numbers of energy barriers along the reaction path, and different sequences of assembly of the reactants. Use of the terms "merging" and "spectrum" is likely to confuse the analysis of reaction mechanisms, because they suggest that different mechanisms cannot be clearly distinguished from one another.

For a two-step reaction it has been shown[5,6] that if the barrier for collapse of the triple ion complex $Nu_2^-{\cdot}R^+{\cdot}Nu_1^-$ (Scheme II) back to starting materials is smaller than the barrier for diffusion away of Nu_2^- ($k_{-1}' > k_{-a}$), then the lowest energy pathway for the stepwise bimolecular substitution reaction necessarily involves preassociation of Nu_2^- with the starting materials before the first step occurs (K_{as} and k_1', Scheme II). However, for the triple ion complex to be an intermediate in a potential well it must exist for longer than a bond vibration ($\sim 10^{-13}$ s), so that there is a significant barrier for its collapse. If there is no significant barrier for the reaction of either Nu_1^- or Nu_2^- within the triple ion complex, then the complex does not exist as an intermediate and the reaction must be concerted (k_c).[5,6]

The following argument shows that bimolecular reaction through the upper pathway, by a Sneen-type mechanism, cannot be a significant portion of an observed second-order reaction in good ionizing solvents such as water.

(1) This mechanism involves the reversible ionization of the substrate to give an ion pair, so that collapse of the ion pair back to starting materials (k_{-1}) must be faster than its encounter with the nucleophile ($k_a[Nu_2^-]$) and its diffusional separation (k_{-d}) to give the free carbocation, R^+ (Scheme II). However, in a good ionizing solvent such as water, the reaction with dilute nucleophiles will be unimolecular through R^+, rather than bimolecular. This is because in a good ionizing solvent the first-order rate constant k_{-d} will be larger than the pseudo-first-order rate constant $k_a[Nu_2^-]$ when Nu_2^- is dilute.[32,33] Therefore, the ion pair separates before diffusional encounter with the nucleophile can occur.

(2) In good ionizing solvents such as water, the rate constant for diffusional separation of an ion pair is essentially equal to that for diffusion of a nucleophile out of a triple ion complex, i.e. $k_{-d} = k_{-a}$. Therefore, the requirement $k_{-1} > k_{-d}$ means that the rate constant for collapse of the triple ion complex to starting materials ($k_{-1}' \approx k_{-1}$) is larger than that for diffusion away of the nucleophile, i.e. $k_{-1}' > k_{-a}$. This is the requirement for a preassociation mechanism, so that a preassociation mechanism will be followed. In other words, in good ionizing solvents such as water, the requirements for bimolecular substitution by diffusion-controlled trapping of a reversibly formed ion pair are the very requirements for an enforced preassociation mechanism through K_{as} (Scheme II). This preassociation mechanism may be stepwise (through k_1') or concerted (through k_c), depending on whether or not there is a barrier for collapse of the triple ion complex to either starting materials or products.[5,6]

The bimolecular reactions of **1a**, **1b**, **2**, and **3** in water must, therefore, represent preassociation stepwise or concerted mechanisms.

The following evidence shows that the bimolecular reactions proceed through concerted displacement, k_c, not through a two-step reaction, k_1' and k_{nuc}.

(1) If there is an intermediate, then the reaction involves both a bond-breaking (k_1') and a bond-making (k_{nuc}) step and either may be rate limiting, depending on the relative nucleophilicities of Nu_1^- and Nu_2^-. If the leaving group is the better nucleophile, then k_{-1}' is larger than k_{nuc}, the bond-making step will be rate limiting (k_{nuc}), and different nucleophiles may have different reactivities. If the entering group is a better nucleophile than the leaving group, then k_{nuc} is larger than k_{-1}', k_1' is rate limiting, and all such nucleophiles will react with the same rate constant. This change in rate-limiting step should lead to a corresponding break in the Swain–Scott correlation, from a line of positive slope to a line of zero slope.

