Solvolyses of 2-Deoxy-α- and β-D-Glucopyranosyl 4′-Bromoisoquinolinium Tetrafluoroborates

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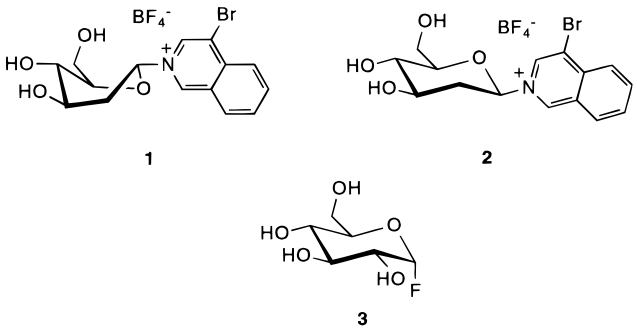
Received March 21, 2000

The solvolyses of 2-deoxy-α- and β-D-glucopyranosyl 4′-bromoisoquinolinium tetrafluoroborates (**1** and **2**) were monitored in aqueous methanol, ethanol, trifluoroethanol, and binary mixtures of ethanol and trifluoroethanol. The observed rate constants are consistent with the solvolyses of **1** and **2** proceeding via dissociative (D_N * A_N) transition states. In comparison to the α-anomer, solvolysis of the β-compound gives a greater transition state charge delocalization onto the ring oxygen atom. Analysis of the solvolysis product ratios indicates that the 2-deoxyglucosyl oxacarbenium ion is not solvent-equilibrated in the solvent mixtures studied. In the solvolysis of compound **1**, the solvent trifluoroethanol facilitates diffusional separation of the leaving group and, in so doing, promotes the formation of the retained trifluoroethyl glycoside.

Introduction

Despite the apparent simplicity of nucleophilic substitution at acetal and ketal centers, deciphering the intimate mechanistic details of these reactions continues to be an ongoing research goal.[1] Historically, it was considered that the specific acid-catalyzed hydrolysis of glycopyranosides occurs with unassisted, rate-limiting, exocyclic C−O bond cleavage of the protonated glycoside to generate a solvent-equilibrated, cyclic oxygen-stabilized carbocationic intermediate and a neutral alcohol.[2,3] Yet the hydrolyses of methoxymethyl derivatives proceed through so-called "exploded" associative transition states in which there are weak bonding interactions to both the nucleophile (nuc) and the leaving group (lg).[4,5] In 1991, Banait and Jencks reported that, in water, α-D-glucopyranosyl fluoride reacts via a concerted A_ND_N (S_N2) mechanism.[6] Furthermore, these authors noted that in aqueous methanol (up to 90% v/v MeOH) the only observed carbohydrate product was glucose.[6] This unprecedented selectivity for water in a nucleophilic substitution reaction must arise from a stringent transition state requirement for water to act as the nucleophile, perhaps with general-base catalysis from a second molecule of solvent. In a more recent study, Zhang et al.[7] concluded that, based on measured anomeric carbon kinetic isotope effect (KIE, k^{12}_C/k^{13}_C) data, the hydrolysis of α-D-glucopyranosyl fluoride occurs via an "exploded" S_N2 transition state.[8]



In contrast to the above mechanistic picture for α-D-glucopyranosyl fluoride (**3**), recent studies by Bennet and co-workers concluded that nucleophilic substitution reactions of 2-deoxy-α- and β-D-glucopyranosyl 4′-bromoisoquinolinium salts (**1** and **2**) occur via solvent-separated ion−molecule complexes, involving a stepwise D_N * A_N mechanism.[9]

The anomeric 4′-bromoisoquinolinium salts (**1** and **2**), which are models for O-protonated glycosides, react to form nonconformationally equilibrated diastereomeric intermediates that are captured by solvent approximately 2-fold more readily on the α- than on the β-face.[9] From their data, Bennet and co-workers estimated that the lifetimes for the two diastereomeric 2-deoxyglucopyranosyl oxacarbenium ions in water are between ∼1.4×10^{-11} and 2.7×10^{-11} s.[9b,10] After correcting these data for the effect of the 2-hydroxyl group,[11] an estimated lifetime of between 3.5×10^{-12} and 6.8×10^{-12} s is

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(1) For some recent examples, see: Liras, J. L.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1997**, *119*, 8191−8200. Horenstein, B. A.; Bruner, M. *J. Am. Chem. Soc.* **1996**, *118*, 10371−10379. Jagannadham, V.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 8465−8466.

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(8) Melander, L.; Saunder, W. H. *Reaction Rates of Isotopic Molecules*; Wiley Interscience: New York, 1980; pp 235−248.

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(10) The quoted k_{SOH} values in refs 9b (p 3892) are 2-fold too large, although the quoted lifetimes ($1/k_{SOH}$) are correct.

10.1021/jo0004106 CCC: $19.00
Published on Web 06/16/2000

obtained for the glucosyl cation, a value that is slightly larger than the lifetime of 1×10^{-12} s predicted by Amyes and Jencks.[11]

In 1980, Sinnott and Jencks observed that solvolysis of several glucopyranosyl derivatives generated products that depended on both the identity of the leaving group and the anomeric configuration of the starting material.[12] From their study, Sinnott and Jencks concluded that no solvent-equilibrated intermediates were formed in the reactions. Recently, a semiempirical approach was used to calculate the kinetic and thermodynamic stabilities of pyranosyl oxacarbenium ions generated from pyridinium[13] and protonated methyl glycosides.[14] However, when the semiempirical results were compared with those from published kinetic data of reactions in solution, these researchers were unable to interpret whether the cyclic oxacarbenium 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.[13,14]

The present report addresses the question of whether the 2-deoxyglucosyl oxacarbenium ion becomes a solvent-equilibrated intermediate when the solvolysis reactions are run in the absence of good nucleophiles such as azide. To this end, rate constant data and product study results are presented for the solvolysis of the two anomeric 2-deoxyglucosyl 4′-bromoisoquinolinium tetrafluoroborates (**1** and **2**) in aqueous mixtures of methanol, ethanol, and trifluoroethanol, as well as in binary combinations of ethanol and trifluoroethanol.

