(C-1), 170.72 (OAc), 192.70, 193.40 (2 × SAc). Anal. Calcd for $C_{18}H_{29}O_{10}SP$: C, 43.23; H, 5.79; S, 12.82. Found: C, 43.30; H, 5.89; S, 12.79.

The aqueous layer (56.0 ppm) was evaporated to dryness. Examination of the resulting syrup (1.5 g) by TLC ($R_f$ 0.05 and 0.20, ethyl acetate–chloroform, 1:1, v/v) showed that it was composed of two products. The phosphorus-containing product was identified as the pyridinium 5,5-dimethyl-1,3,2-dioxaphosphorinanylthioate **16**. The $^{31}P$ NMR spectrum did not change when an authentic sample of the salt **16**, obtained independently, was added to the reaction mixture. The syrup was acetylated (15 mL $Ac_2O$/8 mL Py, 24 h), and the acetyl derivative was isolated by dilution of the reaction mixture with water (0 °C, 50 mL) and extraction with chloroform (3 × 20 mL). The aqueous layer contained the pyridinium salt **16** ($\delta(^{31}P)$ = 56.0 ppm). The combined chloroform extracts were washed successively with 1 N HCl, saturated aqueous $NaHCO_3$, and water. The chloroform solution was dried ($MgSO_4$) and filtered and the solvent removed to yield a colorless oil (0.8 g). Purification of the product by silica gel column chromatography gave the syrupy methyl 4,6-di-*O*-acetyl-2,3-dideoxy-2,3-epithio-α-D-mannopyranoside (**17a**). $[\alpha]^{20}_{578}$: +107 (*c* 2.06). IR (film): $\nu_{max}$ 1720 and 1700 $cm^{-1}$ (OAc). $^1H$ NMR ($CDCl_3$): δ 2.05 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 3.03 (s, 2 H, H-2, H-3), 3.42 (s, 3 H, $OCH_3$), 3.70–3.95 (m, 1 H, H-5), 3.95–4.20 (m, 2 H, H-6,6′), 4.95 (d, 1 H, $^3J_{4,5}$ = 10.0 Hz, H-4), 5.00 (s, 1 H, H-1). $^{13}C$ NMR ($CDCl_3$): δ 20.67 and 20.82 (2 × –OAc), 33.07 and 35.08 (C-2 and C-3), 63.38 (C-6), 65.54 (C-4 and C-5), 97.64 (C-1), 169.68 and 170.51 (2 × OAc). Anal. Calcd for $C_{11}H_{15}O_6S$: C, 47.85; H, 5.76; S, 11.6. Found: C, 47.89; H, 5.99; S, 11.8.

**Methyl 4,6-Di-*O*-acetyl-2-*S*-acetyl-3-*O*-(5′,5′-dimethyl-2′-thiono-1′,3′,2′-dioxaphosphorinan-2′-yl)-2-thio-α-D-altropyranoside (19a).** In order to isolate the thionophosphate **19**, the following procedure was applied on the basis of the results of $^{31}P$ NMR monitoring of the reaction progress. The altropyranoside **15** (1.5 g) was dissolved in dry pyridine (10 mL). After 0.5–1.0 h at ambient temperature when the signal corresponding to the thionophosphate **19** ($\delta(^{31}P)$ = 59.2 ppm) reached its highest intensity, acetic anhydride (5 mL) was added. After 24 h at 20 °C, the reaction mixture was worked up by a standard procedure. On evaporation of the chloroform extracts to the volume of 5 mL, colorless crystals precipitated and were filtered off. The precipitate (0.3 g), mp 136–137 °C, was identified (IR, $^1H$, $^{13}C$, and $^{31}P$ NMR) as the tri-*O*-acetyl derivative of **15**. The mother liquors were evaporated under vacuo. Silica gel column chromatography (eluent, benzene–acetone–chloroform, 3:1:1, v/v) of the residual oil gave the triacetyl derivative of **19** as colorless hexagonal crystals (0.3 g). Mp 95–96 °C (chloroform–diethyl ether). $[\alpha]^{20}_{578}$: +83 (*c* 1.9). IR: $\nu_{max}$ 1740 and 1730 (OAc), 1700 (SAc) and 690 $cm^{-1}$ (P=S). $^{31}P$ NMR ($CHCl_3$): δ 61.08. $^1H$ NMR ($CDCl_3$): δ 0.90 (s, 3 H, $CCH_3$ (e)), 1.28 (s, 3 H, $CCH_3$ (a)), 2.12 (s, 6 H, 2 × OAc), 2.40 (s, 3 H, SAc), 3.40 (s, 3 H, $OCH_3$), 3.60–4.5 (m, 8 H, H-2, H-6,6′, 2 × $OCH_2$ (a), 2 × $OCH_2$ (e)), 4.72 (d, 1 H, $^3J_{1,2}$ = 1 Hz, H-1), 4.83–5.41 (m, 2 H, H-3, H-4). $^{13}C$ NMR ($CDCl_3$): δ 20.90 ($CCH_3$ (e)), 21.94 ($CCH_3$ (a)), 32.23 (d, $^3J_{P,C}$ = 7.6 Hz, $C(CH_3)_2$), 45.39 (C-2), 55.69 ($OCH_3$), 62.56 (C-6), 65.22 (d, $^3J_{P,C}$ = 5.7 Hz, C-4), 73.40 (d, $^2J_{P,C}$ = 5.6 Hz, C-3), 100.8 (C-1). Anal. Calcd for $C_{18}H_{29}O_{10}S_2P$: C, 43.23; H, 5.79; S, 12.82. Found: C, 43.20; H, 5.69; S, 12.69.

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# Reactions of Anionic Nucleophiles with α-D-Glucopyranosyl Fluoride in Aqueous Solution through a Concerted, $A_ND_N$ ($S_N2$) Mechanism[1]

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*Contribution No. 1727 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254-9110.* *Received March 26, 1991*

**Abstract:** The first-order rate constants for the disappearance of α-D-glucopyranosyl fluoride in the presence of anionic nucleophiles show a linear dependence on the concentration of the nucleophile in water at 30.0 °C and ionic strength 2.0 M, maintained with KCl. The products from the reactions with azide and acetate anions, identified by $^1H$ NMR, show complete inversion of stereochemistry. These results provide evidence for a concerted bimolecular $S_N2$ (or $A_ND_N$) reaction of anionic nucleophiles at the anomeric carbon atom of α-D-glucosyl fluoride. The second-order rate constants for the nucleophiles follow the Swain–Scott correlation with a slope of $s$ = 0.18, indicating a small sensitivity of the displacement reaction to the nature of the nucleophile. No reaction is observed with uncharged amine nucleophiles, which do not provide electrostatic stabilization to the carbocation-like transition state for substitution. The solvolysis of α-D-glucosyl fluoride in mixtures of $H_2O$, EtOH, and $CF_3CH_2OH$, and in $H_2O$ and MeOH, has a high selectivity for reaction with water. The lifetime of the glucosyl cation is probably too short to allow diffusion, so that this suggests that the rate of formation of the unstable glucosyl oxocarbenium ion is increased in the presence of water molecules that stabilize the cationic transition state. These results are consistent with the conclusion that the glucosyl oxocarbenium ion exists for a short time in water but has no significant lifetime when it is in contact with a strong nucleophile, so that the reaction mechanism is forced to become concerted. They also suggest that glycosides may undergo concerted displacement reactions by anionic groups at the active sites of enzymes.

