Hydrolysis of (2-Deoxy-α-D-Glucopyranosyl)pyridinium Salts: The 2-Deoxyglucosyl Oxocarbenium Is Not Solvent-Equilibrated in Water

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Abstract: The hydrolysis reactions of four 2-deoxy-α-D-glucopyranosyl pyridinium salts exhibit first-order rate constants that are independent of pH in the range of 4.4−10.5 pH units. Derived second-order rate constants for the hydrolysis reactions of 2-deoxy-α-D-glucopyranosyl 4′-bromoisoquinolinium tetrafluoroborate (**4d**) conducted in the presence of nucleophilic monoanions ($\mu = 2.0$) including AcO^-, Cl^-, Br^-, and N_3^- exhibit a Swain−Scott parameter (s) of 0.03 ± 0.10, indicating that these reactions show no sensitivity to the nature of the anion. In the presence of azide ion, a substantial quantity of the 2-deoxy-α-glucopyranosyl 4′-bromoisoquinolinium salt hydrolysis product results from a post rate-limiting reaction of a cationic intermediate with azide. Analysis of the hydrolysis product ratios indicates that the 2-deoxyglucosyl oxocarbenium ion is not solvent-equilibrated in water. Furthermore, the reaction of solvent occurs about 2-fold faster with the cationic intermediate that is formed during solvolysis of the β-anomeric salt than with the corresponding intermediate produced from the reactions of the α-anomer **4d**.

Introduction

There continues to be interest in the intimate mechanistic details of nucleophilic substitution reactions at carbon[1] and because of their biological significance at acetal and ketal centers.[2] Specific acid-catalyzed hydrolysis of glycopyranosides is generally considered to occur with unassisted, rate-limiting, exocyclic C−O bond cleavage of the protonated glycoside to generate a cyclic oxocarbenium ion intermediate and a neutral alcohol.[3,4] In a recent study, the rate for the hydrolysis of 2-deoxy-β-D-glucopyranosyl 4′-bromoisoquinolinium bromide (**1**), a stable model for an O-protonated glycoside, showed no sensitivity to the addition of nucleophilic monoanions.[5] Furthermore, it was reported that the majority of the product formed from **1** with azide ion had an inverted anomeric configuration and that this product resulted from a post rate-limiting reaction.[5] Based on these results, Huang *et al.*[5] proposed that the reactions of **1** follow a stepwise D_N * A_N[6] mechanism, and the first-formed intermediate is a solvent separated ion-pair:molecule encounter complex (**SSIP:M**).

From their data, Huang *et al*. estimated a lifetime in aqueous solutions of greater than 2.5×10^{-12} s for the glucopyranosyl oxocarbenium ion.[5] A critical assumption made in the analysis

$N_3^- \parallel Glu^+ \cdot Py$

(**SSIP:M**)

is that reaction of a solvent-equilibrated oxocarbenium ion in aqueous solution with azide ion will not produce the α-azide as the predominant product.[5] There is some evidence that more stable six-membered oxocarbenium ions display an enhanced reactivity of the α-face relative to the β-face.[7] Specifically, Perrin and Engler measured the rate constants for methanol capture of the dioxocarbenium ion **2** to generate the two diastereomers **3a** and **3e**.[7] These authors observed a 9-fold axial selectivity (to give **3a**) for the reactions of **2** with methanol in methanol/chloroform solutions.[7] In contrast, Jencks and Sinnott observed that solvolyses in mixtures of ethanol and trifluoroethanol of several glucopyranosyl derivatives gave products that depended on both the leaving group and the anomeric configuration of the starting material.[8] These results were interpreted to indicate that leaving group departure is facilitated by the solvent and that no solvent-equilibrated intermediates are formed in these reactions. Recently, a semiempirical approach was used to calculate the kinetic and thermodynamic stabilities of pyranosyl oxocarbenium ions generated from pyridinium[9] and protonated methyl glycosides.[10] In this study, Buckley and Oppenheimer compared their semiempirical results to those from published kinetic data of reactions in solution but were unable to interpret whether the cyclic oxocarbenium ion produced during the reactions of glycopyranosyl pyridinium ions is formed as a solvent-equilibrated species or as an element of an ion−neutral complex.[9] The present report addresses the question of whether the 2-deoxyglucopyranosyl oxocarbenium ion is solvent-

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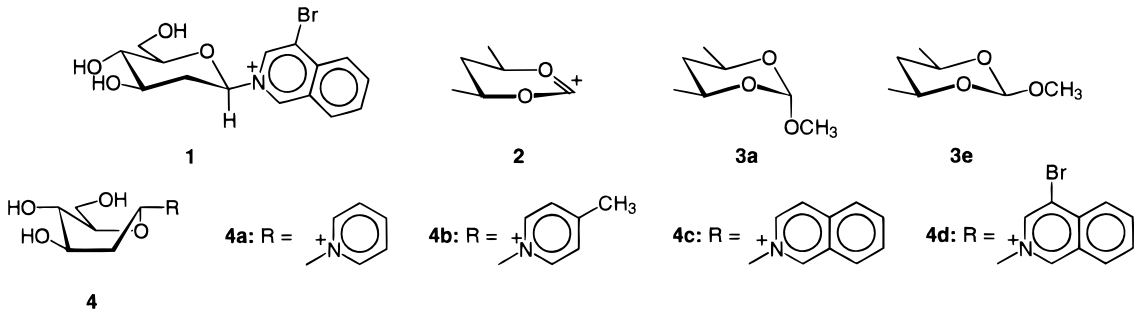


equilibrated, and, to this end, results are presented from kinetic and product studies on the reactions of four 2-deoxy-α-D-glucopyranosyl pyridinium salts (**4a**−**d**) in the presence of added anionic nucleophiles. In addition, to determine if nucleophilic attack by the solvent occurs with equal propensity on the two diastereotopic faces of the proposed reaction intermediate (**SSIP: M**), the reactions of **1** and **4d** were conducted in 20% aqueous methanol, and the resulting product distributions were determined.