There is no evidence for a break in the Swain–Scott correlation for **1b** (Figure 2), for which the break is expected around the point for bromide,[34] and the data are correlated by a single line. However, the possibility of a break from a line of very shallow slope to one of zero slope for this compound cannot be excluded. Stronger evidence for the absence of a break is the absence of curvature in the plot of log k_N for **1b** against log k_N for the *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion (Figure 3), for which a concerted mechanism is established.[8] The positive deviation of the rate constant for azide from the Swain–Scott correlation by ~3-fold for **1b** is not expected for a stepwise reaction, because for this nucleophile bond-breaking (k_1') would be rate limiting.

For the reaction of **2**, most of the nucleophiles examined are weaker than the leaving azide ion, so that, if the reaction were stepwise, the bond-making step (k_{nuc}) would be rate limiting. Conversely, for **1a** all of the nucleophiles studied are stronger than the leaving acetate ion, so that k_1' would be rate limiting. The *s* values for the two compounds are similar ($\sim 0.1 \pm 0.05$ and 0.18, respectively), which suggests that the reaction of one or both of these compounds is concerted. However, the differences in reactivity of different nucleophiles toward **1a** are not large (Table I) so that the slope of the Swain–Scott correlation for this compound may be close to zero.

(2) The rate constant for the reaction with water of the oxocarbenium ions derived from **1** and **2** is $\geq 2 \times 10^{10}$ s^{-1},[4,9] and the reaction with strong nucleophiles within an encounter pair should be much faster. An estimate of the rate constant k_{nuc} (eq 1) for

$$R^+ + N_3^- \overset{K_{as}}{\rightleftharpoons} R^+{\cdot}N_3^- \overset{k_{nuc}}{\rightleftharpoons} R\text{-}N_3 \qquad (1)$$

the reaction of azide within an ion pair can be made by combining the value of k_{HOH} for these oxocarbenium ions with the known rate constant ratio $k_{az}/k_{HOH} \approx 10^6$ M^{-1} for the activation-limited reactions of azide and water with free carbocations.[35] An association constant of $K_{as} = 0.3$ M^{-1} for encounter complex formation[33] and the relationship $k_{nuc} = k_{az}/K_{as}$ then give a rate constant for the reaction of azide within the oxocarbenium ion encounter complex of $k_{nuc} \geq 10^{16}$ s^{-1}. This is much larger than a bond vibration frequency ($\sim 10^{13}$ s^{-1}) so that the oxocarbenium ions derived from **1** and **2** will not have a significant lifetime if they are in contact with a correctly oriented azide ion. Therefore, the ion pair or a triple ion complex cannot exist as an intermediate, and the bimolecular reactions with azide must be concerted.

Similarly, the value of $k_{HOH} = 2 \times 10^9$ s^{-1} for the oxocarbenium ion derived from **3**[4] and the manipulations described above give a value of k_{nuc} for azide of 10^{15} s^{-1}, so that the (degenerate) bimolecular reaction of **3** with azide must also be concerted. The calculation of k_{nuc} values for the poorer nucleophiles such as chloride and bromide is less certain, because there is relatively little available data for their reactivities compared with water in aqueous solution.[36,37] However, the bimolecular reactions of these nucleophiles with **1a**, **1b**, **2**, and **3** must be concerted, because there is no significant barrier for recombination of the leaving groups of these compounds with the oxocarbenium ions within the triple ion complex (see below).

Most of the substitution products that are formed in these bimolecular reactions are considerably less stable than the starting materials, so that they do not accumulate during the reaction. The

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[32] The estimated rate constant for separation of a carbocation–azide ion pair is 1.6×10^{10} s^{-1}.[33]

[33] Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383.

[34] The *n* value of 5.75 for the reaction of phenoxide ion with methyl iodide in methanol[13] is almost identical with that for bromide and provides an upper limit on the value for 4-nitrophenoxide ion.

[35] 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.

[36] The ratio $k_{Br}/k_{SOH} = 160$ M^{-1} in 80% EtOH for the reactions of bromide and solvent with the carbocation derived from 9-(α-bromoanisylidene)anthrone[37] is a lower limit for the value in water. When combined with $k_{HOH} = 2 \times 10^9$ s^{-1} for the oxocarbenium ion derived from **3**[4] and a value of $K_{as} = 0.3$ M^{-1},[33] the relationship $k_{nuc} = k_{Br}/K_{as}$ gives a value of $k_{nuc} \geq 10^{12}$ s^{-1} for bromide, so that the oxocarbenium ion derived from **3** may have a very short lifetime in the presence of Br$^-$.