## Introduction

The stereochemistry of the products from the solvolysis of α- and β-glucose derivatives in methanol and in 1:1 ethanol–2,2,2-trifluoroethanol is consistent with a mechanism of hydrolysis of the pyranose ring through rate-determining formation of a short-lived oxocarbenium ion intermediate, followed by rapid trapping by a solvent molecule to give products with both inversion and retention of configuration (eq 1). Different product ratios are observed with different leaving groups, which shows that the lifetime of the cation is too short to allow diffusional equilibration with the bulk solvent, and the increased yield of the trifluoroethyl glycoside in the reaction with retention of configuration when

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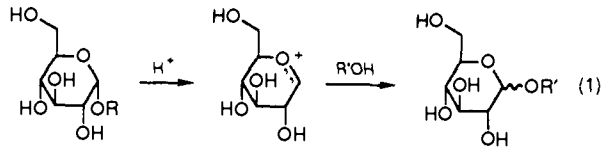

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fluoride ion is the leaving group suggests that hydrogen bonding of the fluoride ion to the hydroxyl group of trifluoroethanol in a solvent-separated ion pair facilitates the reaction with this relatively acidic alcohol.[2] A comprehensive examination of the primary and secondary hydrogen, carbon, and oxygen isotope effects on the rates of hydrolysis of methyl $\alpha$- and $\beta$-glucopyranosides in water has shown that the rate-determining transition states of these reactions closely resemble an oxocarbenium ion.[3]

The available evidence suggests that the glucosyl oxocarbenium ion has a significant lifetime in ethanol–trifluoroethanol and in water, but not when it is in contact with a good nucleophile.[2,4,5] Therefore, glucosyl derivatives with good leaving groups may react with nucleophilic reagents through a concerted bimolecular displacement mechanism that is "enforced", because the intermediate cation cannot exist when it is in contact with the nucleophile. The mechanism of substitution at carbon can be determined by the lifetime of an intermediate that is formed along the reaction path. It has been suggested that a stepwise reaction through the intermediate is preferred and will be followed if the intermediate exists; the reaction becomes concerted only when the intermediate does not have a significant lifetime when it is in contact with the nucleophilic reagent.[4,6]

A concerted $S_N2$ mechanism is described by $A_ND_N$, according to the nomenclature recommended by IUPAC for naming of reaction mechanisms.[7] The association of the nucleophile and dissociation of the leaving group, each with an unbonded electron pair, are indicated by $A_N$ and $D_N$, respectively. A stepwise preassociation mechanism, in which a short-lived intermediate is formed in the presence of the nucleophile, is described by $D_N{}^*A_N$.[7]

Second-order kinetics and inversion of configuration, which are characteristic of an $A_ND_N$ reaction mechanism, have been observed for the reaction of benzenethiolate anion with 2,3,4,6-tetra-*O*-methyl-$\alpha$-D-glucopyranosyl chloride in 1-propanol, a poor ionizing solvent.[8] This result is consistent with a concerted mechanism of substitution that is enforced by the absence of a lifetime for the intermediate when it is in contact with a strong nucleophile. On the other hand, Bennet and Sinnott observed little or no increase in the rate of disappearance of aldopyranosyl derivatives with equatorial leaving groups in the presence of a number of anionic and neutral nucleophiles in water at 25–80 °C, and concluded that these compounds react through a stepwise, $D_N + A_N$ or $D_N{}^*A_N$ ($S_N1$) mechanism.[3] However, small increases of 1.8-fold over the rate in water were observed in the presence of 1.0 M azide ion. It is possible that the absence of larger rate increases in these reactions arises from the large carbenium ion character of the transition state in a concerted $A_ND_N$ mechanism, in which the small amount of bond making in the transition state results in a small sensitivity to the nature of the nucleophile, and from steric hindrance to nucleophilic attack on cyclic substrates. Steric hindrance decreases the rate constant by a factor of $\sim$100 for reaction of $I^-$ with cyclohexyl bromide compared with isopropyl bromide.[9] Appropriately located carboxylate groups have been shown to increase the rate of disappearance of sugar derivatives and related compounds by intramolecular assistance, but the rate increases are generally small and it is not clear whether they represent nucleophilic substitution or electrostatic stabilization of the developing positive charge of an oxocarbenium ion.[10]

The hydrolysis of substituted acetophenone dimethyl ketals gives solvent-equilibrated oxocarbenium ions with lifetimes that were estimated to be between $10^{-5}$ and $10^{-8}$ s by diffusion-controlled trapping with sulfite dianion[11] and by extrapolation to zero acid concentration of directly measured rates of reaction with water in the presence of strong acids.[12] The lifetimes of oxocarbenium ions formed from derivatives of substituted benzaldehydes and aliphatic aldehydes have been shown to be in the range of $2 \times 10^{-8}$ to $5 \times 10^{-11}$ s by a quantitative evaluation of common ion inhibition by azide ion of the hydrolysis of the corresponding $\alpha$-azido ethers.[5] A short extrapolation of these lifetimes suggested that the glucosyl oxocarbenium ion has a small, but significant, lifetime in water of $\sim 10^{-12}$ s. Therefore, it would be expected that this oxocarbenium ion would not have a significant lifetime when it is in contact with nucleophiles that are stronger than water.

The methoxymethyl oxocarbenium ion, $CH_3OCH_2^+$, has been estimated to have a similar or shorter "lifetime" of $\sim 10^{-12}$–$10^{-15}$ s in water,[5] and methoxymethyl derivatives were shown to undergo bimolecular substitution reactions with added nucleophilic reagents, as predicted by these lifetimes.[13,14] However, the values of $\beta_{lg} = -0.7$ to $-0.9$ and $\beta_{nuc} = 0.14$ for these reactions indicate an "exploded" transition state for the $S_N2$ displacement, with little bond formation to the incoming nucleophiles and almost complete breaking of the bond to the leaving group in the transition state.

Catalysis by enzymes of the hydrolysis of glycosidic bonds and of glucosyl-transfer reactions also proceeds through exploded or dissociative transition states, as suggested by the secondary isotope effect of $k_H/k_D = 1.11$–$1.13$ for 1-deuterium-substituted substrates of lysozyme and $\beta_{lg} = -0.93$ for $\beta$-galactosidase-catalyzed hydrolysis of $\beta$-1-pyridinegalactopyranoside salts.[15] However, the reactions do not occur through dissociation of the leaving group to give a glucosyl oxocarbenium ion intermediate at the active site because glucosyl transfer to a saccharide acceptor in dilute solution is faster than hydrolysis in 55 M water.[11] If such an unstable intermediate were formed, it would be expected to react with water at a much faster rate than it could react with dilute acceptor, even if the acceptor reacted at a diffusion-controlled rate. The structure of the lysozyme chitotriose complex, determined by X-ray diffraction, indicates that the carboxylic acid group of Glu-35 and the carboxylate ion of Asp-52 are in close proximity to the reaction center so that they could participate in the catalytic process as general-acid–base catalysts and by stabilizing the oxocarbenium ion by partial bond formation.[16] A catalytically competent intermediate that is covalently bound to $\beta$-glucosidase through the carboxylate group of a glutamate residue has been isolated and characterized, which is consistent with nucleophilic involvement of the carboxylate group in catalysis.[17]

We have examined the reactions of $\alpha$-D-glucopyranosyl fluoride, **1**, with added nucleophiles in water. It has been reported previously that the rate of hydrolysis of **1** to give glucose is increased in the presence of nucleophilic buffers.[18] We have observed bimolecular substitution reactions with anionic nucleophiles at the anomeric carbon atom of $\alpha$-D-glucosyl fluoride through a

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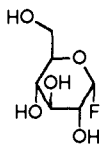

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concerted $A_ND_N$ mechanism. The reactions proceed with inversion of configuration at the 1-carbon atom and follow a Swain–Scott correlation with a small slope, similar to that observed for nucleophilic substitution on methoxymethyl derivatives.[13,14] We conclude that a concerted mechanism of bimolecular substitution is followed because the glucosyl oxocarbenium ion does not have a significant lifetime when it is in contact with these nucleophiles. No second-order reactions were observed with uncharged nucleophiles.