Experimental Section

Materials and Methods. Ethanol and methanol were dried by distillation from their respective magnesium alkoxide salts, while 2,2,2-trifluoroethanol (TFE) was dried by distillation from anhydrous calcium sulfate and sodium carbonate. Deionized water was further purified by use of a "Milli-Q ultra pure water" system. NMR spectra were acquired at operating frequencies of 400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively, using either $CDCl_3$ or D_2O as the solvent and internal reference. Coupling constants are reported in hertz, and melting points are uncorrected. 2-Deoxy-α-D-glucopyranosyl 4′-bromoisoquinolinium tetrafluoroborate (**1**)[9,15] and 1,6-anhydro-2-deoxy-β-D-glucopyranose (**5**)[17] were made using previously published methods. Full synthetic details for the synthesis of methyl-, ethyl-, and trifluoroethyl 2-deoxy-α- and β-D-glucopyranosides and 2-deoxy-β-D-glucopyranosyl 4′-bromoisoquinolinium tetrafluoroborate (**2**) are given in the Supporting Information.

Kinetics. The solvolysis reactions of compounds **1** and **2** ($\sim 2 \times 10^{-4}$ M) were conducted at 65 °C and were monitored by following the decrease in absorbance at 337 nm using a Cary 3E UV−vis spectrophotometer equipped with the Cary six-cell Peltier constant-temperature accessory. Reactions were initiated by the injection of a stock solution of **1** and **2** (5 μL, 40 mM) into a binary solvent mixture (1.00 mL) containing *N*-methylmorpholine (3 equiv). Rate constants were calculated by nonlinear least-squares regression of the absorbance versus time data to a standard first-order rate equation.

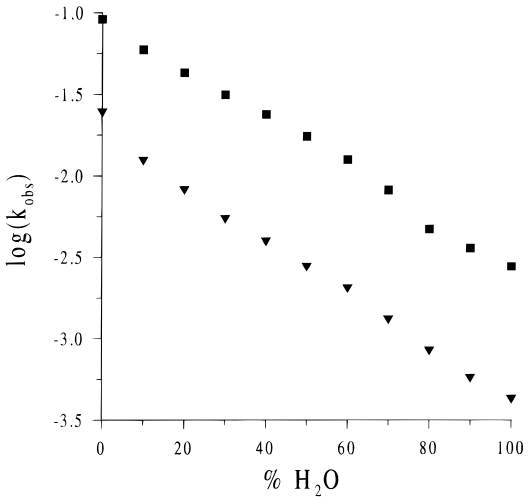

Figure 1. Plot of log(k_{obs}) versus percent water (v/v) for solvolysis of **1** (■) and **2** (▼) in ethanol/water mixtures, T = 65 °C. Error limits are encompassed within the symbol diameter.

Product Studies. The solvolytic product studies were performed by heating for $10 \times t_{1/2hyd}$ at 65 °C a sealed vial that contained a solution of the 4-bromoisoquinolinium salt (1.25 mg/mL) and *N*-methylmorpholine (0, 1, 2, or 3 equiv) in a binary solvent mixture (0.50 mL). After cooling, the reaction vial was opened and a solution of the internal standard methyl α-D-glucopyranoside in methanol (8 μL, 5.0 mg/mL) was added. Removal of the solvent under reduced pressure afforded a solid residue, which was dried under vacuum (∼0.01 mmHg) overnight. After derivatization of the carbohydrate products with a standard silylating reagent,[18] the resultant solution was analyzed using GC as detailed in the Supporting Information. All GC product yields were calculated using a standard calibration curve.

Results

The solvolysis reactions of the anomeric salts (**1** and **2**) were run in aqueous mixtures of methanol, ethanol, and trifluoroethanol and in binary combinations of ethanol and trifluoroethanol and were monitored by UV−vis spectroscopy. All solvolysis reactions in this study were performed without the addition of ionic strength adjusting salts due to the observation that even if the ionic strength is held constant, the reaction products for hydrolysis of **1** and **2** still vary with added salts.[9] Furthermore, to minimize perturbations caused by ion-pair complexes, both anomeric cations (**1** and **2**) were synthesized with the nonnucleophilic tetrafluoroborate counterion.

Listed in Tables S1 and S2 (Supporting Information) are the observed first-order rate constants for the aqueous alcoholysis at 65 °C of **1** and **2**. Table S3 (Supporting Information) details the corresponding rate constants for the reactions of **1** and **2** in ethanol/trifluoroethanol mixtures. A representative plot of the rate constant data for solvolysis of **1** and **2** in aqueous ethanol is shown in Figure 1.

Figure 2 presents a plot of $\log(k_{obs}/k_0)_\alpha$ versus $\log(k_{obs}/k_0)_\beta$, where k_0 is the observed rate constant in 80:20 v/v EtOH/H_2O. From the best linear fit to the data (Figure

(11) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888−7900.
(12) Sinnott, M. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2026−2032.
(13) Buckley, N. Oppenheimer, N. J. *J. Org. Chem.* **1996**, *61*, 8039−8047.
(14) Buckley, N. Oppenheimer, N. J. *J. Org. Chem.* **1996**, *61*, 8048−8062.
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(16) McNaught, A. D. *Pure Appl. Chem.* **1996**, *68*, 1919−2008.
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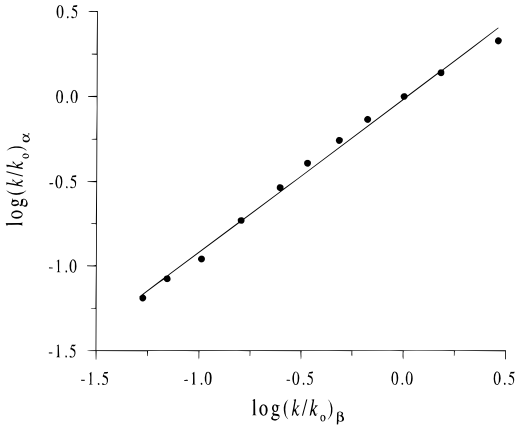

Figure 2. Plot of $\log(k_{obs}/k_0)_\alpha$ versus $(k_{obs}/k_0)_\beta$ for solvolysis of **1** and **2** in ethanol/water mixtures, $T = 65$ °C. The line shown is the best linear least-squares fit through the data points.

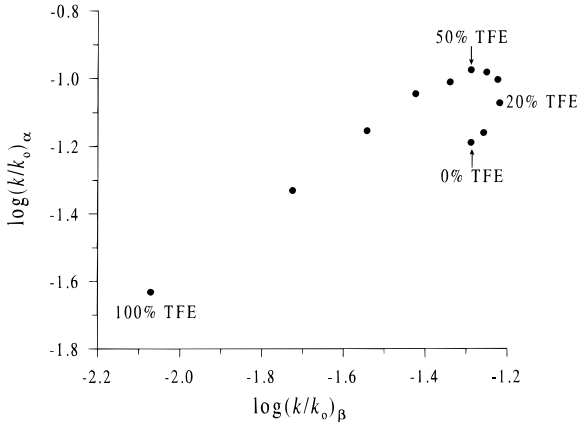

Figure 3. Plot of $\log(k_{obs}/k_0)_\alpha$ versus $(k_{obs}/k_0)_\beta$ for solvolysis of **1** and **2** in trifluoroethanol/water mixtures, $T = 65$ °C.