Materials and Methods

The buffers 2-(*N*-morpholino)ethanesulfonic acid (MES), 3-(*N*-morpholino)propanesulfonic acid (MOPS), *N*-tris(hydroxymethyl)-methyl-3-aminopropanesulfonic acid (TAPS), 2-(*N*-cyclohexylamino)-ethanesulfonic acid (CHES), and 3-(*N*-cyclohexylamino)propanesulfonic acid (CAPS) as well as sodium azide (SigmaUltra) were purchased from Sigma and used without further purification. All other salts used in the hydrolysis studies were of "Analar" grade and were used without further purification. Milli-Q water (18.2 MΩ cm^{-1}) was used for the kinetic experiments. The NMR spectra were acquired on a Bruker AMX-400 spectrometer. Melting points are reported as uncorrected values. Full experimental details for the synthesis of **4a**, **4b**, **4c**, and **8** (^{13}C-labeled **4d**) are given in the Supporting Information.

5,5-Dimethyl-2-thiono-(3,4,6,-tri-*O*-acetyl-2-deoxy-*β*-D-*arabino*-hexopyranosylthio)-1,3,2-dioxaphosphorinane (6). Sodium hydride (0.18 g, 60% in mineral oil) and 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (0.89 g)[11] were mixed in anhydrous THF (2 mL) at −15 °C, under an inert atmosphere. When hydrogen evolution was complete, a solution of 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl bromide[5] (1.03 g) in THF (1 mL) was added to the solution and stirred for an additional 10 min at −15 °C. After removal of the solvent by reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL), and this solution was then washed with H_2O (50 mL), dried ($MgSO_4$), and filtered. Volatile components were removed under reduced pressure, and the resulting syrup (90% crude yield) was then crystallized from EtOAc/hexane to give a colorless solid, mp = 131−133 °C. ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.91 (s, 3 H), 1.26 (s, 3 H), 1.96−2.09 (m, 1 H, H-2a), 2.03 (s 3 H), 2.04 (s, 3 H), 2.07 (s, 3 H), 2.54 (ddd, 1 H, $J_{1,2e}$ = 2 Hz, $J_{2a,2e}$ = 13 Hz, $J_{2e,3}$ = 5 Hz, H-2e), 3.69 (ddd, 1 H, $J_{5,6a}$ = 5.5 Hz, $J_{5,6b}$ = 2 Hz, $J_{4,5}$ = 9.5 Hz, H-5), 3.85−4.00 (m, 2 H), 4.04 (dd, 1 H, $J_{6a,6b}$ = 12 Hz, H-6b), 4.12−4.30 (m, 2 H), 4.31 (dd, 1 H, H-6a), 4.98 (t, 1 H, $J_{3,4} + J_{4,5}$ = 19 Hz, H-4), 5.06 (ddd, 1 H, $J_{2a,3}$ = 11 Hz, $J_{2e,3}$ = 5 Hz, H-3), 5.18 (ddd, 1 H, $J_{1,2a}$ = 13 Hz, $^2J_{H,P}$ = 12 Hz, H-1). Anal. Calcd for $C_{17}H_{27}O_9PS_2$: C, 43.40; H, 5.78. Found: C, 43.48; H, 5.82.

3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl 4′-Bromoisoquinolinium Tetrafluoroborate (7d). Silver tetrafluoroborate (0.23 g, 1.18 mmol) and 4-bromoisoquinoline (1.09 g, 5.23 mmol) were added in one portion, with stirring, to an ice-cold solution of dioxaphosphorinane **6** (0.55 g, 1.17 mmol) in dichloromethane (1 mL). Stirring of the solution was continued for 120 min, at which point addition of methanol (100 mL) induced precipitation of silver salts. After the precipitate had been removed by filtration, the volatiles were evaporated under reduced pressure. The resulting residue was dissolved in a minimum amount of methanol, and diethyl ether (250 mL) was added to precipitate the product **7d**. This procedure was repeated twice, and the final white powder was crystallized from H_2O to give colorless crystals of **7d** (0.43 g, 65%). Mp: 86−91 °C. ^{1}H NMR (400 MHz, D_2O): δ 2.10 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.73 (ddd, 1 H, $J_{2S,1}$ = 4.2 Hz, $J_{2S,2R}$ = 15 Hz, $J_{2S,3}$ = 7.0 Hz, H-2S), 2.99 (ddd, 1 H, $J_{2R,1}$ = 6.9 Hz, $J_{2R,3}$ = 3.9 Hz, H-2R), 4.29−4.35 (m, 2 H, H-5, H-6a), 4.61 (dd, 1 H, $J_{6b,5}$ = 6.9, Hz, $J_{6b,6a}$ = 13 Hz, H-6b), 5.13 (t, 1 H, $J_{4,3} + J_{4,5}$ = 12 Hz, H-4), 5.30 (m, 1 H, H-3), 6.59 (dd, 1 H, H-1), 8.12 (m, 1 H, Ar−H), 8.37 (bd, 1 H, Ar−H), 8.48 (bd, 1 H, Ar−H), 8.52 (m, 1 H, Ar−H), 9.05 (d, 1 H, Ar−H), 9.91 (bs, 1 H, Ar−H).

2-Deoxy-α-D-*arabino*-hexopyranosyl 4′-Bromoisoquinolinium Tetrafluoroborate (4d). The acetylated salt **7d** (0.14 g, 0.25 mmol) was dissolved in cold methanol (3 mL, −16 °C), and following the dropwise addition of tetrafluoroboric acid (54% w/v in ether, 2 mL), the resulting solution was kept at around −20 °C in a freezer. After 10 days an analytically pure sample of **4d** had crystallized from the acidic solution (0.09 g, 82%). Mp: 95−97 °C. ^{1}H NMR (400 MHz, D_2O): δ 2.54 (ddd, 1 H, $J_{2S,1}$ = 4.9 Hz, $J_{2S,2R}$ = 16 Hz, $J_{2S,3}$ = 11 Hz, H-2S), 3.13 (ddd, 1 H, $J_{2R,1}$ = 4.1 Hz, $J_{2S,3}$ = 3.2 Hz, H-2R), 3.49 (ddd, 1 H, $J_{5,4}$ = 8.4 Hz, $J_{5,6a}$ = 3.2 Hz, $J_{5,6b}$ = 5.4 Hz H-5), 3.69 (dd, 1 H, $J_{4,3}$ = 9.1 Hz, H-4), 3.86−3.97 (m, 3 H, H-3, H-6a, H-6b), 6.51 (bt, 1 H, H-1), 8.12 (m, 1 H, Ar−H), 8.37 (m, 1 H, Ar−H), 8.50 (m, 1 H, Ar−H), 8.54 (m, 1 H, Ar−H), 9.08 (bs, 1 H, Ar−H), 9.92 (bs, 1 H, Ar−H). Anal. Calcd for $C_{15}H_{17}BBrF_4NO_4$: C, 40.76; H, 3.88; N. 3.17. Found: C, 40.65; H, 3.74; N, 3.16.