[37] Rappoport, Z.; Apeloig, Y.; Greenblatt, J. *J. Am. Chem. Soc.* **1980**, *102*, 3837–3848.

overall observed reaction is then hydrolysis, so that the concerted substitution reactions represent nucleophilic catalysis of hydrolysis.

Mechanisms. Water. The oxocarbenium ions derived from **1**, **2**, and **3** react with solvent water with rate constants of ~2–5 × 10^{10}, 2 × 10^{10}, and 2 × 10^9 s^{-1}, respectively,[4,9] so that these intermediates have short but significant lifetimes in aqueous solution.

The positive deviation of 35-fold of the rate constant for water from the Swain–Scott correlation for the reaction of **3** with anionic nucleophiles (Figure 4) is consistent with a change in the mechanism of the reaction from concerted substitution with good nucleophiles to a stepwise reaction, through an oxocarbenium ion, with water. However, water shows small (2- to 3-fold) negative deviations from the Swain–Scott correlations for the reactions of **1** and **2**, even though the reaction is stepwise. The reaction of water with methoxymethyl derivatives is probably (but not definitely) concerted because the methoxymethyl cation has a very short or no lifetime in aqueous solution,[2-4] and the rate constants show larger (6- to 10-fold) negative deviations from the Swain–Scott correlations.[7,8]

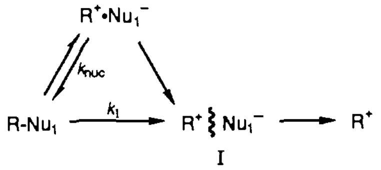
These results illustrate the behavior that is expected when the increasing stability of a putative carbocation intermediate results in a crossing of the mechanistic borderline, from a reaction that is probably concerted because the "intermediate" has no significant lifetime in the presence of solvent, to a reaction that proceeds through an intermediate with a significant lifetime in the presence of solvent, but not in the presence of stronger nucleophiles. At the borderline this may not result in an enhanced reactivity of the solvent in the stepwise reaction compared with the reactivity of stronger nucleophiles in the concerted reactions.[38] However, as the carbocation becomes more stable, the rate constant for formation of the intermediate is expected to increase more rapidly than the rate constants for concerted displacement by stronger nucleophiles, so that the solvent reaction will exhibit a positive deviation from a structure–reactivity correlation. When the cation becomes still more stable this deviation becomes still larger, and the concerted substitution reactions of dilute nucleophiles become insignificant.[39]

Effect of Leaving Group Reactivity. A reaction can be forced to proceed through a concerted mechanism because the cationic "intermediate" has no lifetime *in* the presence of the nucleophile, the leaving group, or both. It was shown above that the oxocarbenium ions derived from **2** and **3** have no significant lifetime in an intimate ion pair with azide ion. This means that the bimolecular substitution reactions of **2** and **3**, even with weak nucleophiles, must be concerted, because there is no barrier for the collapse of the triple ion complex (Scheme II) containing the leaving group; i.e. this complex cannot exist.

The N_+ value of >2.95 for the reaction of acetate ion with carbocations[40] provides an approximate lower limit on the value for 4-nitrophenoxide ion. The oxocarbenium ion derived from **1a** and **1b** reacts with water with $k_{HOH} \geq 2 \times 10^{10}$ s^{-1}.[9] The ratio of $k_{AcO}/k_{HOH} = 10^3$ M^{-1} and the value[33] of $K_{as} = 0.3$ M^{-1} give a rate constant of $k_{nuc} = k_{AcO}/K_{as} \geq 10^{14}$ s^{-1} for collapse of the ion pair containing acetate ion and the oxocarbenium ion, so that this ion pair does not exist if an oxygen atom is in position to react. Therefore, the concerted bimolecular substitution reactions of **1a** and **1b**, like those of **2** and **3**, are enforced because the triple ion complex containing the leaving group does not exist. The absence of a significant lifetime of the ion pair containing the leaving group and the oxocarbenium ion provides additional evidence against a Sneen-type mechanism for the bimolecular reactions of **1**, **2**, and **3**.