2), the apparent linear correlation indicates that the change in polarity of the $EtOH/H_2O$ solvent mixture has a similar, but slightly smaller effect on the solvolytic rate of the α-anomer (**1**) relative to that of the *β*-anomer (**2**). This difference can be quantified by the use of eq 1, where *S* is a sensitivity parameter.

$$\log(k_{obs}/k_0)_\alpha = S \log(k_{obs}/k_0)_\beta + \text{constant} \qquad (1)$$

The derived values of *S* (eq 1) for solvolysis of **1** and **2** in $MeOH/H_2O$, $EtOH/H_2O$, and EtOH/TFE mixtures are 0.934 ± 0.008, 0.906 ± 0.023, and 0.779 ± 0.003, respectively. In Figure 3 by contrast, a similar plot for the solvolytic reactions of **1** and **2** in TFE/H_2O displays a marked nonlinearity.

The standard Grunwald−Winstein equation (eq 2) is commonly used to analyze solvent effects on rate constants for $D_N + A_N$ (S_N1) substitution reactions, where the Y_X parameter is a measure of the solvent's ionizing power and *m* is a sensitivity variable.[19]

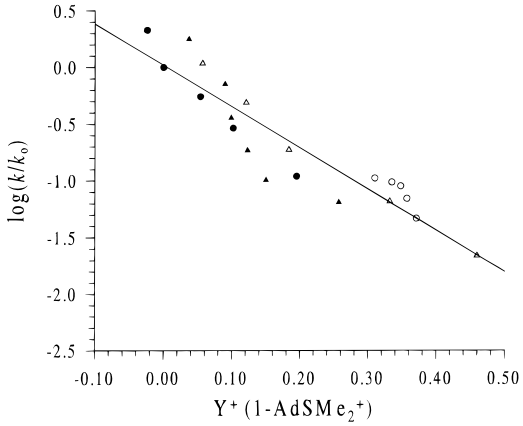

Figure 4. Plot of Grunwald−Winstein correlation for the solvolysis of **1** versus Y^+ in $MeOH/H_2O$ (▲), $EtOH/H_2O$ (●), TFE/H_2O (○), and TFE/EtOH (△) mixtures at $T = 65$ °C. The line shown is the best linear least-squares fit through the data points.

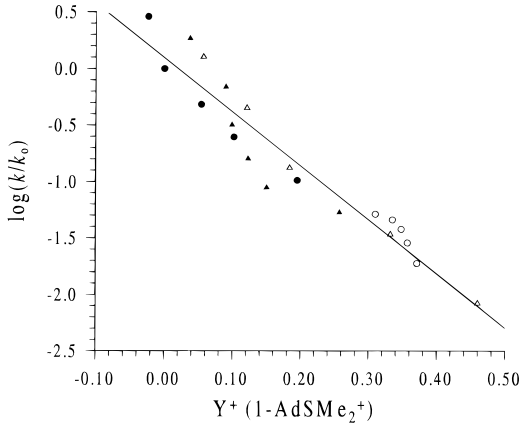

Figure 5. Plot of Grunwald−Winstein correlation for the solvolysis of **2** versus Y^+ in $MeOH/H_2O$ (▲), $EtOH/H_2O$ (●), TFE/H_2O (○), and TFE/EtOH (△) mixtures at $T = 65$ °C. The line shown is the best linear least-squares fit through the data points.

$$\log(k_{obs}/k_0) = m Y_X \qquad (2)$$

When the kinetic data given in Tables 1−3 is fit to eq 2 using Y^+ values that were calculated from the solvolysis of 1-adamantyl dimethylsulfonium triflate (70.4 °C),[20,21] the derived *m* values are −3.64 ± 0.34 and −4.78 ± 0.33 for the reactions of **1** and **2**, respectively. Figures 4 and 5 display the Grunwald−Winstein plots for the solvolyses of **1** and **2**.

To ensure that the alkyl 2-deoxyglucoside products are stable to the solvolytic conditions, all product studies on the solvolysis reactions of **1** and **2** were performed in the presence of 1 molar equiv of *N*-methylmorpholine. The products as well as the respective quantities of each product formed during the solvolysis of **1** and **2** were identified by standard GC analysis. Given in Tables S4−S12 (Supporting Information) are the measured product percentages and yields for the solvolytic reactions of **1** and **2**. In addition, to ensure that the solvolysis reactions

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(20) Kevill, D. N.; Anderson, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 1579−1585.

(21) The Y^+ values for aqueous trifluoroethanol (v/v) were interpolated from the values given in ref 20 that were measured using a weight−weight basis.

Table 1. Product Distribution from the Solvolyses of Compounds 1 and 2 in Aqueous Methanol (v/v) at 65 °C

MeOH	$(k_{MeOH}/k_{HOH})_1$	stereoselectivity$_1$[a]	$(k_{MeOH}/k_{HOH})_2$	stereoselectivity$_2$[a]
100%		2.86 ± 0.08		17.5 ± 1.1
90%	1.22 ± 0.03	2.82 ± 0.05	0.89 ± 0.01	16.9 ± 0.7
80%	1.19 ± 0.03	2.49 ± 0.08	0.89 ± 0.02	15.3 ± 0.7
70%	1.21 ± 0.02	2.25 ± 0.05	0.95 ± 0.01	14.1 ± 0.4
60%	1.32 ± 0.01	2.08 ± 0.03	0.94 ± 0.10	11.3 ± 1.4
50%	1.35 ± 0.02	1.92 ± 0.06	1.07 ± 0.02	12.8 ± 0.6
40%	1.42 ± 0.03	1.80 ± 0.08	1.11 ± 0.02	10.7 ± 0.5
30%	1.43 ± 0.02	1.70 ± 0.06	1.18 ± 0.05	9.7 ± 0.7
20%	1.53 ± 0.04	1.70 ± 0.12	1.30 ± 0.05	8.2 ± 3.0
10%	1.73 ± 0.05	1.65 ± 0.11	1.39 ± 0.09	NI[b]

[a] [Inverted glycoside]/[Retained glycoside]; see eq 4. [b] NI = not integrated; estimated that less than 0.7% methyl 2-deoxy-β-D-glucopyranoside was formed.