Kinetics. Hydrolysis of **4d** (≈ 0.2 mM)[12] at 65 °C was monitored by following the rate of decrease in absorbance at 346 nm using a Cary3E UV−vis spectrophotometer equipped with the Cary six-cell Peltier constant-temperature accessory. The reaction was initiated by the injection of an aqueous stock solution of the glucoside (10 μL, 60 mM) into a 1-cm quartz cuvette that contained 3.0 mL of the required buffer which had been preequilibrated for 5 min at 65 °C. Clean isosbestic points were observed at 262, 295, 300, and 327 nm, and the rate constant for hydrolysis was calculated by performing a standard nonlinear least-squares fit of the absorbance (346 nm) versus time data. The hydrolyses of **4a**−**c** were monitored in an analogous fashion, except that the reactions were initiated by injection of an aqueous stock solution of the glucoside (6.5 μL, 30 mM) into a 1-cm quartz cuvette containing 1.0 mL of buffer solution. For the reactions in which the pH was greater than 6.0 the change in absorbance was monitored at 261, 260, and 338 nm for **4a**−**c**, respectively, whereas at a pH value of 4.42, the hydrolysis reactions were monitored at 270, 264, and 280 nm for **4a**−**c**, respectively.

The solvolysis studies in the presence of added anions were all performed in 0.01 M (1:1 Na_2HPO_4:NaH_2PO_4) phosphate buffer at a pH of around 6.8 (i.e., in the pH independent region of the hydrolysis reaction).

Product Studies. The UV−vis spectrum (240−380 nm) of a completely hydrolyzed (>10 half-lives) sample of **4d** (2.00×10^{-4} M) in 0.01 M phosphate buffer (μ = 0.02, $NaClO_4$) at 65 °C was identical within 0.038 AUs (maximum absorbance = 0.95 AU) of a spectrum of 4-bromoisoquinoline (2.00×10^{-4} M). Identification of

(11) Edmundson, R. S. *Tetrahedron* **1965**, *21*, 2379−2387.

(12) Initial kinetic measurements on **4d** were performed with a sample that contained about 4% of the β-anomer (**1**). However, since the rate of hydrolysis for **1** is approximately 9-fold less than that of **4d** (ref 5), following four-half-times for hydrolysis of **4d**, approximately 1% of the total hydrolyzed material originated from **1**.

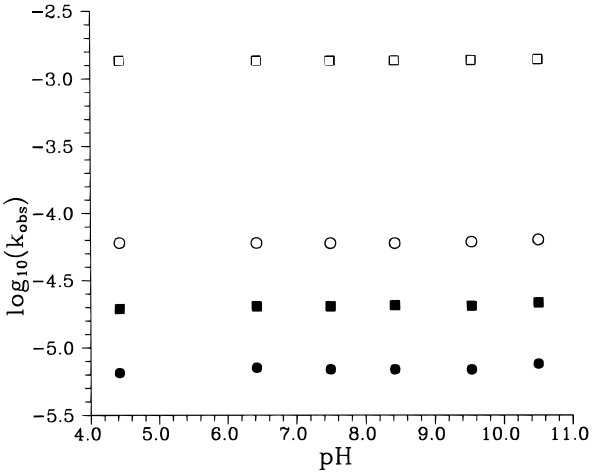


Figure 1. Plots of log(k_{obs}) versus pH for the hydrolysis of four 2-deoxy-α-D-glucopyranosyl pyridinium salts, T = 65 °C, 0.01 M phosphate buffer (1:1 NaH_2PO_4:Na_2HPO_4), μ = 2.0 ($NaClO_4$): ○, **4a**; ●, **4b**; ■, **4c**; and □, **4d**. Error limits are encompassed within the symbol diameter.

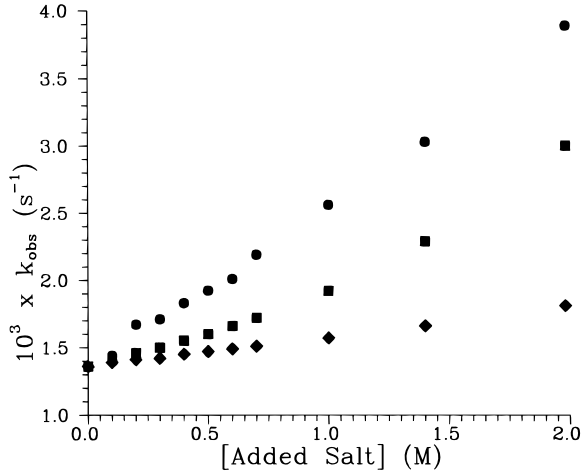
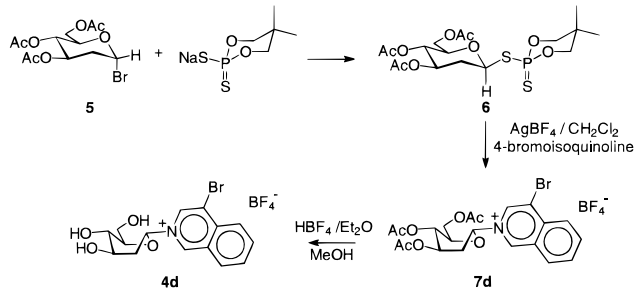


Figure 2. Plots of k_{obs} versus added salt concentration for **4d**, T = 65 °C, 0.01 M phosphate buffer (1:1 NaH_2PO_4:Na_2HPO_4), μ = 2.0 ($NaClO_4$): ◆, NaCl; ■, NaOAc; and ●, NaN_3. Error limits are encompassed within the symbol diameter.

Scheme 1



the hydrolysis products that resulted from the carbohydrate portion of **4d** was performed by ^{13}C-NMR analysis of the products from the reactions of 1-^{13}C-labeled-**4d** (**8**) using a previously published procedure[5] (see Supporting Information for the complete experimental details).