## Experimental Section

**Materials and Measurements.** α-D-Glucopyranosyl fluoride was synthesized as described by Hall et al.[19] or was a gift from Hoechst AG, Germany. It was used without further purification. The mono- and dipotassium salts of (trichloromethyl)- and ethylphosphonic acid were prepared as described previously,[20] and were shown to be pure by $^{31}P$ NMR spectroscopy. Anhydrous methanol, sodium methoxide, pyridine-HF, Gold Label 2,2,2-trifluoroethanol (99+%), and ethylphosphonic acid were purchased from Aldrich Chemical Co. Sodium azide was purchased from Fluka. Glucose and the pentaacetates of α- and β-glucose were purchased from Aldrich or Pfanstiel Laboratories, Inc. Deuterium oxide (99.9%) was purchased from Cambridge Isotopes Ltd. Water was glass-distilled.

NMR spectra of $^1H$ at 300 MHz, $^{19}F$ spectra at 282.2 MHz, $^{31}P$ spectra at 121.4 MHz, and $^{13}C$ spectra at 75.4 MHz were recorded for solutions in $CDCl_3$ with tetramethylsilane as an internal standard, or solutions in $D_2O$ with tetramethylsilane or 2,2,2-trifluoroethanol as an external reference, with a Varian XL-300 spectrometer. Polarimetric measurements were made with a JASCO DIP-370 instrument by using a sodium lamp at 589 nm and a jacketed quartz cell with a 100-mm path length. The pH was measured with an Orion Research Model 611 or 701A pH meter and a Radiometer GK 2321C or a Corning 476541 combination electrode standardized at pH 7.0 and 4.0 or 10.0.

**Kinetics.** The kinetics were measured under pseudo-first-order conditions at 30.0 °C and ionic strength of 2.0 M, maintained with either $NaClO_4$ or KCl. Kinetics in $D_2O$ were followed by NMR; the NMR sample tubes were incubated in a bath at 30.0 °C. Exchangeable protons were removed prior to the kinetic runs by dissolving the compounds in $D_2O$, followed by lyophilization. Approximately 0.018 g of α-D-glucosyl fluoride was weighed directly into the NMR tubes, and the reactions were initiated by the addition of 1.0 mL of the solution containing the buffer or the nucleophile in $D_2O$ to give a final substrate concentration of ~0.1 M. At least five NMR spectra were obtained before the first half-life. The disappearance of the starting material was followed by the decrease in the computer-integrated area under the curve for the C-1 proton of **1**, centered around 5.7 ppm, compared with the six nonexchangeable protons on the C-2–C-6 atoms at 3–4 ppm. First-order rate constants were calculated from the relationship $k_{obs} = -\ln (FG)/t$, in which FG corresponds to the fraction of starting material remaining and $t$ is the time at which the spectrum was taken.

The solvolysis of 0.01 M α-D-glucosyl fluoride in solvent mixtures containing $x$:1:1 of $H_2O$–EtOH–$CF_3CH_2OH$ (v/v/v) or $H_2O$–MeOH, ionic strength 2.0 M ($NaClO_4$), was followed by taking aliquots at various times, removing the solvent by lyophilization, and exchanging the acidic protons by dissolving in $D_2O$. The NMR spectra of solutions in $D_2O$ were obtained, and the rate constants were calculated by following the disappearance of the starting material, as described above. The pH of the reaction solution was measured periodically during solvolysis and was maintained between pH 5 and 8 by the addition of small amounts of 0.1 M KOH.

Pseudo-first-order rate constants for some reactions of α-D-glucosyl fluoride with hydroxide ion and 1.99 M azide ion were obtained by polarimetry from semilogarithmic plots of the change in specific rotation, $[\alpha] - [\alpha]_\infty$, against time, which were found to be linear for 3–4 half-lives, and from the relationship $k_{obs} = \ln 2/t_{1/2}$. Rate constants for other reactions were obtained from the rate, $\nu$, of the initial linear change in optical rotation, $[\alpha]$, of reactions that were followed for the first 5–10% toward completion. The first-order rate constant was obtained from $k_{obs} = \nu/[S]\Delta\epsilon$, in which [S] is the substrate concentration and $\Delta\epsilon$ is the change in optical rotation upon complete reaction. The value of $\Delta\epsilon$ for reaction with azide ions was determined by following the change in $[\alpha]$ upon reaction to completion of a known concentration of substrate in the presence of 1.99 M azide ion, and from the relationship $\Delta\epsilon = ([\alpha]_o - [\alpha]_\infty)/[S]$. The value of $\Delta\epsilon$ for other nucleophiles, which give unstable products that decompose to glucose, was determined by calculating the average value from complete reaction of the substrate in the presence of 0.05 or 0.10 M HCl. Typical data are shown in Figure 1. The reaction solutions typically contained 1.99 M nucleophile, 0.005 M 1:1 mono–dibasic phosphate buffer, and 0.015 M substrate. The pH at the end of each reaction was within the pH-independent region.

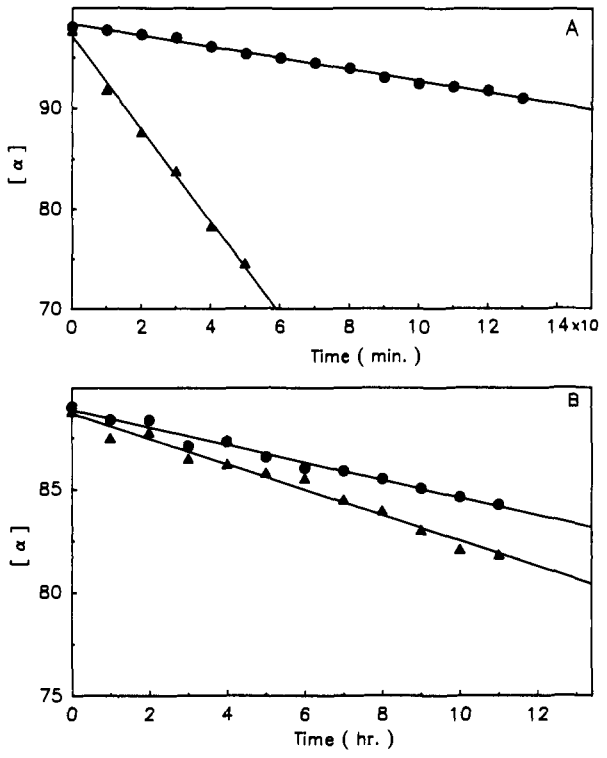


**Figure 1.** Polarimetric measurements of the initial rate of disappearance of α-D-glucosyl fluoride (A) in the presence of 1.75 M azide (●) or 0.06 M hydroxide (▲) ions and (B) in the presence of 1.99 M $Cl^-$ (●) or 0.5 M sulfite (▲) ions, in water at 30 °C, $\mu$ = 2.0 M (KCl). Note the different time scales for (A) and (B).

## Results

The rate constant for the solvolysis of α-D-glucopyranosyl fluoride, **1**, in water at 30 °C was determined by polarimetry and was found to increase by 70% with increasing ionic strength as the result of a salt effect, from $0.9 \times 10^{-6}$ $s^{-1}$ in phosphate buffer at 0.01 M ionic strength to $1.5 \times 10^{-6}$ $s^{-1}$ at 2.0 M ionic strength maintained with sodium perchlorate. Bunton and Huang found that perchlorate ion has a larger stabilizing effect on carbenium ions than a number of other anions.[21] However, an increase in the rate of α-D-glucosyl fluoride disappearance of 13-fold and 3.8-fold over the solvolysis rate at $\mu$ = 0.01 M was observed for reaction solutions containing 2.0 M $NaN_3$ or 2.0 M KCl, respectively. These correspond to rate increases of 7.8-fold and 2.3-fold for azide and chloride anions, respectively, over the solvolysis rate at an ionic strength of 2.0 M ($NaClO_4$). These substantial rate increases are consistent with nucleophilic attack by the anions; they correspond to second-order rate constants of $k_{Cl^-} = 1.0 \times 10^{-6}$ and $k_{N_3^-} = 5.5 \times 10^{-6}$ $M^{-1}$ $s^{-1}$ at ionic strength 2.0 M.