Table 2. Product Distribution from the Solvolyses of Compounds 1 and 2 in Aqueous Ethanol (v/v) at 65 °C

EtOH	$(k_{EtOH}/k_{HOH})_1$	stereoselectivity$_1$[a]	$(k_{EtOH}/k_{HOH})_2$	stereoselectivity$_2$[a]
100%		3.98 ± 0.19		11.4 ± 0.4
90%	0.61 ± 0.03	3.53 ± 0.20	0.41 ± 0.02	10.1 ± 0.4
80%	0.60 ± 0.03	2.87 ± 0.18	0.42 ± 0.01	9.2 ± 0.2
70%	0.64 ± 0.02	2.48 ± 0.12	0.45 ± 0.01	8.2 ± 0.2
60%	0.75 ± 0.04	2.28 ± 0.19	0.49 ± 0.01	7.4 ± 0.3
50%	0.82 ± 0.03	2.11 ± 0.12	0.54 ± 0.01	6.7 ± 0.3
40%	0.91 ± 0.03	2.01 ± 0.09	0.57 ± 0.03	6.7 ± 1.3
30%	0.95 ± 0.02	1.96 ± 0.08	0.53 ± 0.01	NI[b]
20%	1.11 ± 0.07	2.06 ± 0.16	0.58 ± 0.01	ND[c]
10%	1.31 ± 0.03	2.32 ± 0.09	0.68 ± 0.02	ND[c]

[a] [Inverted glycoside]/[Retained glycoside]; see eq 4. [b] NI = not integrated; estimated that less than 0.9% ethyl 2-deoxy-β-D-glucopyranoside was formed. [c] ND = not detected; no peak for ethyl 2-deoxy-β-D-glucopyranoside was observed.

Table 3. Product Distribution from the Solvolyses of Compounds 1 and 2 in Aqueous Trifluoroethanol (v/v) at 65 °C

TFE	$(k_{TFE}/k_{HOH})_1$	stereoselectivity$_1$[a]	$(k_{TFE}/k_{HOH})_2$	stereoselectivity$_2$[a]
100%		0.43 ± 0.05		1.40 ± 0.17
90%	0.51 ± 0.05	0.42 ± 0.02	0.18 ± 0.01	2.96 ± 0.19
80%	0.53 ± 0.01	0.42 ± 0.01	0.16 ± 0.01	4.45 ± 0.14
70%	0.60 ± 0.06	0.43 ± 0.08	0.17 ± 0.01	4.64 ± 0.49
60%	0.49 ± 0.03	0.48 ± 0.05	0.18 ± 0.01	4.19 ± 0.13
50%	0.39 ± 0.02	0.54 ± 0.05	0.18 ± 0.01	3.40 ± 0.17
40%	0.36 ± 0.06	0.50 ± 0.20	0.16 ± 0.01	NI[b]
30%	0.37 ± 0.04	0.53 ± 0.14	0.18 ± 0.01	NI[b]
20%	0.30 ± 0.03	NI[b]	0.20 ± 0.01	NI[b]
10%	0.27 ± 0.18	NI[b]	NI[b,c]	NI[b,c]

[a] [Inverted glycoside]/[Retained glycoside]; see eq 4. [b] NI = not integrated; estimated that less than 0.6% trifluoroethyl 2-deoxy-β-D-glucopyranoside was formed. [c] NI = not integrated; estimated that less than 0.3% trifluoroethyl 2-deoxy-α-D-glucopyranoside was formed.

are not being catalyzed by the added base *N*-methylmorpholine, product studies were performed using various concentrations of base in alcoholic solvents. Tables S13−S18 list the measured product percentages and yields for the solvolytic reactions of **1** and **2** at various concentrations of *N*-methylmorpholine.

Nucleophilic selectivity ($k_{ROH}/k_{R'OH}$)[22] is calculated according to eq 3, using the observed product ratios and the nucleophile concentrations. Stereoselectivity for a single nucleophile is calculated from the ratio of inverted to retained products (eq 4).

$$\frac{k_{ROH}}{k_{R'OH}} = \frac{[Gly{-}OR][R'OH]}{[Gly{-}OR'][ROH]} \quad (3)$$

$$\text{Stereoselectivity} = \frac{[Gly{-}OR]_{inv}}{[Gly{-}OR]_{ret}} \quad (4)$$

Compiled in Tables 1−3 are the nucleophilic selectivities (k_{ROH}/k_{HOH}) and the stereoselectivities calculated from the observed product ratios for solvolysis of **1** and **2** in aqueous mixtures of methanol, ethanol, and trifluoroethanol. Tables 4 and 5 list the nucleophilic selectivities and stereoselectivities for the solvolysis reactions of **1** and **2** run in EtOH/TFE mixtures, as well as in a solvent mixture of EtOH/TFE/H_2O (5:45:50, v/v).

Discussion

The concentration of pyridinium salt (**1** or **2**) used in the product studies is about 14-fold greater than that used in the kinetic experiments (2.83 vs 0.2 mM). General-base catalysis is obviously not involved in the solvolysis reactions of **1** and **2** in methanol and ethanol, since the products formed are invariant when up to at least 2 equiv of base is added to the solvolytic medium (Tables S13−S16).[23] In addition, the quantities of products formed in trifluoroethanol-containing solvents remain invariant at lower concentrations of *N*-methylmorpholine, while 2−3 equiv generate a greater amount of trifluoroethyl glycosides at the expense of glucal **4** and

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(23) These observations also rule out the possibility that *N*-methylmorpholine could act as a nucleophile.