Results

Synthesis of the thermodynamically less stable α-anomers of the 2-deoxyglucopyranosyl pyridinium salts proved problematic. Many different synthetic routes, including that utilized by Lemieux and Morgan for the synthesis of the parent α-D-glucosyl compounds,[13] gave mixtures, enriched in the more stable β-compound, from which the α-anomer could not be purified. Eventually, the preparation of the desired compounds (**4a**−**d**) from the available starting material tetra-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide[5] (**5**) followed the route that is outlined in Scheme 1. The anomeric configuration of the glycoside linkage was confirmed by the observed coupling constants of the anomeric proton to the two protons on C-2 of 4.1 and 4.9 Hz (see Materials and Methods).

Plots of the experimentally determined relationship between log(k_{obs}) and the solution pH for the four 2-deoxy α-D-glucopyranosyl pyridinium salts (**4a**−**d**) are presented in Figure 1. A complete record of the experimental data obtained for these hydrolysis reactions is given in Table S1 of the Supporting Information.

A nonlinear, negative salt effect similar to that reported for **1**[5] is exhibited by **4d** during its solvolysis in water. The relevant hydrolysis rate constant data for **4d** is given in Table S2 of the Supporting Information. The effect of added salts on the rates of hydrolysis of **4d** was investigated under conditions in which the ionic strength was maintained at 2.0 M with $NaClO_4$, enabling a comparison of the results with that of the published hydrolysis data for both 2-deoxy-β-D-glucopyranosyl pyridinium salts[5] and for α-D-glucopyranosyl fluoride hydrolysis.[7] Plots of the experimentally determined relationship between k_{obs} and the salt concentration for three of the six monoanionic nucleophiles are presented in Figure 2. A complete record of the experimental data obtained for the hydrolysis of **4d** (μ = 2.0; $NaClO_4$) is given in Table S3 of the Supporting Information.

Table 1. Calculated Second-Order Rate Constants for the Reaction of **4d** with Various Anions at 65 °C, in 0.01 M Phosphate Buffer, μ = 2.0[a]

salt	$10^4 \times k_2^{calc}$ [b] (M^{-1} s^{-1})	n (MeBr in H_2O)[c]
$NaNO_3$	2.74 ± 0.15	1.0
NaOAc	4.74 ± 0.07	2.7
NaCl	2.66 ± 0.13	3.0
NaBr	2.11 ± 0.12	3.9
NaN_3	11.5 ± 1.0	4.0
NaSCN	2.74 ± 0.15	4.77

[a] Linear fit of the data from Table S2, with [NaX] ≤ 0.500 M; ionic strength maintained with $NaClO_4$. [b] Mean value of three kinetic runs; quoted error = σ_{n-1}. [c] Swain−Scott parameter for reactions of methyl bromide in water.[14b]

In order to compare the effect of added salts on the reaction rates of **4d** to the previously reported hydrolysis rates for α-xylopyranosyl 4′-bromoisoquinolinium bromide,[4] hydrolysis rate constants for **4d** (k_{obs}) were also measured using 0.99 M salt in 0.01 M phosphate buffer (μ = 1.01) at 65 °C. The observed rate constants as well as with the Swain−Scott nucleophilic parameter n for each anion studied are tabulated in Table 2.[14]

The aromatic product obtained from the reactions of **4d** was shown by UV−vis spectroscopy to be 4-bromoisoquinoline, while the carbohydrate-based products were analyzed by ^{13}C-

(13) (a) Lemieux, R. U.; Morgan A. R. *Can. J. Chem.* **1965**, *43*, 2205−2213. (b) Hosie, L.; Marshall, P. J.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1121−1131.

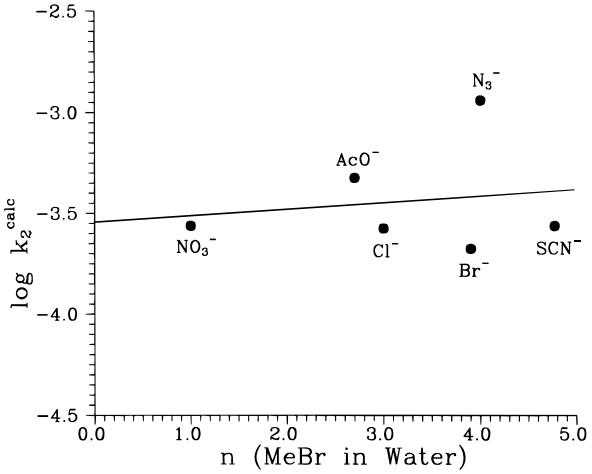


Figure 3. Plot of the Swain−Scott correlation of the calculated second-order rate constants log k_2^{calc} versus n (CH_3Br in H_2O)[14b] for **4d**, T = 65 °C, 0.01 M phosphate buffer (1:1 NaH_2PO_4:Na_2HPO_4; μ = 2.0, $NaClO_4$). Error limits are encompassed within the symbol diameter. The line shown is the least-squares fit through the data points (see Discussion). The calculated slope of the line is 0.03 ± 0.10.

Table 2. Observed Rate Constants (k_{obs}) for the Hydrolysis of 2-Deoxy-α-D-*arabino*-Hexopyranosyl 4′-Bromoisoquinolinium Tetrafluoroborate with Added Salts (0.99 M) at 65.0 °C in 0.01 M Phosphate Buffer (μ = 1.01)

added salt	$10^3 \times k_{obs}$[a] (s^{-1})	n (MeBr in H_2O)[b]
$NaClO_4$	1.75 ± 0.01	0[c,d]
$NaNO_3$	2.26 ± 0.01	1.0
NaF	2.99 ± 0.01	2.0
NaOAc	2.81 ± 0.01	2.7
NaCl	2.33 ± 0.01	3.0
NaBr	2.14 ± 0.01	3.9
NaN_3	3.51 ± 0.01	4.0
NaSCN	2.15 ± 0.01	4.77
NaI	1.87 ± 0.03	5.04

[a] Mean value of three kinetic runs; quoted error = σ_{n-1}. [b] Swain−Scott parameter for reactions of methyl bromide in water.[14b] [c] Swain−Scott constant for H_2O. [d] Rate constant in the absence of added salts = 2.83 ± 0.01 × 10^{-3} s^{-1} (μ = 0.02).