The kinetics for the reactions of α-D-glucosyl fluoride with a large excess of added nucleophiles in water were measured by polarimetry at 30.0 °C and 2.0 M ionic strength, maintained with

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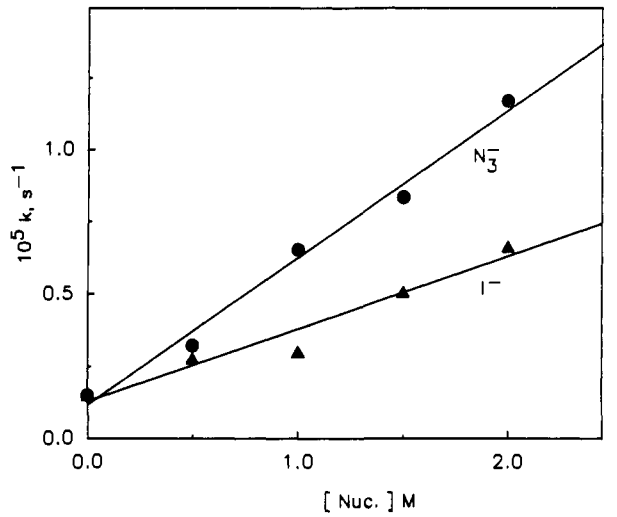


**Figure 2.** Dependence of the pseudo-first-order rate constant for reaction $k$, on the concentration of the nucleophile for the reaction of α-D-glucosyl fluoride with azide (●) and iodide (▲) ions at 30 °C, $\mu$ = 2.0 M (KCl). The rate increase from reaction with chloride ion has been subtracted from $k_{obs}$, as described in the text.

**Table I.** Second-Order Rate Constants for the Reactions of α-D-Glucosyl Fluoride with Nucleophilic Reagents at 30.0 °C and Ionic Strength of 2 M (KCl)

| nucleophile | $n$ (MeBr in $H_2O$)[a] | $10^6k$, $M^{-1}$ $s^{-1}$ [b] |
|---|---|---|
| $H_2O$ | 0 | 0.016,[c] 0.027[d] |
| $NO_3^-$ | 1.0 | 0.44 |
| $F^-$ | 2.0 | 1.61 |
| $CH_3CO_2^-$ | 2.7 | 0.82 |
| $Cl^-$ | 3.0 | 1.0 |
| $Br^-$ | 3.9 | 1.26 |
| $N_3^-$ | 4.0 | 5.5 |
| $HO^-$ | 4.2 | 450 |
| $NCS^-$ | 4.77 | 2.1 |
| $I^-$ | 5.04 | 2.8 |
| $S_2O_3^{2-}$ | 6.36 | 3.9 |

[a] Swain–Scott parameter for reaction with methyl bromide.[31] [b] Rate constants are corrected for the reaction with chloride ion, as described in the text. [c] At ionic strength 0.01 M, maintained with 1:1 $KH_2PO_4$–$K_2HPO_4$ buffer. [d] In 0.005 M 1:1 $KH_2PO_4$–$K_2HPO_4$ buffer, ionic strength 2.0 M, maintained with sodium perchlorate.

KCl. Typical initial rates of change in specific rotation, $\alpha$, are shown in Figure 1. The observed pseudo-first-order rate constants for the reactions with azide, iodide, and hydroxide ions were corrected for the reaction with $Cl^-$ by subtracting $k_{Cl}$-$[Cl^-]$ from $k_{obs}$. Second-order rate constants for the reactions with azide, iodide, and hydroxide ions were obtained from the slopes of plots of corrected first-order rate constants against the concentration of the nucleophile, as shown for $N_3^-$ and $I^-$ in Figure 2. Second-order rate constants for other anionic nucleophiles were obtained from the observed first-order rate constant in the presence of 1.99 M nucleophile, $k_{obs}$, and $k_{HOH}$ = 1.5 × $10^{-6}$ $s^{-1}$ (2.0 M $NaClO_4$), according to eq 2. The second-order rate constants are collected in Table I.

$$k = \frac{k_{obs} - k_{HOH}}{[Nu]} \qquad (2)$$

The solvolysis of α-D-glucosyl fluoride in $H_2O$–EtOH–TFE ($x$:1:1 by volume), and in $H_2O$–MeOH (v/v), was measured at 30.0 °C and ionic strength of 2.0 M maintained with $NaClO_4$. The rate constants were obtained by NMR measurements by observing the decrease with time in the area under the curve from the resonance of the anomeric proton of **1**, as described in the Experimental Section, and are reported in Tables II and III. The volumes and concentrations of the individual components in the solvent mixture were calculated from their weight and density. $^{19}F$ NMR spectra showed that a product containing the trifluoroethyl substituent was not formed, and $^1H$ NMR spectra

**Table II.** First-Order Rate Constants for the Solvolysis of α-D-Glucosyl Fluoride in $H_2O$–EtOH–$CF_3CH_2OH$ ($x$:1:1, by Volume) at 30 °C and Ionic Strength of 2 M ($NaClO_4$)

| % $H_2O$ | [$H_2O$], M | $k_{obs}$, $s^{-1}$ |
|---|---|---|
| 100 | 55.5 | 1.5 × $10^{-6}$ |
| 95 | 52.8 | 1.56 × $10^{-6}$ |
| 80 | 44.7 | 9.2 × $10^{-7}$ |
| 50 | 28.4 | 4.1 × $10^{-7}$ |
| 40 | 21.8 | 3.6 × $10^{-7}$ |
| 30 | 16.2 | 3.2 × $10^{-7}$ |
| 20 | 10.8 | 3.0 × $10^{-7}$ |
| 10 | 5.4 | 2.3 × $10^{-7}$ |
| 5 | 2.7 | 1.5 × $10^{-7}$ |

**Table III.** First-Order Rate Constants for the Solvolysis of α-D-Glucosyl Fluoride in $H_2O$–MeOH at 30 °C and Ionic Strength of 2 M ($NaClO_4$)

| % $H_2O$ (v/v) | [$H_2O$], M | $Y_{Cl}$[a] | $k_{obs}$, $s^{-1}$ |
|---|---|---|---|
| 100 | 55.5 | | 1.5 × $10^{-6}$ |
| 80 | 44.9 | 4.10 | 9.9 × $10^{-7}$ |
| 70 | 39.5 | 3.73 | 7.9 × $10^{-7}$ |
| 60 | 34.0 | 3.25 | 4.8 × $10^{-7}$ |
| 50 | 26.7 | 2.70 | 2.2 × $10^{-7}$ |
| 40 | 22.5 | 2.07 | 2.0 × $10^{-7}$ |
| 30 | 16.8 | 1.46 | 2.3 × $10^{-7}$ |
| 20 | 11.1 | 0.67 | 5.6 × $10^{-8}$ |
| 10 | 5.5 | −0.2 | 3.2 × $10^{-8}$ |

[a] For the solvolysis of 1-adamantyl chloride.[37]