Table 4. Product Distribution from the Solvolyses of 1 in EtOH/TFE at 65 °C

TFE	$(k_{EtOH}/k_{TFE})_{ret}$	$(k_{EtOH}/k_{TFE})_{inv}$	$(\text{stereoselectivity})_{TFE}$[a]	$(\text{stereoselectivity})_{EtOH}$[a]
100%			0.43 ± 0.05	
90%	15.1 ± 0.9	49.6 ± 6.4	0.37 ± 0.05	1.21 ± 0.05
80%	12.4 ± 1.5	38.3 ± 4.6	0.39 ± 0.06	1.21 ± 0.06
70%	10.9 ± 1.0	32.4 ± 2.8	0.41 ± 0.05	1.21 ± 0.06
60%	9.4 ± 0.9	25.5 ± 3.8	0.44 ± 0.08	1.20 ± 0.03
50%	8.7 ± 0.3[b]	24.0 ± 0.9[c]	0.44 ± 0.02[d]	1.21 ± 0.04[e]
40%	8.0 ± 0.8	20.5 ± 1.0	0.48 ± 0.05	1.22 ± 0.05
30%	6.6 ± 0.3	15.3 ± 0.5	0.53 ± 0.03	1.22 ± 0.02
20%	5.1 ± 0.3	10.7 ± 0.5	0.58 ± 0.04	1.23 ± 0.06
10%	5.3 ± 0.4	NI[f]	NI[f]	1.23 ± 0.05
0%				3.98 ± 0.19
ETW[g]	2.14 ± 0.08	10.6 ± 0.4	0.53 ± 0.02	2.60 ± 0.09

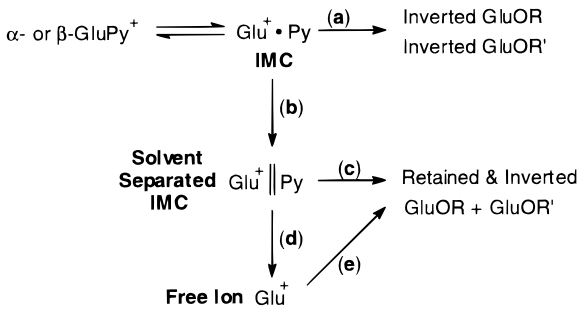
[a] [Inverted glycoside]/[Retained glycoside]; see eq 4. [b] The value for solvolysis of α-D-glucopyranosyl 4′-methylpyridinium triflate in 56% v/v TFE/EtOH is 2.0 ± 0.2.[12] [c] The value for solvolysis of α-D-glucopyranosyl 4′-methylpyridinium triflate in 56% v/v TFE/EtOH is 9.3 ± 1.3.[12] [d] The value for solvolysis of α-D-glucopyranosyl 4′-methylpyridinium triflate in 56% v/v TFE/EtOH is 0.83 ± 0.13[12] [e] The value for solvolysis of α-D-glucopyranosyl 4′-methylpyridinium triflate in 56% v/v TFE/EtOH is 3.8 ± 0.2.[12] [f] NI = not integrated; estimated that less than 0.2% trifluoroethyl 2-deoxy-β-D-glucopyranoside was formed. [g] Solvent ETW is 5:45:50 v/v/v EtOH/TFE/H_2O.

Table 5. Product Distribution from the Solvolyses of 2 in EtOH/TFE at 65 °C

TFE	$(k_{EtOH}/k_{TFE})_{Ret}$	$(k_{EtOH}/k_{TFE})_{inv}$	$(\text{stereoselectivity})_{TFE}$[a]	$(\text{stereoselectivity})_{EtOH}$[a]
100%			1.40 ± 0.17	
90%	8.0 ± 0.6	8.2 ± 0.4	1.71 ± 0.10	1.76 ± 0.11
80%	7.2 ± 0.5	7.8 ± 0.4	2.21 ± 0.14	2.39 ± 0.15
70%	7.3 ± 0.4	8.0 ± 0.3	3.02 ± 0.16	3.32 ± 0.12
60%	7.0 ± 0.3	8.1 ± 0.3	3.79 ± 0.20	4.38 ± 0.08
50%	7.0 ± 0.5[b]	8.5 ± 0.2[c]	4.7 ± 0.4[d]	5.70 ± 0.10[e]
40%	5.8 ± 0.7	8.8 ± 0.2	4.7 ± 0.6	7.23 ± 0.11
30%	NI[f]	9.5 ± 0.3	NI[f]	9.24 ± 0.16
20%	ND[g]	9.7 ± 0.2	ND[g]	$10.9 \pm 0.1_4$
10%	ND[g]	10.5 ± 2.2	ND[g]	13.1 ± 0.2
0%				11.4 ± 0.4
ETW[h]	5.49 ± 0.92	4.14 ± 0.50	3.40 ± 0.20	2.56 ± 0.51

[a] [Inverted glycoside]/[Retained glycoside]; see eq 4. [b] The value for solvolysis of β-D-glucopyranosyl 3′-bromopyridinium triflate in 56% v/v TFE/EtOH is 13 ± 7.[12] [c] The value for solvolysis of β-D-glucopyranosyl 3′-bromopyridinium triflate in 56% v/v TFE/EtOH is 4.5 ± 0.4.[12] [d] The value for solvolysis of β-D-glucopyranosyl 3′-bromopyridinium triflate in 56% v/v TFE/EtOH is 11 ± 3.[12] [e] The value for solvolysis of β-D-glucopyranosyl 3′-bromopyridinium triflate in 56% v/v TFE/EtOH is 3.8 ± 0.9.[12] [f] NI = not integrated; estimated that less than 0.1% trifluoroethyl 2-deoxy-β-D-glucopyranoside was formed. [g] ND = not detected; no peak for trifluoroethyl 2-deoxy-β-D-glucopyranoside was observed. [h] Solvent ETW is 5:45:50 v/v/v EtOH/TFE/H_2O.

Scheme 1



1,6-anhydro-2-deoxy-β-D-glucopyranose (**5**) (Tables S17 and S18). Therefore, in the current system there is no kinetically significant, bimolecular, general-base-catalyzed pathway, and given that the observed products are independent of the addition to the solvolysis medium of up to 2 equiv of *N*-methylmorpholine, the product-forming steps are not base-catalyzed.

In light of the absence of base-catalyzed pathways, the solvolysis reactions of the diastereomeric 2-deoxy glucosyl 4′-bromoisoquinolinium salts were analyzed in terms of Scheme 1.[9] In this scheme, the first-formed intermediate is an ion−molecule complex (IMC) which can react initially in one of two ways to generate the observed products. It can react to form 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 (Scheme 1, pathway **a**). Alternatively, diffusional separation of the pyridine from the IMC complex can occur, giving a solvent-separated ion−molecule complex (Scheme 1, pathway **b**). At this point, the solvent-separated IMC can partition in one of two ways. Solvent can capture the IMC on either of its two diastereomeric faces, as shown in Scheme 1, pathway **c**, or the IMC can give an oxacarbenium ion intermediate (Scheme 1, pathway **d**), which is then captured by solvent to give both retained and inverted products (Scheme 1, pathway **e**).