NMR spectroscopy using 1-^{13}C-labeled **4d** (**8**) as the starting material. Compound **8** was synthesized from the (1-^{13}C)-labeled isotopomer of hexopyranosyl bromide **5** (Scheme 1).[5] The observed ^{13}C-NMR resonances in the anomeric region of the spectrum for the carbohydrate-based reaction products of **8** in perchlorate- and acetate-containing buffers coincided with those from an authentic sample of 2-deoxyglucose. Two additional products that formed in the presence of azide ion were identified as 2-deoxy-α- and 2-deoxy-β-D-glucopyranosyl azide (**9** and **10**, respectively). The relative proportions of the anomeric azide products were quantified by ^{13}C-NMR spectroscopy using acquisition parameters that were selected so as to exclude NOE enhancements of ^{13}C-signal intensity.[5] Table 3 presents the relative peak heights observed in the ^{13}C-NMR spectra (between 85 and 105 ppm) of the water soluble products that were obtained from the hydrolysis of **8** in the presence of added salts.

Since 2-deoxy-β-glucopyranosyl azide (**10**) undergoes a slow S_N2 reaction with azide ion to form the α-anomer (**9**), a small correction to the observed product distribution (Table 3) is required in order to calculate the intrinsic fraction of inverted azide product.[5] When **4d** is subjected for 15 min to the reaction conditions (Table 3), every product molecule of **10** resides in the aqueous medium an average of almost 11 min.[15] Therefore, since a small quantity of **10** (≈1.5%)[16] reacts with azide ion via an S_N2 (A_ND_N) reaction to form **9**, an estimated 92% of the initial azide product is formed with inversion of anomeric configuration.

Table 3. Relative Peak Heights from the ^{13}C NMR Spectra (100 MHz; H_2O:D_2O 2:1) of the Carbohydrate-Based Products Obtained from the Hydrolysis of **8** in 0.01 M Phosphate Buffer, [NaN_3] = 0.99 M, and [Salt] = 0.99 M at 65 °C[a]

entry	salt	2-deoxy-β-D-glucose	2-deoxy-α-D-glucose	2-deoxy-α-D-gluco-pyrano-sylazide **9**	2-deoxy-β-D-gluco-pyrano-sylazide **10**	n[b]
1	NaN_3	0.18	0.16	0.09	1.00	4.0
2	KF	0.39	0.37	0.10	1.00	2.0
3	KCl	0.38	0.37	0.11	1.00	3.0
4	NaCl	0.37	0.36	0.11	1.00	3.0
5	NaBr	0.38	0.39	0.09	1.00	3.9
6	NaOAc	0.37	0.35	0.10	1.00	2.7

[a] Peak heights are relative to that of 2-deoxy-β-D-glucopyranosyl azide (**10**). [b] Swain−Scott parameter for the reaction of CH_3Br in H_2O taken from ref 14b.

Table 4. Relative Peak Heights Measured from the ^{13}C NMR Spectra (100 MHz; H_2O:D_2O 2:1) of the Carbohydrate-Based Products Obtained from the Reactions of **8** and **13** in 20% Aqueous Methanol with 0.01 M Phosphate Buffer Containing [NaN_3] = 0.99 M and [NaOAc] = 0.99 M at 65 °C

	2-deoxy-α-D-gluco-sylazide **9**	2-deoxy-β-D-gluco-sylazide **10**	methyl 2-deoxy-α-D-glucoside **11**	methyl 2-deoxy-β-D-glucoside **12**	2-deoxy-β-D-glucose	2-deoxy-α-D-glucose
alpha[a]	0.08	1.00	0.04	0.06	0.26	0.25
alpha[a,b]	0.09	1.00	0.03	0.06	0.23	0.24
beta[c,d]	1.00	0.08	0.18	ND[e]	0.63	0.60
beta[b,c,d]	1.00	0.11	0.18	ND[e]	0.66	0.52

[a] Reaction time 15 min. [b] Repeat measurement. [c] Reaction time 120 min. [d] Observed ratio of **9:10**:2-deoxy-β-D-glucose:2-deoxy-α-D-glucose formed in the absence of methanol is 1.00:0.10:0.84:0.80, ref 5. [e] Not detected, <0.02.

When the solvolysis medium contains methanol, both anomers of methyl 2-deoxyglucopyranoside are potential products. The presence of these isomers in the product mixture was confirmed by a comparison of the observed signals with the reported ^{13}C NMR chemical shifts of δ = 89.8 and δ = 89.4 for methyl 2-deoxy-α-D-*arabino*-hexopyranoside **11** and methyl 2-deoxy-β-D-*arabino*-hexopyranoside **12**, respectively.[18] Tables 4 and 5 list the relative peak heights that are observed in the ^{13}C NMR spectra obtained for the solvolysis of **8** and **13** [(1-^{13}C)-labeled **1**[5]] in a 20% v/v aqueous methanol solution containing 0.01 M phosphate buffer, 0.99 M NaN_3, and either 0.99 M NaOAc (Table 4) or 0.99 M $NaClO_4$ (Table 5).

Discussion

The derived rate constants for the hydrolysis reactions of **4a**−**d** (Table S1, Supporting Information) were all independent of pH between 4.4 and 10.5 pH units, indicating that these

(14) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141−147. Ibne-Rase, K. M. *J. Chem. Educ.* **1967**, *44*, 89−94. Koivurinta, J.; Kyllönen, A.; Leononen, L.; Valaste, K.; Koskikallio, J. *Finn. Chem. Lett.* **1974**, 239−243.

(15) This is calculated by subtracting the average time before a molecule of **3d** reacts (i.e., 1/k)[16] from the total time of the reaction.

(16) Wilkinson, F. *Chemical Kinetics and Reaction Mechanisms*; Van Nostrand Reinhold: New York, 1980; p 17.

(17) When **11** is reacted in the presence of 1.98 M NaN_3 for 2 h at 65 °C, the ratio of **10**:**11** is 0.15:1.00.[5]

(18) Bock, K.; Pedersen, C. *Adv. Carbohyd. Chem. Biochem.* **1983**, *41*, 27−66.