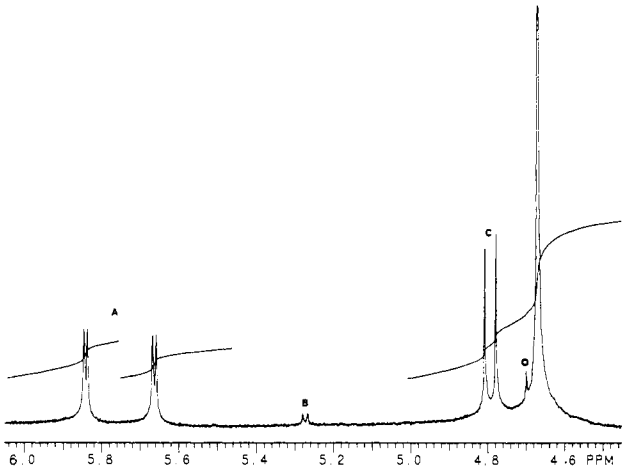


**Figure 3.** 300-MHz $^1H$ NMR spectrum of a reaction solution containing α-D-glucosyl fluoride and 2.0 M $NaN_3$ in $D_2O$ after 21 h at 30.0 °C. The resonances of the anomeric proton are assigned as (A) α-D-glucosyl fluoride, (B) α-glucose, (C) β-D-glucopyranosyl azide, and (D) β-glucose.

excluded the formation of significant amounts of 1-*O*-ethyl- or 1-*O*-methylglucopyranoside in the reaction mixtures. The 300-MHz NMR spectrometer is estimated to have a sensitivity that would detect a 1% yield of these products under the conditions of the measurements, from which a limit for the product ratio of GluOH/GluOEt of >18 was calculated.

The reactions of α-D-glucosyl fluoride with azide and acetate ions in $D_2O$ were shown to give β-D-glucopyranosyl azide (Figure 3C) and 1-*O*-acetyl-β-D-glucose as products, respectively, by NMR measurements; these products are stable enough to accumulate under the reaction conditions. The reaction with 2 M acetate in $D_2O$ gave a 2-fold increase in $k_{obs}$ and a 40% yield of the acetate product by proton NMR. The stereochemistry of the product from the reaction with azide was assigned by comparing the shift of the anomeric proton at 4.8 ppm ($J$ = 8.7 Hz) with a reported value of 4.74 ppm.[22,23] The shift of the anomeric proton of the product

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from the reaction with acetate is at 5.45 ppm ($J$ = 7.5 Hz). The resonance for the anomeric proton of 1-acetyl-α-glucose at 6.27 ppm ($J$ = 3.0 Hz)[24] was not observed. The yields of α products from the reactions with azide and acetate ions were estimated to be less than 1%.

The reaction of 0.01 M **1** with 0.06 M deuteroxide ion in $D_2O$ gave glucose and 1,6-anhydroglucose as products in a 1:1 ratio. The 1,6-anhydroglucose product is formed from base-catalyzed intramolecular displacement by the 6-hydroxyl group and was identified by the chemical shift of the C-1 proton at 5.23 ppm ($J$ = 1.0 Hz) in $D_2O$, compared with the literature value[25] of 5.17 ($J$ = 1.2 Hz) in $Me_2SO$. The rate constant for the nucleophilic reaction with deuteroxide ion was obtained by dividing the second-order rate constant for the disappearance of α-D-glucosyl fluoride by 2, to account for the 1,6-anhydroglucose product (the observed rate constants were corrected for the reaction with $Cl^-$). Glucose is the only product that was observed from the reactions with the other nucleophiles shown in Table I.

β-D-Glucosyl fluoride was not identified as a product of the reaction with fluoride ion by NMR analysis. However, this does not exclude a nucleophilic reaction with fluoride ion because the rate constant for the hydrolysis of β-D-glucosyl fluoride was estimated to be $\sim 2 \times 10^{-5}$ $s^{-1}$ at 25 °C in 1 M $NaClO_4$, from the rate of hydrolysis of β-D-galactosyl fluoride and the assumption that the glucose adduct reacts by a factor of 3 slower than the galactose adduct.[26] The rate of hydrolysis of β-D-glucosyl fluoride is 40-fold larger than $k = 10^{-6}$ $s^{-1}$ for the hydrolysis of α-D-glucosyl fluoride,[27] so that little β-D-glucosyl fluoride would be expected to accumulate under the reaction conditions.

Incubation of α-D-glucosyl fluoride, **1**, with primary, tertiary, and α-effect amines did not increase its rate of disappearance. The disappearance of α-D-glucosyl fluoride in the presence of 2.0 M triethylamine in water at pH 12.4 ($\mu$ = 2.0 M with KCl) was followed by polarimetry, and reactions in the presence of 1 M trifluoroethylamine, ethanolamine, and hydroxylamine, present as 50% base, at 30 °C in $D_2O$ were followed by proton NMR. There was no detectable increase in rate in the presence of amine (<5%) over the background rate (the concentration of chloride ion was constant). The $^1H$ resonance of an amine adduct of glucose was detected only for the solution containing hydroxylamine. A separate experiment showed that glucose, the product of the solvolysis of **1** in water, reacts rapidly with hydroxylamine under the reaction conditions, as has been observed previously[28] and the intensity of the $^1H$ resonance was of the magnitude expected from solvolysis and reaction with $Cl^-$ of **1** under the conditions of the experiment. In the solvolysis of **1** in the presence of unbuffered 2.0 M pyridine-$d_5$ in $D_2O$ (without added salt), a 1.5-fold increase in the rate constant was observed compared with the rate constant for solvolysis at $\mu$ = 0.01 M. However, the 1-glucopyranosylpyridinium salt was not detected as a reaction product by NMR, although it is stable under the conditions of the experiment.[29]

## Discussion

The strongest evidence for a concerted bimolecular reaction of anionic nucleophiles at the C-1 atom of α-D-glucosyl fluoride, **1**, is the linear dependence of the increase in the pseudo-first-order rate constant for disappearance of the starting material with an increase in the concentration of the added nucleophile at a constant ionic strength of 2.0 M (Figure 2), and the >99% inversion of stereochemistry exhibited by the stable product of the reaction with azide (Figure 3). These two observations are consistent with the Ingold criteria for an $S_N2$ mechanism that "contains only one stage, in which two molecules simultaneously undergo covalency change".[30]

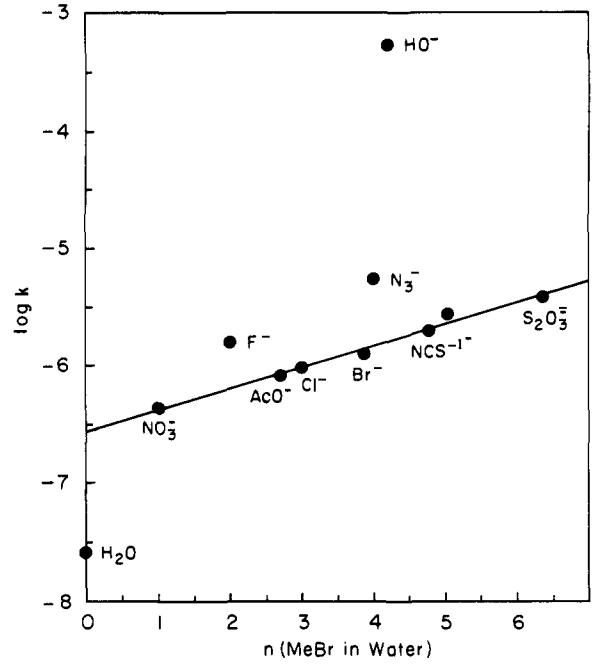


**Figure 4.** Swain–Scott plot of the second-order rate constants, log $k$, against the $n$ (MeBr)[31] value of the nucleophile for reactions with α-D-glucosyl fluoride at 30 °C, $\mu$ = 2.0 M. The line has a slope of $s$ = 0.18.