Although a reaction can be forced to be concerted if the leaving group is a good nucleophile, a significant bimolecular reaction will only be observed if the incoming group is also a good nucleophile that will assist leaving group expulsion. A concerted reaction could occur with a weak nucleophile that is in the correct position for reaction when the leaving group departs, but this will not give much product with a dilute nucleophile because of the small value of K_{as} (Scheme II).

Scheme III



In solvolysis the incoming nucleophilic reagent is always present when bond-breaking occurs, although it may not be oriented correctly for reaction. Scheme III shows two possible mechanisms for the ionization of a substrate to give a free carbocation. The upper pathway involves formation of an intimate ion pair, followed by separation or rotation of the components to give a species (I) in which the leaving group is not in position to give internal return. However, if the intimate ion pair does not have a significant lifetime, then the ionization must occur by the lower pathway of Scheme III (through k_i) and leads directly to the formation of I; the intimate ion pair might be the transition state for the k_i step. The lower pathway of Scheme III must be followed in all solvolysis reactions through a carbocation intermediate in which the intimate ion pair containing R^+ and the leaving group has no barrier for collapse back to the reactant.

The stepwise reactions of **1**, **2**, and **3** with water proceed through k_i, because there is no significant lifetime of the oxocarbenium ion in the presence of the leaving group for these compounds. Any reaction of the substrate with water that occurs before departure of the leaving group must, therefore, be concerted. However, the following exclude an important contribution of such a concerted process to the reaction of **3** with water.

(1) The hydrolysis of this compound is subject to common ion inhibition by added azide ion, and there is a good fit of all the experimental inhibition data to the equation for a mechanism that includes only a stepwise pathway through an oxocarbenium ion intermediate.[4] Therefore all of the reaction of **3** with water can be inhibited by azide ion, so that concerted displacement of the azide leaving group by water is not important.

(2) The rate constant for the reaction of this compound with water is ~35-fold greater than that predicted by the Swain–Scott correlation (Figure 4), which suggests that essentially 100% of the reaction with water is stepwise.

These results indicate that water does not provide significant nucleophilic assistance to leaving group departure and that ionization gives the separated ion pair, I; ionization to $H_2O{\cdot}R^+{\cdot}N_3^-$ does not occur, because formation of this intimate ion pair should result in a concerted reaction with water.

Concurrent S_N1 and S_N2 Mechanisms for the Reactions of Anionic Nucleophiles. The common ion inhibition of the hydrolysis of **3** by azide ion[4] shows that azide can react with **3** by a $D_N + A_N$ (S_N1) mechanism. The partitioning ratio for reaction of the oxocarbenium ion intermediate with azide and water is $k_{az}/k_{HOH} = 2.6$ M^{-1}, so that one azide ion has the same trapping ability as 140 water molecules. Bromide is only about 3-fold less reactive than azide toward unstable carbocations,[41] so that $k_{Br}/k_{HOH} \approx 0.9$ M^{-1}, and there must be significant trapping of the oxocarbenium ion intermediate by bromide also. The substitution reaction of bromide with **3** does not give a stable product. However, from the known values of k_N for bromide (Table I), k_{solv},[42] and $k_{Br}/k_{HOH} = 0.9$ M^{-1}, the ratio of the rate constants

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[38] A change from a concerted to a stepwise mechanism need not result in a deviation from a structure–reactivity correlation: Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937–1951.

[39] The unexpectedly large value of *s* for the concerted reactions of **3** with dilute anionic nucleophiles allows their detection despite the large positive deviation of the rate constant for water from the Swain–Scott correlation.

[40] Ritchie, C. D. *J. Am. Chem. Soc.* **1975**, *97*, 1170–1179.

[41] In 1:1 (v:v) TFE:H_2O the 1-(4-methoxyphenyl)-2,2,2-trifluoroethyl carbocation reacts with azide at the diffusion-controlled limit; the partitioning ratios for its reaction with azide and solvent and azide and bromide are 90 M^{-1} and ~3, respectively: Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455–1464.