Rates of Solvolysis. Since positively charged glycosyl pyridinium salts hydrolyze via transition states having significant C−N bond cleavage,[9,24,25] it is expected that a small increase in the solvolysis rate constant would be associated with a decrease in polarity of the solvent.[26] Accordingly, in the binary solvent mixtures MeOH/H_2O, EtOH/H_2O (Figure 1), and EtOH/TFE, the observed solvolytic rate constants for both **1** and **2** increase in response to a solvent mixture containing a decreased fractional composition of the more polar solvent. It is notable that the relative increase in rate constant for the β-anomer (**2**) is larger than that for the diastereomeric α-anomer (**1**).

(24) Huang, X.; Tanaka, K. E. S.; Bennet, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 11147−11154.
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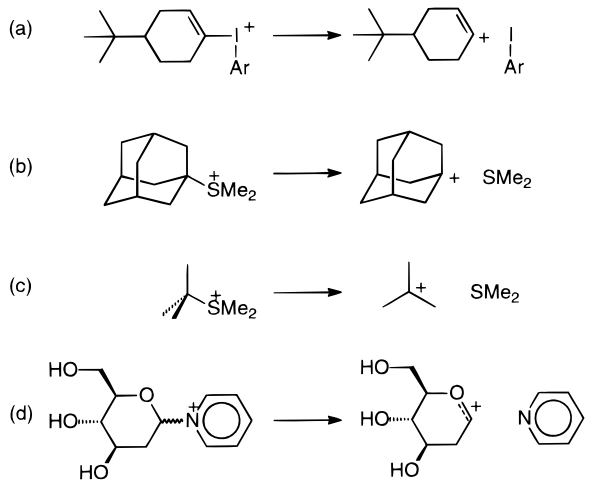
Scheme 2



Grunwald−Winstein *Y* Scale. The effect of the solvent on the rates of $D_N + A_N$ substitution reactions can be analyzed using the standard Grunwald−Winstein equation (eq 2).[19] A series of Y_X scales have been constructed for a variety of leaving groups (X) in order to allow for solvent-based electrophilic assistance to ionization.[27] Although it would be ideal to analyze the kinetic data for the two anomeric 2-deoxyglucosides using a Y^+_{Pyr} scale, insufficient kinetic data are available for the establishment of a pyridine leaving group-based scale due to the extremely sluggish nature of the solvolysis reactions of 1-adamantyl pyridinium perchlorate.[28,29] As a result, the effect of solvent on the hydrolytic rate constants for **1** and **2** is analyzed using Kevill and Anderson's Y^+ scale, which is derived from the rates of solvolysis for 1-adamantyl dimethylsulfonium triflate.[20] The derived *m* values for the solvolysis of **1** and **2** are -3.64 ± 0.34 and -4.78 ± 0.33, respectively (Figures 4 and 5). The negative *m* values measured in the present study indicate that the effect of solvent on the solvolysis rate constants for **1** and **2** will be opposite of that reported for 1-adamantyl dimethylsulfonium triflate.[20]

It is important to remember that, in the work presented herein, the leaving group is a neutral molecule. Therefore, both the ground state (GS) and the transition state (TS) are positively charged, and as a consequence, a change in the ionizing power of the solvent could have a more pronounced effect on either the GS or the TS.

For (4-*tert*-butyl-1-cyclohexenyl)aryliodonium tetrafluoroborates[30] and 1-adamantyl dimethylsulfonium triflate (Scheme 2a,b),[20] the solvolytic rates increase in parallel to increasing ionizing power of the solvent, with the larger effect observed for the aryliodonium salts. For these two compounds, positive charge localization occurs at the respective TS's onto carbon atoms that will become either a bent sp-hybridized cyclohexene carbocation as in the case of the aryliodonium salts or a pyramidalized sp^2-hybridized carbenium ion as occurs for the 1-adamantyl compound. However, as the carbenium ion stability increases due to charge delocalization, there is a decrease in the importance of TS solvation relative to solvation of the positively charged GS, and this results in the observation of an inverted trend for the effect of solvent on the hydrolysis rate constants. This inversely related reactivity pattern was observed by Kevill and Anderson for the solvolyses of *tert*-butyl and 1-adamantyl dimethylsulfonium triflates in binary mixtures of TFE and EtOH (Scheme 2b,c).[20,28] In the present study, solvolysis of **1** and **2** generates oxacarbenium ions in which the charge can be more extensively delocalized than in the case of the *tert*-butyl cation. This results in a more pronounced decrease in the observed reaction rate in response to an increase in the solvent polarity. When the solvolysis data for **1** and **2** (Table S3) are fit to the Grunwald−Winstein equation using Y^+ values that were derived from $^tBuSMe_2^+$ solvolyses,[28] *m* values greater than 1 are obtained. Specifically, the evaluated *m* values are 2.63 ± 0.11 and 3.38 ± 0.14 for the reactions of **1** and **2**, respectively (Figure 6). Thus, the observed greater sensitivity of the solvolysis rates for both **1** and **2** as compared with *tert*-butyl dimethylsulfonium triflate results from greater positive charge delocalization occurring at the transition states for glycoside hydrolysis.

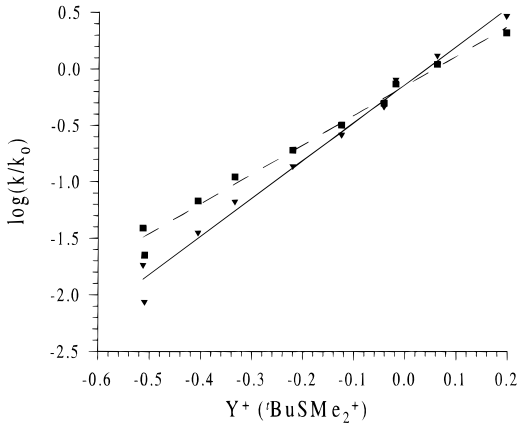


Figure 6. Plot of Grunwald−Winstein correlation for the solvolysis of **1** (■) and **2** (▼) versus Y^+_{tBu} in TFE/EtOH mixtures at $T = 65$ °C. The lines shown are the best linear least-squares fits through the data points (see discussion section for details).