The sensitivity toward the nucleophilic reactivity of the attacking reagent is smaller for displacement reactions of **1** than for displacement reactions of methyl bromide in water.[31] The second-order rate constants for reaction with nucleophilic reagents follow a Swain–Scott correlation for nucleophilic reactivity toward methyl bromide in water, $n$, with a slope of $s$ = 0.18, as shown in Figure 4. This slope indicates that the sensitivity of **1** to nucleophilicity is about one-fifth of that for attack on methyl bromide. A similar slope of $s$ = 0.14 was obtained by correlation with nucleophilic constants for the reactions of methyl iodide in methanol[32] (not shown).

The sensitivity of the reactions of α-D-glucosyl fluoride, **1**, to the nucleophilicity of the nucleophiles is the same as that for acetal derivatives of propionaldehyde with $p$-$O_2NPhO^-$ and $N_3^-$ leaving groups;[33] however, it is smaller than that for methoxymethyl derivatives.[13,14] Displacement reactions of the less hindered $N$-(methoxymethyl)-$N$,$N$-dimethyl-$m$-nitroanilinium ion follow a Swain–Scott correlation with $s$ = 0.28,[14] and the same reactions with 2,4-dinitrophenolate ion as the leaving group follow a slope of $s$ = 0.2–0.3.[13] Bimolecular substitution reactions of acetal derivatives of propionaldehyde and benzaldehyde with $p$-nitrophenolate or azide leaving groups follow similar slopes in the range $s$ = 0.1–0.4.[33a] Swain–Scott correlations for the reactions of 1-(4-nitrophenyl)ethyl chloride and tosylate with halide ions give slopes of $s$ = 0.69 and 0.49, respectively.[34]

Azide ion shows a positive deviation of 4-fold from the Swain–Scott correlation for **1** (Figure 4). Similar deviations were

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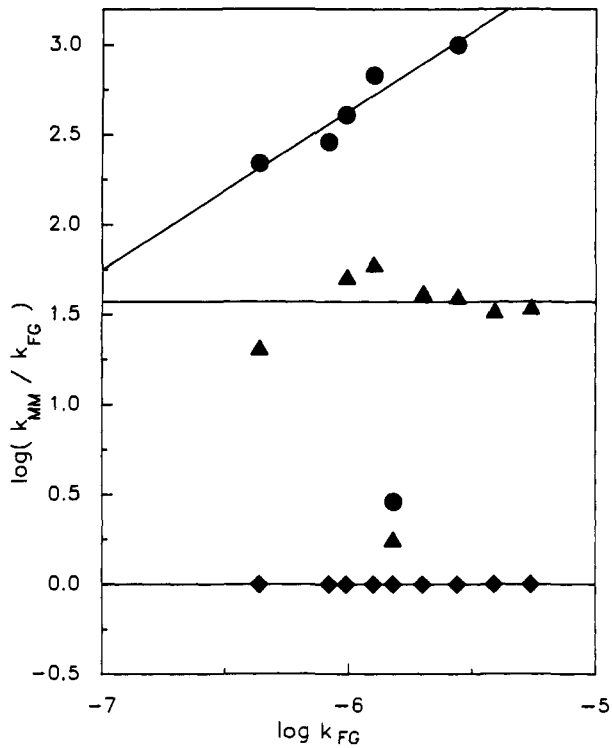


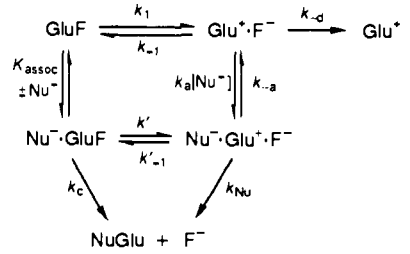

**Figure 5.** Ratios of rate constants for reactions of nucleophilic reagents with α-D-glucosyl fluoride (FG) (◆) (30 °C, $\mu$ = 2.0 M (KCl) with 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane (▲) (41 °C, $\mu$ = 2.0 M ($NaClO_4$)),[33] and with *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilium ion (●)[14] (25 °C, $\mu$ = 1.0 M ($NaClO_4$), slope 0.9).

observed for the reaction of azide with methoxymethyl derivatives (2.7-fold)[14] and with an acetal derivative of propionaldehyde (3-fold).[33] This deviation is characteristic of a transition state for nucleophilic substitution that has a large amount of carbocation character.

Figure 5 shows that a logarithmic correlation of the ratios of rate constants for reactions of nucleophilic reagents with a propionaldehyde acetal derivative, 1-methoxy-3-(4-methoxyphenyl)-1-(*p*-nitrophenoxy)propane[33] and α-D-glucosyl fluoride, has a slope of zero, while the corresponding slope for reactions with *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion[14] and α-D-glucosyl fluoride is 0.9 (excluding the reaction with water). Thus, the sensitivity toward the reactivity of the nucleophile is very similar for α-D-glucosyl fluoride and 1-methoxy-3-(4-methoxyphenyl)-1-(*p*-nitrophenoxy)propane, but there is a considerably larger interaction of the methoxymethyl derivative with the nucleophiles, in spite of its larger reaction rate. This difference may reflect less dissociative character and possibly a steric effect that allows more bond formation in the transition state for reactions of methoxymethyl derivatives.

The reaction of α-D-glucosyl fluoride, **1**, with azide ion does not follow concurrent concerted ($A_ND_N$) and stepwise ($D_N + A_N$) mechanisms. The 83% yield of β-D-glucopyranosyl azide from the reaction of **1** with 2.0 M $NaN_3$ in $D_2O$, determined by NMR analysis of the reaction mixture at the end point, agrees well with the yield of 87% calculated from the observed rate increase of 7.8-fold. The same rate increase was observed with 2.0 M $NaN_3$ in $H_2O$ by polarimetry. This result indicates that the reaction with azide ion is bimolecular; there is no detectable trapping by azide ion of the glucosyl oxocarbenium ion intermediate. Concurrent stepwise and concerted reactions of azide with acetal derivatives of benzaldehyde[33] and some 1-phenylethyl and 4-methoxybenzyl derivatives[34] are known, but are seldom of major significance. Concurrent stepwise and concerted reactions with a nucleophilic reagent can be observed if (1) the carbenium ion has a sufficient lifetime that it can diffuse through the solvent and be trapped by the nucleophile and (2) the substrate undergoes a bimolecular reaction with the nucleophile that is concerted

Scheme I




because the carbenium ion does not have a significant lifetime when it is in contact with the nucleophile.

The second-order rate constants for the reactions of **1** with fluoride and hydroxide ions show positive deviations of 2.5- and 270-fold, respectively, from the Swain–Scott correlation in Figure 4. The intramolecular displacement reaction accounts for only half of the rate increase with hydroxide ion. The reaction with water is believed to occur through a stepwise $D_N{}^*A_N$ mechanism with a glucosyl oxocarbenium ion intermediate.[5] However, the absence of any detectable trapping of this ion by azide and its estimated lifetime of $\sim 10^{-12}$ s suggest that it does not exist long enough to diffuse through the solvent.[5] The negative deviation of 10-fold for the rate constant of the water reaction in the Swain–Scott correlation is similar to the 6–10-fold negative deviation for methoxymethyl derivatives,[14] which have been estimated to have lifetimes of $\leq 10^{-12}$ s in water and may undergo bimolecular reactions with water.[14,33] There are smaller negative deviations of 2–3-fold for the reactions of water with derivatives of propionaldehyde acetals and a positive deviation for a benzaldehyde derivative; these compounds generate oxocarbenium ions with a longer lifetime.[5,33]

The positive deviations of the rate constants for the bimolecular reactions with fluoride and hydroxide ions may represent "synergism" between the "hard", weakly polarizable attacking and leaving groups. There is a tendency for hard nucleophilic reagents with a low polarizability to show enhanced reactivity toward electrophiles with hard, weakly polarizable leaving groups, and for "soft", polarizable nucleophiles to react rapidly with compounds with polarizable leaving groups; this represents a synergism, or "symbiosis",[35] between the entering and leaving groups in the transition state for bimolecular substitution.