[42] k_{solv} is the observed rate constant for solvolysis in the presence of $NaClO_4$ at the ionic strengths indicated in Table I.

for bimolecular and unimolecular substitution of **3** by 1.0 M bromide can be calculated from eq 2 to be 0.33. Therefore, at 1.0 M bromide, the substitution reaction of bromide with **3** occurs ~25% by an A_ND_N (S_N2) mechanism and ~75% by a concurrent $D_N + A_N$ mechanism.[43]

$$k(S_N2)/k(S_N1) = k_N[Br^-]\{(k_{Br}[Br^-]/k_{HOH}) + 1\}/\{k_{solv}(k_{Br}[Br^-]/k_{HOH})\} \quad (2)$$

The concerted bimolecular reaction of azide (and probably bromide[36]) with **3** is enforced by the absence of a significant lifetime of the oxocarbenium ion in its presence; but the concurrent stepwise reaction with azide or bromide can occur if the nucleophile is not present when R^+ is formed, because the oxocarbenium ion does have a significant lifetime in the presence of solvent water.

These concurrent mechanisms are shown in the reaction coordinate diagram of Scheme I, in which diffusional steps are shown in the "wings".[21] When a preassociation complex between the substrate and the nucleophile is formed (K_{as}), enforced concerted substitution occurs inside the box of Scheme I. The stepwise $D_N + A_N$ reaction occurs around the outside wings, through R^+.

Concurrent concerted and stepwise reactions of azide and solvent, respectively, occur with some 1-phenylethyl derivatives,[21] but we know of no other significant concurrent A_ND_N and $D_N + A_N$ substitution reactions with a single nucleophile in aqueous solution. Concurrent mechanisms for the reaction of **1a** with azide are predicted to be of minor significance;[44] this agrees with the observation that in the presence of 1.0 M azide the yield of the stable α-azido ether is 48% and k_{obsd} increases 1.8-fold, which predicts a yield of 45%.[9]

Bimolecular Reactions of Glycosyl and Tetrahydropyranyl Acetal Derivatives. The concerted bimolecular reactions of the acetal derivatives of propionaldehyde and benzaldehyde described here are enforced by the absence of a significant lifetime of the oxocarbenium ion intermediates in the presence of good nucleophiles. Therefore, it is expected that those acetals that generate oxocarbenium ions of similar or higher reactivity toward water would also undergo bimolecular substitution. This has been observed for methoxymethyl (formaldehyde) derivatives, where the estimated rate constant for reaction of the oxocarbenium ion with water is 10^{12}–10^{15} s^{-1}.[2-4] The pH-independent hydrolysis of 2,4-dinitrophenyl-β-D-glucoside[45] is ~20-fold slower than that of (methoxymethyl)-2,4-dinitrobenzene,[7] which suggests that the stabilities of the two oxocarbenium ion "intermediates" may not differ greatly; we have estimated[4] that the rate constant for reaction of the glucosyl cation with water is $k_{HOH} \sim 10^{11}$–10^{12} s^{-1}. The rate constant for the pH-independent hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran[46] is ~2-fold larger than that for **1b**, and the structurally similar oxocarbenium ions should have similar reactivities toward water. The simple expectation, then, is that glycosides and tetrahydropyranosides, like **1**, **2**, and **3**, should undergo bimolecular enforced concerted reactions with good nucleophiles.

However, there is considerable steric hindrance in the S_N2 transition state for a cyclohexyl halide and the bimolecular reaction of iodide ion with cyclohexyl bromide is ~100-fold slower than that with isopropyl bromide.[47] Similarly, Eliel and Ro[48] found that the bimolecular reaction of thiophenoxide ion with 2-butyl tosylate is 15-fold faster than that with cyclohexyl tosylate. Therefore, the bimolecular reactions of glycosides and tetrahydropyranosides are expected to be considerably slower than the reactions of the corresponding acyclic compounds.

Kirby et al.[7] found that the observed rate constant, at constant ionic strength, for the pH-independent hydrolysis of 2-(3,4-dinitrophenoxy)tetrahydropyran, a cyclic analogue of **1**, is essentially unchanged by the addition of strong nucleophiles such as azide and thiosulfate, at concentrations of up to 1.0 M. The increase in k_{obsd} for the reaction of **1b** with 1.0 M azide is 120% (Table I). If the second-order reaction of this compound with azide were diminished 15-fold, then the increase in k_{obsd} at 1.0 M azide would be only 8%. The leaving groups of **1b** and 2-(3,4-dinitrophenoxy)tetrahydropyran are similar, and the decrease of >10-fold in the rate of S_N2 reactions for cyclic substrates with six-membered rings compared with acyclic systems[47,48] would render bimolecular reactions of the latter compound too slow to detect at the concentrations of the nucleophile examined.