The larger *m* value associated with the reactions of **2** as compared to **1** is consistent with greater TS charge delocalization occurring onto the endocyclic oxygen atom during solvolysis of the β-anomer. This conclusion is consistent with the reported ring oxygen kinetic isotope effects (^{18}O KIEs) for the specific acid-catalyzed hydrolyses of methyl glycosides,[31,32] where bonding between the ring oxygen and the anomeric carbon strengthens during the formation of a cyclic oxacarbenium ion. Greater C−O double bond character at the transition state results in a more inverse ring ^{18}O KIE. The measured ^{18}O KIEs for methyl α-D- and β-D-xylopyranoside are 0.986 ± 0.001 and 0.978 ± 0.001,[31] respectively, while the corresponding values for methyl α-D- and β-D-glucopyranoside are $0.996_5 \pm 0.001$ and 0.991 ± 0.002.[32]

Solvolysis Products. Since formation of the bicyclic acetal (**5**) results from an intramolecular nucleophilic attack, the solvolysis of both **1** and **2** generates predominately substitution products (>85%) rather than the

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(28) Kevill, D. N.; Kamil, W. A. *J. Org. Chem.* **1982**, *47*, 3785−3787.
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(30) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360−3367.
(31) Indurugalla, D.; Bennet, A. J. Manuscript in preparation.
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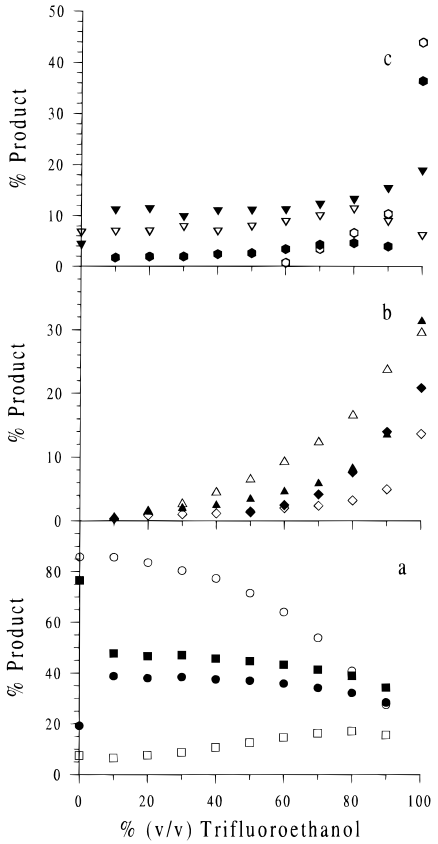
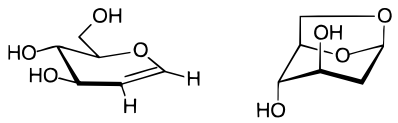


Figure 7. Plot of the observed product percentages versus percent trifluoroethanol (v/v) for solvolysis reactions of **1** (filled symbols) and **2** (open symbols) in ethanol/trifluoroethanol mixtures: (a) ethyl 2-deoxy-α-D-glucoside (●) and ethyl 2-deoxy-β-D-glucoside (■); (b) trifluoroethyl 2-deoxy-α-D-glucoside (▲) and trifluoroethyl 2-deoxy-β-D-glucoside (◆); (c) D-glucal (▼) and 1,6-anhydro-2-deoxy-β-D-glucopyranose (⬢); T = 65 °C.

glucal **4** elimination product. The complete formation of solvent-equilibrated oxacarbenium ion intermediates can be ruled out, because for all of the solvent mixtures investigated, solvolysis of the two anomeric glycosyl salts gives rise to different product ratios.



4 **5**

Figure 7 displays the product percentages formed during the reactions of both **1** and **2** in ethanol/trifluoroethanol mixtures.[33]

Solvolyses in Aqueous Methanol and Ethanol. With respect to the reaction products formed, several trends can be delineated from the observed product distributions for the solvolysis reactions of **1** and **2** in binary mixtures of MeOH/H_2O and EtOH/H_2O (Tables 1, 2, S4−S5, S8−S9, and S19), including (1) the formation of more inverted, rather than retained alkyl glycoside; (2) decreased nucleophilic selectivity for alcoholysis (k_{ROH}/k_{HOH}) as [ROH] increases; (3) increased stereoselectivity of alcoholysis as [ROH] increases; (4) $(k_{ROH}/k_{HOH})_1$ is always greater than $(k_{ROH}/k_{HOH})_2$; and (5) the stereoselectivity for the β-anomer is always greater than for the α-anomer.

Two conclusions can be drawn from the above observations. First of all, nucleophilic solvation cannot be important in the solvolysis reactions of **1** and **2**. One would expect to observe vestiges of a nucleophilic solvation effect for the capture of these short-lived (≈2×10^{-11} s), cationic intermediates,[9] and as such, this would translate into increased nucleophilic selectivity (k_{ROH}/k_{HOH}) in conjunction with reduced solvent polarity (Tables 1−3). In contrast, the observed selectivity is lower in the less polar, more nucleophilic, alcoholic solvents (EtOH and MeOH). Second, it can be concluded that the selectivity of the first formed ion−molecule complex[9] is reduced as the fraction of alcohol in the binary solvent mixture increases. This effect arises from a reduced ability of the less polar solvent to solvate positive charges, thereby decreasing the extent of reorganization that occurs within the IMC prior to solvent capture of the cationic intermediate.

Solvolyses in Ethanol/Trifluoroethanol Mixtures. As pointed out by Sinnott and Jencks,[12] it is expected that the selectivity ratios $(k_{EtOH}/k_{TFE})_{inv}$ from competing S_N1 and S_N2 reactions would increase as the fraction of the more nucleophilic, less ionizing solvent ethanol is increased. Given that the exact opposite trend is observed during solvolysis of **1**, and that no changes are perceived for the reactions of **2**, the following two reasonable conclusions can be drawn: (1) solvolyses of **1** and **2** occur via a single dissociative reaction channel; and (2) no nucleophilic component emerges in ethanol-rich, low-polarity solvents. This latter conclusion reaffirms the previously discussed point that there is no significant role for nucleophilic solvation in these solvolysis reactions. Recent results from several research groups suggest that nucleophilic solvation is either unimportant[34] or very weak for dissociative solvolysis reactions in general.[35] This can also be applied to six-membered rings where nucleophilic attack is sterically inhibited.[36]

Since the addition of 10% TFE to pure EtOH causes a dramatic change in the observed products arising from the solvolysis of **1** (but not of **2**), trifluoroethanol facilitates diffusional separation of the 4-bromoisoquinoline from the α-anomer in such a way that solvent capture with retention of configuration is promoted (Figure 7). However, trifluoroethanol cannot provide electrophilic assistance to the departure of the neutral pyridine leaving group by way of the formation of H-bonds during cleavage of the anomeric C−N bond. This is in contrast to the situation that occurs for loss of fluoride ion during the reactions of α-D-glucopyranosyl fluoride.[12]

The substitution reactions of the α-anomer **1** with TFE primarily give the retained glycoside, while the corre-

(33) In aqueous EtOH and MeOH solvent mixtures that had a water content of >20% (v/v), a small (≤0.9%) but detectable quantity of 1,6-anhydro-2-deoxy-β-D-glucopyranose was generated.