Possible pathways for the reaction of α-D-glucosyl fluoride, **1**, with nucleophiles are shown in Scheme I. A diffusionally equilibrated glucosyl oxocarbenium ion is not an intermediate in these reactions because its lifetime is too short, as noted above, and a reaction through free $Glu^+$ would not show a dependence of the observed rate on the concentration of added nucleophile. A bimolecular reaction of an ion pair through the upper pathway by a Sneen-type mechanism is not significant in good ionizing solvents, such as water, because the ion pair will separate ($k_{-d}$) before a dilute nucleophile can diffuse up to it ($k_a[Nu^-]$), and because collapse of the ion pair to the starting material must be faster than diffusion away of the nucleophile in order that reaction with the nucleophile will be rate-limiting; i.e., $k_{-1} \approx k'_{-1} > k_{-a} \approx k_{-d}$. This is the requirement for a preassociation mechanism.[33] Therefore, the bimolecular reactions of **1** in water must proceed through either a stepwise preassociation mechanism ($k'$ and $k_{Nu}$) or a concerted mechanism ($k_c$).

The following evidence supports a concerted, $A_ND_N$ reaction mechanism for the displacement reactions of α-D-glucosyl fluoride.

(a) The substitution reactions of α-D-glucosyl fluoride, **1**, with azide and acetate ions give products that have exclusively inverted stereochemistry. The absence of racemization is consistent with a concerted bimolecular reaction mechanism.

(b) In a stepwise preassociation mechanism, there is a change in the rate-determining step, which will be evident as a break in a linear free energy correlation, such as the Swain–Scott plot shown in Figure 4. For all nucleophiles stronger than $F^-$, the

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bond-breaking step, $k'_1$, would be rate-limiting and the nucleophiles would be expected to react at the same rate. For nucleophiles weaker than $F^-$, the bond-making step, $k_{Nu}$, would be rate-limiting so that there should be a change in rate-limiting step and a break in the Swain–Scott correlation. There is no evidence for a break in the correlation, or for a leveling of the rate constant for nucleophiles with $n$ values larger than that of fluoride. Therefore, the Swain–Scott plot is consistent with a concerted bimolecular reaction mechanism.

Figure 5 shows that there is no break in the correlation of ratios of rate constants for reactions of nucleophiles with *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilium ion[14] and α-D-glucosyl fluoride, and for reactions with 1-methoxy-3-(4-methoxyphenyl)-1-(4-nitrophenyl)propane[33] and α-D-glucosyl fluoride. The methoxymethyl and methoxypropyl derivatives have been shown to react with good nucleophiles by a concerted mechanism,[14,33] so that the correlations in Figure 5 are also consistent with a concerted, $A_ND_N$ mechanism for α-D-glucosyl fluoride.

(c) The estimated rate constant for reaction of the glucosyl oxocarbenium ion with water[5] is $\sim 10^{12}$ s$^{-1}$. An estimate of the rate constant for reaction of the oxocarbenium ion with azide ion in an encounter complex, $k_{Nu}$, can be made from the $N_+$ value (log $k_{az}/k_{HOH}$)) for azide of 7.8 for activation-limited reactions with carbocations,[36] an association constant of $K_{assoc} = 0.3$ M$^{-1}$ for formation of an encounter complex, and the relationship $k_{Nu} = k_{az}/K_{assoc}$. The calculated value of $k_{Nu} \simeq 10^{11} \times 10^8 = 10^{19}$ s$^{-1}$ is much larger than the C–F bond vibration frequency of $\sim 10^{13}$ s$^{-1}$, so that the glucosyl oxocarbenium ion is not expected to have a significant lifetime in the presence of azide ion. Therefore, the encounter complex cannot exist as an intermediate, and the reaction with azide must be concerted.

**Solvolysis in Aqueous Alcohols.** The rate constants for the solvolysis of α-D-glucosyl fluoride in methanol–water mixtures increase with increasing ionizing power of the medium with a slope of $m = 0.34$, compared with rate constants for the solvolysis of 1-adamantyl chloride,[37] as shown in Figure 6A.

We were surprised to find that there is no detectable trapping of the glucosyl cation by methanol, ethanol, or trifluoroethanol when α-D-glucosyl fluoride undergoes solvolysis in water–methanol or water–ethanol–trifluoroethanol mixtures in which the fraction of methanol was varied from 90% to 0% by volume and the fraction of ethanol–trifluoroethanol (1:1) was varied from 95% to 0%. Glucose, from the capture of the glucosyl oxocarbenium ion by water, was identified as the only product by proton and $^{19}$F NMR.

The glucosyl oxocarbenium ion does react with ethanol and trifluoroethanol in 1:1 EtOH–TFE (M/M) solvent to give both α- and β-glycosides and different product ratios with different leaving groups.[2] The identification of products that have the same configuration as the reactant argues against an $A_ND_N$ ($S_N2$) mechanism, but is consistent with a stepwise preassociation mechanism in which the entering group is present as the bond to the leaving group is cleaved when glycopyranosyl derivatives undergo solvolysis. The reactions of α- and β-D-glucosyl fluoride in these solvents give relative yields of trifluoroethyl glucoside compared with ethyl glucoside that are increased by 3–20-fold in the reactions that proceed by retention; this suggests that reaction of the glucosyl oxocarbenium ion with trifluoroethanol is assisted by fluoride ion in a solvent-separated ion pair, as noted above. The intimate ion pair with fluoride probably cannot exist as an intermediate in these reactions, because fluoride is a stronger nucleophilic reagent than solvent and the intimate ion pair with fluoride ion is not expected to have a significant barrier for collapse to reactants. However, the reactions that proceed with inversion show selectivities of up to 20-fold that favor reaction with ethanol compared with trifluoroethanol, although the cation is not diffusionally equilibrated. This high selectivity may be accounted for by a charge–dipole interaction between the developing oxocarbenium ion and ethanol that orients the hydroxyl group of ethanol in position to react with the cation. This dipole interaction may also increase the rate of formation of the cation. However, trifluoroethanol has a large dipole moment that draws electron density toward the trifluoromethyl group, so that trifluoroethanol is likely to be oriented in an unreactive position, such as **2**, when the carbocation is formed.[38] The $\sigma_I$ value of 0.45 for $CF_3$ is nearly twice as large as $\sigma_I = 0.25$ for OH.[39]

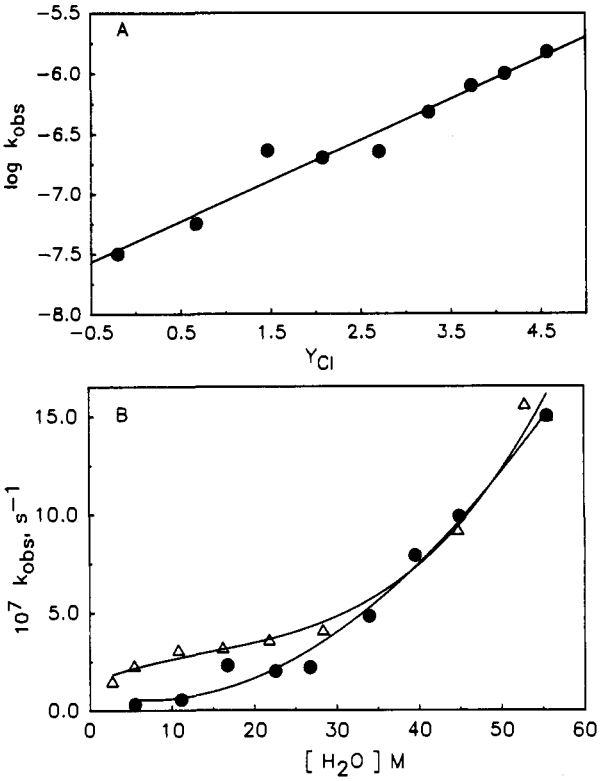
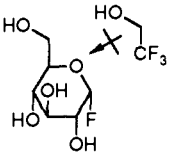



**Figure 6.** (A) Sensitivity to solvent ionizing power of the solvolysis of α-D-glucosyl fluoride in aqueous methanol at 30 °C and $\mu = 2.0$ M ($NaClO_4$); the $Y_{Cl}$ values are for solvolysis of 1-adamantyl chloride.[37] (B) The dependence of the rate of solvolysis of α-D-glucosyl fluoride, $k_{obs}$, on the concentration of water in $H_2O$–EtOH–$CF_3CH_2OH$ (△), and in MeOH–$H_2O$ (●) solvents at 30 °C and $\mu = 2.0$ M ($NaClO_4$).