Bennet and Sinnott[49] have examined the effects of added nucleophiles on the rate of reaction of glycosyl isoquinolinium salts in aqueous solution. Although the effects are small, azide is about 2-fold more reactive than most other anions toward an α-4-bromoisoquinolinium derivative. In view of the steric constraints for nucleophilic substitution on cyclic compounds, this represents a significant rate increase and is consistent with nucleophilic participation; correction for a steric effect would give a rate increase of ~20–30-fold. If an enzyme can interact with its substrate in such a way as to overcome steric hindrance, intramolecular nucleophilic assistance could then produce a significant contribution to the rate increase of the bound substrate from catalysis.

Capon and Thacker[50] have reported that in aqueous solution the acid-catalyzed cyclization of D-glucose dimethyl acetal to give furanosides is 340-fold faster than the expected rate of hydrolysis of the acetal functionality. It was suggested that a concerted displacement of the methanol leaving group by the 4-hydroxyl group takes place, and that if there is nucleophilic assistance to leaving group departure by a weakly nucleophilic hydroxyl group, then there should be considerably more assistance with stronger nucleophiles.

The solvolysis of α- and β-D-glucopyranosyl derivatives in mixtures of ethanol and trifluoroethanol gives both inverted and retained ether products,[51] and the selectivities k_{EtOH}/k_{TFE} of up to 20 vary widely with both the leaving group and the stereochemical course of the reaction. This shows that both the incoming nucleophile and the leaving group are involved in the product-determining transition state, but this interaction may not represent concerted nucleophilic substitution.[4,51]

Conclusions

We have shown that acetal derivatives of propionaldehyde and benzaldehyde undergo hydrolysis through oxocarbenium ion intermediates,[4] but also undergo concerted bimolecular substitution reactions with anionic nucleophiles. The concerted mechanism appears when the oxocarbenium ion "intermediate" has no significant lifetime in the presence of the attacking nucleophile; it is *enforced* because a stepwise mechanism is not possible. Glycosyl cations are even shorter lived,[4] so that concerted nucleophilic displacement by catalytic groups of glycosyl transfer enzymes to give covalent glycosyl–enzyme intermediates should be possible; there is evidence for such intermediates with several of these enzymes.[52] A nucleophilic role for the carboxylate group of the

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(43) It is interesting that the procedure used to follow the reaction of bromide with **3** allows detection of only the concerted S_N2 reaction, because the α-bromo ether product is not stable under the experimental conditions; but it should be emphasized that the principal pathway for the substitution is in fact a stepwise S_N1 reaction.

(44) Eq 2 may be rewritten for the reaction of azide rather than bromide. The values of k_N and k_{solv} for **1a** (Table I), and $k_{as}/k_{HOH} \le 0.25$ M^{-1},[9] can then be combined to show that the substitution of **1a** at 1.0 M azide occurs less than 20% by an S_N1 pathway.

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Asp 52 residue in the active site of hen's egg white lysozyme has been considered; but there is no clear evidence to support the formation of a covalent intermediate for this enzyme.[53] Intramolecular participation of a neighboring carboxylate anion has been shown to accelerate acetal hydrolysis in a few non-enzymatic systems by up to 10^3-fold[54,55] and probably represents nucleophilic participation, but it may arise simply from electrostatic stabilization of the transition state by the negative charge.

The results reported here show that there should be no barrier for the collapse of an intimate ion pair containing a carboxylate anion and a glycosyl oxocarbenium ion. Therefore, assistance to leaving group displacement by a carboxylate group at the active site of an enzyme should represent concerted nucleophilic substitution that gives an acylal intermediate. However, it is possible that steric constraints at the active site prevent close approach and formation of a full covalent bond between the carboxylate group and C_1 of the glycoside. In this situation nucleophilic assistance can facilitate leaving group departure but the immediate product is an unstable species that can be described as either a stabilized oxocarbenium ion or a strained acylal.[56]

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Photochemical Isomerization of Cyclobutene Radical Cation to 1,3-Butadiene Radical Cation. A "Nonelectrocyclic" Ring-Opening Reaction?