Table 5. Relative Peak Heights Measured from the ^{13}C NMR Spectra (100 MHz; H_2O:D_2O 2:1) of the Carbohydrate-Based Products Obtained from the Reactions of **8** and **13** in 20% Aqueous Methanol with 0.01 M Phosphate Buffer Containing [NaN_3] = 0.99 M and [$NaClO_4$] = 0.99 M at 65 °C

	2-deoxy-α-D-glucosyl-azide **9**	2-deoxy-β-D-glucosyl-azide **10**	methyl 2-deoxy-α-D-glucoside **11**	methyl 2-deoxy-β-D-glucoside **12**	2-deoxy-β-D-glucose	2-deoxy-α-D-glucose
alpha[a]	0.07	1.00	0.04	0.06	0.25	0.23
alpha[a,b]	0.05	1.00	0.05	0.07	0.19	0.19
beta[c]	1.00	0.07	0.21	0.03	0.56	0.45
beta[b,c]	1.00	0.09	0.19	0.03	0.52	0.45

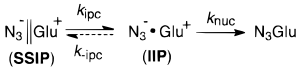
[a] Reaction time 15 min. [b] Repeat measurement. [c] Reaction time 120 min.

reactions are neither acid- nor base-catalyzed. Using the kinetic data from Table S1 and literature values for the leaving group pK_a's,[19] a β_{lg} value of 0.84 ± 0.08 can be calculated for the hydrolysis of 2-deoxy-α-glucopyranosyl pyridinium salts at 65 °C. This value for β_{lg} is derived from four data points and is similar to the values reported for the hydrolysis of 2-deoxy-β-glucopyranosyl pyridinium salts (three data points, 1.0 ± 0.1$_6$, 65 °C),[5] α-xylopyranosyl pyridinium ions (five data points, 1.28 ± 0.08, 25 °C),[13] and α-D-glucopyranosyl pyridinium salts (four data points, 1.06 ± 0.12, 25 °C).[13] All four of the above-listed β_{lg} values are consistent with the occurrence in these hydrolysis reactions of "late" transition states that involve substantial C−N bond cleavage.

Effect of the C-2 Hydroxyl Group and Added Salts on Reactivity. Using the data of Hosie *et al.*,[13] an estimated rate constant of 1.8×10^{-5} s^{-1} can be calculated for the hydrolysis of α-D-glucopyranosyl 4′-bromoisoquinolinium bromide at 65 °C. When both this value and the corresponding rate constant for hydrolysis of **4d** (Table 2) are considered, a rate-retarding effect of 97-fold at 65 °C can be correlated to the presence of the 2-OH group. This calculated value is lower than the reported rate retardation factor of 680 that is caused by the 2-OH group in the 2-deoxy-β-glucosyl pyridinium salt series.[5] The smaller effect on the reaction rate of the α-anomer is probably a result of steric destabilization of the $^1S_3$ skew-boat ground state conformation caused by the 2-OH group.[13] Whereas, for the β-pyridinium series which reside in the normal $^4C_1$ chair conformation, steric ground-state destabilization is absent. The calculated value of 0.03 ± 0.10 (μ = 2.0, $NaClO_4$) for the Swain−Scott sensitivity parameter (*s*) shows that, in a medium of approximately constant ionizing strength, the reaction rate of **4d** is insensitive to the nature of the added anion. Although evaluation of the effect of either fluoride or iodide on the reactivity of **4d** was unfeasible at high ionic strengths, the single point determinations reported in Table 2 indicate that $k_{obs}(F^-) > k_{obs}(Cl^-) > k_{obs}(Br^-) > k_{obs}(I^-)$. Consequently, the calculated value of *s* would be reduced even further if points for both fluoride and iodide were included on the graph shown in Figure 3.

Mechanism for the Hydrolysis of 2-Deoxy-α- and -β-Glucosyl Pyridinium Salts. Since the two anomeric 2-deoxyglucopyranosyl 4′-bromoisoquinolinium salts give different product ratios under identical conditions, these reactions cannot proceed through a common intermediate, thus reaffirming the conclusion that the 2-deoxyglucosyl oxocarbenium ion is not solvent-equilibrated in water.[5] The product distributions reported here for **4d** (Table 3) and for its β-anomer (**1**)[5] show

Scheme 2



that the reaction of **4d** in the presence of 1.98 M sodium azide gives more azide-substituted product than does the corresponding reaction of **1** (75% versus 50%[20]).

The observed variation in the product ratios that are formed during the reactions of **1** and **4d** with azide could originate from two possible sources, namely the following: (1) the reaction of α-D-glucopyranosyl pyridinium salts with azide has an S_N2 component or (2) the different intermediates formed in the reactions of **1** and **4d** have intrinsically different reactivities (and selectivities). Although the possibility of an S_N2 component to the reaction is an attractive explanation given that azide displays a positive deviation from the Swain−Scott correlation (Figure 3), several other observations suggest that it is the intrinsic reactivity differences of the two intermediates that accounts for the variation in product composition.

The critical observations are as follows:

(1) The relative rate ratios for the reaction of **4d** with added salts are similar to those reported for α-xylopyranosyl 4′-bromoisoquinolinium bromide,[4,21] despite the presence in the latter compound of a 2-hydroxyl group which should destabilize an oxocarbenium ion intermediate.[22] As a consequence, it would be expected that the reactions of α-xylopyranosyl 4′-bromoisoquinolinium salts should display a greater positive deviation than **4d** in a Swain−Scott correlation.

(2) In comparison to **1**, the reactions of **4d** with azide give more inverted product (70% for **4d** versus 50% for **1**)[20] and more retained product (6% for **4d** versus 2% for **1**). However, if the reactions of α-D-glucopyranosyl pyridinium salts with azide have an S_N2 component, then less of the reaction would proceed via cationic intermediates and less retained product would be observed (see also the discussion on lifetimes given below).