**2**

The high selectivity for the reaction of the glucosyl oxocarbenium ion with water compared with alcohols in the work reported here is in marked contrast to selectivities for reaction with ring-substituted 1-phenylethyl carbocations, which show ratios of $k_{EtOH}/k_{HOH}$ of up to 37, $k_{MeOH}/k_{HOH}$ up to 70 and $k_{EtOH}/k_{TFE}$ of 140. These selectivities decrease with increasing reactivity of the carbenium ion, but even 1-(4-nitrophenyl)ethyl tosylate is more reactive toward each of seven alcohols than toward water.[38] The selectivities of oxocarbenium ions formed from α-azido ethers derived from propionaldehyde and butanone are smaller, in the range $k_{MeOH}/k_{HOH} = 1.5$–3.4 and $k_{EtOH}/k_{HOH} = 1$–2, but there is still a high reactivity toward alcohols.[5] The glucosyl oxocarbenium ion is more reactive than propionaldehyde oxocarbenium ion and might exhibit a further decrease in selectivity, but this does not account for exclusive reaction with water.

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We suggest that this high selectivity for reaction with water instead of alcohols represents a localized solvent effect that arises from the development of a high charge density in a restricted environment in the transition state for formation of the oxocarbenium ion. Space-filling CPK molecular models indicate that a large fraction of the reaction center is surrounded by hydrocarbon, the 6-hydroxymethyl group, and the leaving group, so that its access to solvent is severely restricted. The high selectivity for reaction with water instead of alcohols suggests that the development of this charge is favored when it is surrounded by water molecules, rather than alcohol. The lifetime of the oxocarbenium ion is too short to allow diffusion and a choice between different nucleophiles once it is formed, so that it is very likely to react with water if it is formed in the presence of water. There is a large increase in the rate of hydrolysis of α-D-glucosyl fluoride with an increase in the concentration of water in the mixed solvent system (Figure 6B). In methanol–water mixtures, the rate increases by 50-fold with a 10-fold increase in the concentration of water, from 5.5 to 55 M (Table III); over most of this range, the increase in rate is approximately second-order with respect to the concentration of water (not shown).

These conclusions are supported by the results of a comprehensive study of the reactions of a series of *p*-nitrophenyl β-D-ribofuranoside derivatives by Czarnik and co-workers.[10] The rate of pH-independent hydrolysis in this series of compounds is decreased by 330-fold in the fluorenone ketal, which provides a nonpolar environment near the 1-carbon atom. Slightly smaller decreases are observed with fluorenone derivatives that have amide and ester groups below the 1-carbon atom, but a small rate increase is observed with a carboxylate group in the same position.

The same localized solvation and electrostatic effects, as well as steric effects, may account for the occurrence of bimolecular nucleophilic reactions of anions, but not of amine nucleophiles, with α-D-glucosyl fluoride. There is a large amount of bond breaking and little bond making in the dissociative transition state of these $A_ND_N$ reactions, so that there is a large amount of positive charge development at the reaction center. This charge interacts favorably with an anionic nucleophile, but not with an uncharged amine nucleophile. It is conceivable that the attack of anionic nucleophiles is also assisted by hydrogen bonding to the 6-OH group of α-D-glucosyl fluoride.

**Registry No.** 1, 2106-10-7; β-D-glucopyranosyl azide, 20379-59-3; 1-*O*-acetyl-β-D-glucopyranose, 135758-71-3; α-D-glucopyranose, 492-62-6; 1,6-anhydro-β-D-glucopyranose, 498-07-7; β-D-glucopyranose, 492-61-5.

# General-Acid and General-Base Catalysis of the Cleavage of α-D-Glucopyranosyl Fluoride[1]

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**Abstract:** The hydrolysis of α-D-glucopyranosyl fluoride is catalyzed by phosphate and phosphonate buffers in the pH-independent region in water and in deuterium oxide at 30.0 °C and $\mu$ = 2.0 M (KCl). General-base catalysis by the dianions accounts for most of the rate increase, but there is also significant general-acid catalysis by the monoanions. The solvent isotope effect for catalysis by phosphate buffers is $k_H/k_D$ = 1.9 for the dianion and $k_H/k_D$ = 2.0 for the monoanion. The Brønsted slopes are small, with $\beta$ = 0.06 for catalysis by general bases and $\alpha$ = 0.15 for catalysis by general acids; however, $\alpha$ = 0.4 if the rate constant for $H_3O^+$ is included. Catalysis by $L_3O^+$ shows a solvent isotope effect of $k_H/k_D$ = 1.4; this differs from the value of $k_H/k_D \simeq 0.5$ that is expected for specific-acid catalysis with equilibrium protonation of the substrate. Catalysis by $LO^-$ and the uncatalyzed solvolysis in $L_2O$ show inverse solvent isotope effects of $k_D/k_H$ = 1.5 and $k_D/k_H$ = 1.1, respectively. No reaction with methanol is observed in the absence of catalysts, but the addition of methanol to α-D-glucosyl fluoride in methanol–water (45:55 by volume) is catalyzed by phosphate buffer, 50% dianion, and gives 1-*O*-methyl-β-glucopyranoside as the product. It is suggested that the general-base catalysis represents a concerted mechanism of nucleophilic attack and proton abstraction that is enforced by the absence of a significant lifetime for the glucosyl cation in the presence of fluoride ion, and that general-acid catalysis occurs by hydrogen bonding to the leaving fluoride ion. Both mechanisms of catalysis are facilitated by an electrostatic interaction between the anionic catalyst and the developing positive charge of the transition state. The significance of these results for the mechanism of catalysis by glycosidases is discussed.

We would like to understand the mechanisms that are utilized by lysozyme and related enzymes to catalyze the cleavage of glycosidic bonds. Possible mechanisms include nucleophilic catalysis and electrostatic stabilization of the carbocation-like transition state by a carboxylate group, ground-state distortion toward the structure of the transition state, and general-acid–base catalysis of proton transfer to or from leaving or entering groups.[2] However, it has generally been believed that the hydrolysis of glycosides occurs by specific-acid catalysis, with complete protonation of the leaving oxygen atom followed by bond breaking to form an unstable oxocarbenium ion intermediate that reacts rapidly with water.[3] The lifetime of the glucosyl oxocarbenium ion has been estimated to be approximately $10^{-12}$ s, so that the reaction of this cation with water is expected to occur rapidly without assistance by general-base catalysis.[4] The Brønsted $\beta$ value for general-base catalysis of the addition of water to electrophilic centers decreases with increasing reactivity of the cation, according to the relationship $p_{xy} = -\partial\beta/\partial\sigma = \partial\rho/-\partial pK_{BH^+}$, and general-base catalysis is not observed for the hydration of highly unstable cations.[3,5-7] If there is no general-base catalysis of

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