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(36) (a) Fierens, P. J. C.; Vershelden, P. *Bull. Soc. Chim. Belg.* **1952**, *61*, 427−451. (b) Eliel, E. L.; Ro, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 5995−6000.

sponding reactions of **2** afford mainly the inverted product. With respect to the α-anomer **1**, it appears that a significant fraction of the cationic intermediate that is trapped by TFE is produced by way of general-base catalysis by the departing 4-bromoisoquinoline, a process that must occur at the stage of the solvent-separated IMC (Scheme 1).

The observed nucleophilic selectivities $(k_{EtOH}/k_{TFE})_{ret}$ for solvolysis with retention of configuration of compounds **1** and **2** (Tables 4 and 5) are greater than those observed for the reactions of 1-adamantyl pyridinium ($k_{EtOH}/k_{TFE} = 1.67$; $T = 190$ °C) and 1-adamantyl dimethylsulfonium triflates ($k_{EtOH}/k_{TFE} = 1.10$; $T = 40$ and 190 °C).[37] This selectivity difference could be caused either by the 1-adamantyl carbenium ion being less stable than the 2-deoxyglucosyl cation or by the nonplanar 1-adamantyl cation possessing an inherently different reactivity than planar, delocalized oxacarbenium ions.

Effect of the 2-OH Group. Sinnott and Jencks suggested that, due to the greater tendency of β-D-glucopyranosyl derivatives to solvolyze with overall inversion of configuration, the 2-OH group might facilitate the delivery of a solvent nucleophile via a general-base-catalyzed pathway.[12] The results listed in Table S11 show that, under comparable conditions,[38] β-D-glucopyranosyl 3′-bromopyridinium triflate solvolyzes to give slightly more inverted product than does 2-deoxy β-D-glucopyranosyl 4′-bromoisoquinolinium tetrafluoroborate. Therefore, product formation from the 2-deoxy glucosyl compound is associated with a selectivity value $(k_{EtOH}/k_{TFE})_{inv}$ approximately 2-fold greater than the corresponding value for the glucopyranosyl derivative. These modest selectivity changes between glucosyl and 2-deoxyglucosyl derivatives possessing leaving groups with similar pK_a's[39] suggest that, in the case of pyridine leaving groups, the glucosyl 2-OH group is not active in promoting solvent capture of cationic intermediates.

Formation of Glucal. Since the percentage of compound **4** formed during these solvolysis reactions is nearly independent of the solvent composition (Tables S4, S5, S8, and S9), glucal formation is likely to occur at the stage of the ion−molecule complex via a subsequent deprotonation of the C-2 carbon. A similar conclusion was reported by Thibblin and Saeki: for the solvolysis of 1-(1-methyl-1-phenylethyl)pyridinium cations in 25 vol % acetonitrile in water, the elimination products are formed with assistance for proton-abstraction provided at the point of the ion−molecule complex by the leaving group pyridine.[41]

Formation of 1,6-Anhydro-2-deoxyglucose. The products formed during the spontaneous hydrolyses of **1**,[9b] **2**,[9a] α-D-glucopyranosyl 3′-bromopyridinium bromide,[25] and β-D-galactopyranosyl 3′-chloropyridinium bromide[42] are the corresponding sugars, whereas in the presence of base, the α-D-glucopyranosyl 3′-bromopyridinium ion gives a significant quantity of 1,6-anhydro-β-D-glucopyranose.[25] In the present study, addition of 3 equiv of *N*-methylmorpholine causes an increase in the fraction of trifluoroethyl glycoside formed. Therefore, it appears that 1,6-anhydro-2-deoxy-β-D-glucose (**5**) formation occurs without general-base catalysis and that formation of a greater amount of **5** in TFE-containing solvents results from a longer-lived intermediate being able to attain the required pyranosyl ring conformation necessary in order for ring closure to occur.

Intermediate Lifetimes. In 1984, Jencks and coworkers showed that the nucleophilic selectivity (k_{ROH}/k_{TFE}) for capture of substituted 1-phenylethyl carbenium ions in mixtures of 5:45:50 (v/v) ROH/TFE/H_2O[43] decreased as the lifetime of the cation, measured in 50:50 (v/v) TFE/H_2O, decreased.[44] A similar relationship has been noted for the solvolysis reactions of substituted cumyl derivatives.[34e] Using the published values for nucleophilic selectivity[43] and cation lifetime,[44] and the nucleophilic selectivity values listed in Tables 4 and 5, the computed lifetime for a 2-deoxyglucosyl cation falls in the range of 1.0×10^{-12} to 3.3×10^{-10} s. Given that these estimated lifetimes for the 2-deoxyglucosyl oxacarbenium ion are extrapolated from lifetime values of substituted 1-phenylethyl carbenium ions, it is remarkable that there is agreement between these values and the previously estimated value of approximately 2.0×10^{-11} s for the lifetime of the 2-deoxyglucosyl cation in water. Although this level of consistency might be due to fortuity, some similarities do exist between 2-deoxyglucosyl and 1-phenylethyl carbenium ions. Namely, both ions are secondary, resonance-stabilized cations, with electron donation occurring by either an adjacent oxygen atom or a neighboring aryl group.

Conclusions

Solvolyses of **1** and **2** proceed via dissociative ($D_N * A_N$) transition states in which there is no significant nucleophilic solvation. In addition, the observed values for the Grunwald−Winstein sensitivity parameter *m* are consistent with greater transition state charge delocalization occurring during solvolysis of the β-anomer. The 2-deoxyglucosyl oxacarbenium ion is not solvent-equilibrated in any of the solvent mixtures studied. Trifluoroethanol facilitates diffusional separation of the leaving group, and this results in greater quantities of the substitution product that has a retained configuration.

Acknowledgment. The authors gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada and Simon Fraser University for financial support of this work. The authors would also like to thank Dr. T. E. Kitos for editorial assistance with the manuscript.

Supporting Information Available: Experimental details for the synthesis of **2**, methyl-, ethyl-, and trifluoroethyl 2-deoxy-α- and β-glucosides, and for the GC analysis of the solvolytic products. Complete tables of observed rate constants and products for the solvolysis reactions of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) The solvolysis studies reported in ref 12 were performed in equimolar TFE/EtOH, which is equivalent to approximately 56% v/v TFE/EtOH.

(39) Values taken from ref 40, pK_a (3-bromopyridine-H^+) = 2.90 and pK_a (4-bromoisoquinoline-H^+) = 3.31.

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