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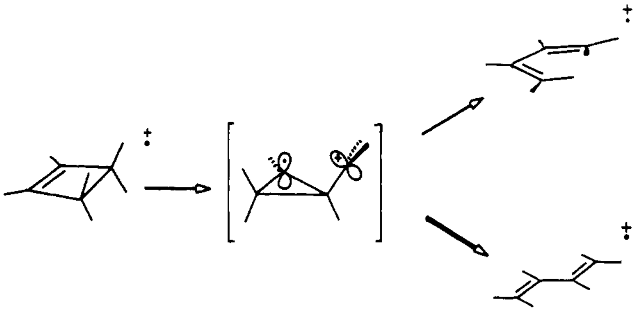
Abstract: The photochemical isomerization of cyclobutene radical cation ($\mathrm{CB}^{\bullet+}$) to 1,3-butadiene radical cation ($\mathrm{BD}^{\bullet+}$) is studied by optical as well as ESR/ENDOR spectroscopy in different cryogenic media. While in Ar matrices complete conversion of $\mathrm{CB}^{\bullet+}$ to $\mathrm{BD}^{\bullet+}$ occurs already upon radiolytic ionization, $\mathrm{CB}^{\bullet+}$ remains intact in various frozen glasses. Both methods indicate that photolysis of $\mathrm{CB}^{\bullet+}$ leads to *s-trans*-$\mathrm{BD}^{\bullet+}$. Theoretical considerations show that a rapid *thermal s-cis-* to *s-trans*-$\mathrm{BD}^{\bullet+}$ rearrangement can be excluded, while previous experience with longer polyene radical cations suggests that *s-cis*-$\mathrm{BD}^{\bullet+}$ should be observable at some stage of the reaction, if it occurs as a *photochemical* intermediate. It is, therefore, concluded that the photochemical $\mathrm{CB}^{\bullet+} \rightarrow \mathrm{BD}^{\bullet+}$ rearrangement must occur via a pathway leading *directly* to *s-trans*-$\mathrm{BD}^{\bullet+}$, perhaps analogous to that previously postulated for the corresponding thermal isomerization. The applicability of orbital correlation diagrams to problems of electrocyclic reactions of $\mathrm{M}^{\bullet+}$ is critically discussed.

Recently, pericyclic reactions of organic radical ions ($\mathrm{M}^{\bullet+}$) have attracted considerable attention.[1,2] Prototypical of these are electrocyclic ring-opening reactions of cyclic polyene cations,[3] in particular that involving the "parent" systems, cyclobutene radical cation ($\mathrm{CB}^{\bullet+}$) and 1,3-butadiene radical cation ($\mathrm{BD}^{\bullet+}$)[2,3a,4,5a] or aryl-substituted derivatives thereof.[5b,6,7] In the gas phase, the $\mathrm{CB}^{\bullet+} \rightarrow \mathrm{BD}^{\bullet+}$ isomerization proceeds with a very low activation barrier,[5] an observation that at first sight seems to contrast with the picture emerging from orbital or state correlation diagrams of the Woodward–Hoffmann type such as that for the title case depicted in Figure 1.[3a] These show that the reactant $\mathrm{M}^{\bullet+}$ ground states always correlate with product $\mathrm{N}^{\bullet+}$ *excited states* if synchronous concerted pathways (i.e., maintenance of a 2-fold axis or a mirror plane during the reaction) are followed. Furthermore, the ground states of the reactant cyclic precursor and the product open-chain polyene always transform differently with regard to the conserved symmetry element, and therefore, thermal $\mathrm{M}^{\bullet+}$ electrocyclic processes are invariably *state symmetry forbidden* along concerted pathways involving synchronous con- or disrotation.[3a]

Scheme I



The fact that thermal $\mathrm{M}^{\bullet+}$ electrocyclic reactions still proceed with considerable ease can be rationalized by comparing the

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