(3) Jencks and Banait showed that the reaction of α-D-glucopyranosyl fluoride with pyridine does not yield any β-D-glucopyranosyl pyridinium salt, i.e., there is no S_N2 component in this reaction containing a neutral nucleophile and an anionic leaving group.[23]

(4) A greater fraction of methyl glycoside product (Tables 4 and 5) is formed with inversion in the reactions of the β-anomer (**1**) rather than in the reactions of the α-anomer (**4d**). Thus, the face reactivity is opposite to what would be expected if the reactions of **4d** have an S_N2 component, whereas this relative face reactivity is in the same direction to that reported by Perrin and Engler for attack on the dioxocarbenium ion **2**.[7]

Unified Scheme. The hydrolysis reactions of **1** follow a stepwise $D_N * A_N6$ mechanism, with the first formed intermediate being a solvent separated ion-pair:molecule complex (**SSIP: M**).[5] Formation of azide substitution products requires the conversion of a solvent-separated ion-pair **SSIP**, either prior to or following diffusional separation of the pyridine from the complex, into an intimate ion-pair (**IIP**), and collapse of this ion-pair to yield a covalent adduct (Scheme 2).

(19) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965.

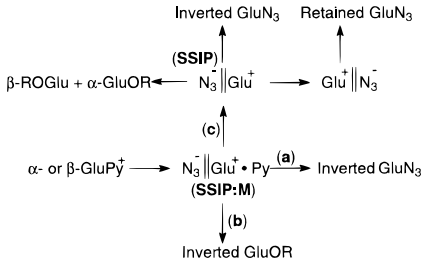
(20) Rounded to nearest 5%.

(21) The rate ratios $k_X^-/k_{ClO_4^-}$ for the reactions of **4d** are 1.61, 1.71, 2.01, 1.33, and 1.22 (65 °C) for X = OAc, F, N_3, Cl, and Br, respectively, whereas the corresponding ratios for α-D-xylopyranosyl 4′-bromoisoquinolinium bromide (80 °C) are 2.03, 1.95, 2.17, 1.54, and 1.50 (ref 4).

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

(23) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951−7958.

Scheme 3



The procedure of Banait and Jencks[23] can be used to estimate a rate constant (k_{nuc}) for collapse of the intimate ion-pair to give glucosyl azide of around $10^{16}-10^{18}$ s^{-1}. Since this predicted value for k_{nuc} is much greater than the rate constant for dissociation of the intimate ion-pair (k_{-ipc}), the slow step for formation of azide product from the solvent-separated ion pair involves ion-pair interconversion k_{ipc}.

Scheme 3 illustrates the mechanistic outline for the reaction of the solvent-separated ion-pair:molecule complexes (**SSIP: M**) formed during the reactions of each of the anomeric 2-deoxyglycopyranosyl pyridinium salts with azide ion.

The three pathways for evolution of the diastereomeric complexes produced during the reactions of **1** and **4d** into products are labeled as (**a**), (**b**), and (**c**) in Scheme 3 and involve: (**a**) formation of inverted azide product via initial conversion to an intimate ion-pair; (**b**) formation of an inverted solvolysis product by direct capture of the glucosyl-cation by solvent prior to the dissociation of the pyridine leaving group from the complex; and (**c**) diffusional separation of the pyridine from the complex, which yields an **SSIP**, a process with a rate constant of approximately 10^{11} s^{-1}.[24] The newly formed **SSIP** can then collapse to give both anomers of the solvolysis product or, alternatively, inverted azide product. However, to yield a retained azide product, the **SSIP** must first be transformed into the diastereomeric **SSIP**. This transformation could occur either via a free oxocarbenium ion followed by azide association or via translocation of the intimate azide ion onto the opposite face of the cation.

Nevertheless, since the majority of azide product formed in these reactions is generated with inversion of stereochemistry, it is likely that most of the azide reaction occurs via pathway (**a**) shown in Scheme 3. Solvent reorganization is required for the conversion of the initial ion-pair intermediate to give an intimate ion-pair (**IIP**). This process (k_{ipc}), which requires reorganization of the local solvation shell by the dielectric relaxation of solvent, is anticipated to occur at a rate of about 10^{11} s^{-1}.[25] Therefore, if the approximation is made that the fraction of reaction which generates an azide-containing **SSIP:M** ($X = N_3^-$, Scheme 4) at constant ionic strength is directly related to fraction of azide present $f_{N_3^-} = [N_3^-]/([N_3^-] + [X^-])$, i.e., the rate constant for formation of the complex (k_{form}) is independent of the nature of X^-,[26] then eq 1 can be derived from Scheme 4 ($k_{N_3^-} = 0$).[27]

$$f_{az} = 1 - \frac{f_{az}}{f_{N_3^-}}\left(\frac{k_{SOH}}{k_{ipc}}\right) \qquad (1)$$

Given the approximation noted above, eq 1 should generate estimates for the solvent capture rate constants (k_{SOH}) if there are no S_N2 components in these substitution reactions, i.e., $k_{N_3^-} = 0$. Figure 4 shows a plot of the fraction of azide product (f_{az}) versus f_{az} divided by $f_{N_3^-}$ for the reactions of **4d** and **1** in 0.01 M phosphate buffer (μ = 2.0, $NaClO_4$) at T = 65 °C.[29] Assuming that the rate constant k_{ipc} is on the order of 10^{11} s^{-1}, the derived estimates for the rate of reaction of solvent (k_{SOH}) with the two oxocarbenium ion intermediates generated from **1** and **4d** are 1.4×10^{11} s^{-1} and 7.3×10^{10} s^{-1}, respectively. These calculated values for the rate of solvent capture of the cationic intermediates formed in the reactions of both **1** and **4d** provides further evidence that the majority of azide product arises from a SSIP intermediate and not via an S_N2 reaction, specifically. (1) If a large proportion of product in these reactions were formed via an S_N2 pathway ($k_{N_3^-}$) the *y*-axis intercept of the calculated best-fit lines to eq 1 should not be equal to 1; however, the computed intercepts are 1.04 ± 0.02 and 0.94 ± 0.02 for the reactions of **4d** and **1**, respectively. (2) In solutions containing 1.98 M NaN_3 about 6% of the total product formed in the reactions of **4d** is retained azide, while the corresponding value for retained azide in the reactions of **1** is approximately 2%,[5] (3) The maximal pseudo-first-order rate for the capture of a free carbenium ion by 2.0 M azide to give a specific azide product is around 5×10^9 s^{-1}.[30] (4) Using the estimated values for k_{SOH} the expected fractions of retained azide products are

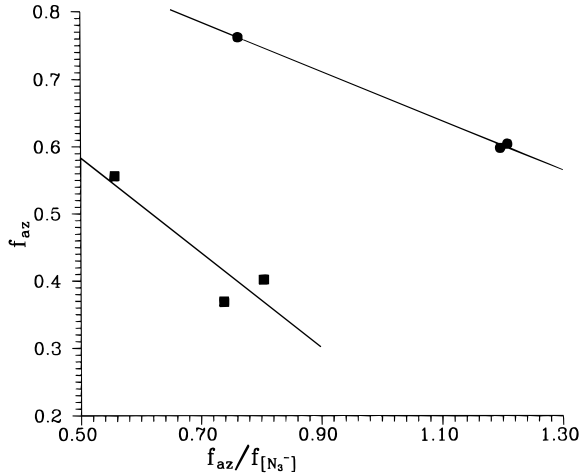
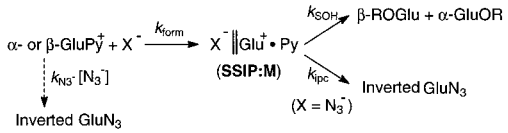


Figure 4. Plot of the fraction of azide product (f_{RN_3}) versus the fraction of azide product divided by the fraction of azide ion $f_{N_3^-}$ for the reactions of ●, **4d**; and ■, **1**; in 0.01 M phosphate buffer (1:1 NaH_2PO_4:Na_2HPO_4; μ = 2.0, $NaClO_4$) at T = 65 °C. The lines shown are the least-squares fits to the data points.

Scheme 4



(24) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1−19.

(25) Giese, K.; Kaatze, U.; Pottel, R. *J. Phys. Chem.* **1970**, *74*, 3718−3725. Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371−374. Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys. Chem.* **1992**, **96**, 6017−6020.

(26) Using the data from Table 2, k_{form}(azide)/k_{form}(fluoride) = 1.17 and k_{form}(azide)/k_{form}(acetate) = 1.25.

(27) Equation 1 is a slight modification from that utilized in the Jencks "azide-clock" methodology[28] where the term $k_{N_3^-} \times [N_3^-]$ has been replaced by the term $f_{N_3^-} \times k_{ipc}$.

(28) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689-4691. Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361-1372. Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455-1465.

(29) Only shown are the data where the introduction of a second anion does not effect the quantity of retained azide formed, specifically shown are the three points: (1) 1.98 M azide; (2) 0.99 M azide containing 0.99 M acetate; and (3) 0.99 M azide containing 0.99 M fluoride.

(30) Assuming that one-half of the attack by azide on a glucosyl oxocarbenium ion gives the α-azide product (the other one-half gives the β-anomer), i.e., 5×10^9 M^{-1} $s^{-1} \times 2.0$ M × 0.5 = 5×10^9 s^{-1}.

3.4% and 6.4% for the reactions of **1** and **4d**, respectively (in close agreement with the experimental values). (5) If there was an S_N2 (A_ND_N) component to these reactions, the computed values for k_{SOH} would be underestimated and thus, less retained azide product should have been formed. Consequently, the fraction of retained azide product formed in these reactions is consistent with little or no reaction occurring via direct nucleophilic displacements on the starting pyridinium salts (i.e., $k_{N_3^-} \approx 0$, Scheme 4).

Reaction with Solvent. Solvolysis of both **1** and **4d** in 20% aqueous methanol yields appreciably quantities of methyl glycosides, whereas Banait and Jencks reported that even in 90% aqueous methanol the reaction of α-D-glucopyranosyl fluoride gave only glucose as the product.[23] These markedly different results deserve comment, the reactions of glycosides with pyridine leaving groups display all of the features associated with dissociative (S_N1) reactions namely (a) independence of reaction rate on nucleophilicity; (b) a reaction center ^{13}C-kinetic isotope effect (KIE) in the range associated with S_N1 reactions;[31,32] and (c) capture by both components of a binary solvent mixture (Tables 4 and 5). The reactions of α-D-glucopyranosyl fluoride with water at 30 °C have been analyzed by Banait and Jencks as proceeding via an S_N1 transition state based on the measured value for the solvent deuterium KIE (k_{H2O}/k_{D2O}) of 0.91.[33] In contrast at the higher temperature of 80 °C, Zhang *et al*. analyzed the measured anomeric ^{13}C-KIE for the water reaction of α-D-glucopyranosyl fluoride of 1.032 as consistent with an S_N2-like reaction transition state.[31,34] Therefore, the water reaction of α-D-glucopyranosyl fluoride might be another example of a reaction that is finely balanced between two different mechanistic pathways as a result of the borderline existence of an intermediate. For example, the acid-catalyzed hydrolysis of 4-nitrophenyl β-D-glucopyranoside at 80 °C proceeds via specific-catalysis[35] but goes by way of a general-catalyzed reaction at 50 °C.[35,36] Alternatively, since the estimated lifetimes of the **SSIP**s generated from **1** and **4d**, and that of any intermediate formed in the water reaction of α-D-glucopyranosyl fluoride, are very short, the pyranosyl ring cannot become conformationally equilibrated before reaction with solvent occurs. Consequently, it cannot be ruled out that the observed selectivities for the solvent reactions of α-D-glucopyranosyl fluoride, **1**, and **4d** originate from intrinsic reactivity differences of various ring conformations of the carbenium ion intermediates.

Conclusions

The work presented in this paper shows that the hydrolyses of the 2-deoxy-α-glucopyranosyl 4′-bromoisoquinolinium salt (**4d**) and the corresponding β-anomer do not give a common intermediate. In addition, the diastereotopic intermediate (**SSIP: M**) formed in the reaction of the α-anomeric pyridinium salt (**4d**) has a longer lifetime ($\approx 2.7 \times 10^{-11}$ s) than the corresponding intermediate formed during the reactions of **1** ($\approx 1.4 \times 10^{-11}$ s). This conclusion is also supported by the observation that a greater fraction of both retained glycosyl azide and methyl glycoside are formed in the reactions of **4d** than in the reactions of **1** (Tables 4−6). Hence, these data are consistent with the rate of solvent reaction that occurs on the two diastereomeric faces of a 2-deoxyglucosyl cationic intermediate differing by approximately 2-fold, with attack occurring more rapidly on the α-face.

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Supporting Information Available: Text giving experimental details for the synthesis of **4a**−**c** and **8** and tables listing observed rate constants for the hydrolysis of **4a**−**d** as a function of pH and for the hydrolysis of **4d** as a function of added nucleophile concentration (8 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

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