8, 29 (1965).
(49) G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959); A. F. S. A. Habeeb, *Methods Enzymol.*, **25**, 457 (1972).
(50) K. Gawehn and H. U. Bergmeyer in ref 10, Vol. 3, p 1496.
(51) H. U. Bergmeyer, K. Gawehn, and M. Grassl in ref 10, Vol. 1, p 469.
(52) N. F. Chamberlain and J. J. R. Reed in "The Analytical Chemistry of Sulfur and Its Compounds", Part III, "Nuclear Magnetic Resonance Data of Sulfur Compounds", J. H. Karchmer, Ed., Wiley, New York, 1971.

Solvolysis of D-Glucopyranosyl Derivatives in Mixtures of Ethanol and 2,2,2-Trifluoroethanol[1]

Michael L. Sinnott*[2] and William P. Jencks*

Contribution No. 1294 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. *Received July 30, 1979*

Abstract: The products of solvolysis of α- and β-D-glucopyranosyl fluorides, 2,4-dinitrophenyl β-D-glucopyranoside, and the trifluoromethanesulfonates of the β-D-glucopyranosyl 3-bromopyridinium and α-D-glucopyranosyl 4-methylpyridinium ions in an equimolar mixture of ethanol and trifluoroethanol buffered with ~2 equiv of 2,6-lutidine have been examined by GLC of their trimethylsilyl ethers. The initial products of the solvolyses of phenyl α- and β-D-glucopyranosides catalyzed by trifluoromethanesulfonic acid in an equimolar mixture of ethanol and trifluoroethanol, and the products of uncatalyzed solvolysis of β-D-glucopyranosyl-*p*-nitrophenyltriazene, have been likewise examined. The composition of the medium for solvolysis of the glucosyl fluorides has also been systematically varied from pure ethanol to pure trifluoroethanol. The percentage of products with the same anomeric configuration as the starting material is in the range 8.1–88.5%; change of leaving group, at constant anomeric configuration, or of anomeric configuration, at constant leaving group, yields different product distributions. Therefore the transition state for the product-determining step contains the leaving group. The preference for attack by ethanol as compared with trifluoroethanol varies from 0.9 to 20 in a way which shows no general systematic distinction between pathways for retention or inversion. The nucleophilic selectivity for retention is lowered by anionic leaving groups, especially fluoride, which preferentially stabilize the transition state containing trifluoroethanol by hydrogen bonding. Nucleophilic attack at the α face is preferred over nucleophilic attack at the β face, and exhibits a lower selectivity: this is ascribed to hydrogen bonding between the oxygen atom of the 2-hydroxyl group and the hydroxyl group of the approaching alcohol. A model for solvolysis involving a reversibly formed ion pair or encounter complex is incompatible with the selectivities still observed with leaving groups less nucleophilic than the solvent components: a model involving selection between the components of a pool of solvent molecules by an irreversibly formed ion pair or encounter complex requires an implausibly large pool to explain observed specificities. It is therefore concluded that the observed selectivities are a consequence of the facilitation of the departure of the leaving group by the solvent, from either side of the reaction center.

Widely accepted mechanistic descriptions of nucleophilic substitutions at C-1 of pyranose rings have commonly invoked aldopyranosyl cations as intermediates in reactions in neutral and acidic media.[3] In aqueous solution product formation was usually held to take place from the free cations, but in less polar solvents the predominance of products in which the configuration of the reaction center was inverted led to the proposal that the species whence products are formed still contained the leaving group, but only in the capacity of a steric obstruction.[4,5] A direct, S_N2 reaction has also been observed.[4]

For the purposes of this discussion we define an intermediate as a species with a lifetime longer than a molecular vibration. A more stringent and experimentally accessible criterion for an intermediate is a lifetime which is long enough that the various fragments from its precursor are not still surrounded by a common solvent shell when the products are formed. In water at 25 °C this requires a lifetime of ~10 ps or more.

It has recently proved possible to estimate the lifetimes of oxocarbonium ions of the type $ArCMe{=}O^+Me$ by using the diffusion-controlled reaction of these ions with SO_3^{2-} (to give $ArC(Me)(OMe)SO_3^-$) as a "clock" with which to time their reactions with solvent water.[6] The lifetimes so estimated are surprisingly short (e.g., 10 ns for $PhCMe{=}O^+Me$), but extrapolation of the results of direct measurements in aqueous sulfuric acid to pure water give essentially the same results.[7]

A linear free energy relationship exists between the rate of reaction of $ArCMe{=}O^+Me$ with solvent water and the rate of reaction of the parent ketone ArMeCO with bisulfite. If this relationship is extrapolated to $CH_2{=}O$ and $CH_2{=}O^+Me$, the predicted lifetime of the latter is $\sim10^{-15}$ s, below the period of even the fastest bond vibration. The methoxymethyl cation is thus too unstable to exist as a free solvent-equilibrated intermediate in aqueous solution. The solvent molecule or another nucleophile with which a methoxymethyl center reacts must therefore be present in the transition state in which the leaving group departs. Second-order reactions with nucleophiles have been observed with both methoxymethyl 2,4-dinitrophenolate[8] and methoxymethyl *N,N*-dimethylanilinium ions.[9] These reactions, even though bimolecular, are very S_N1-like in the high degree of positive charge on the central atom in the transition state, as shown by high-β_{lg} and low β_{nuc} values. The presence of a nucleophile in the transition state is enforced by the instability of the potential intermediate, just as the presence of proton donors and acceptors in the transition states of certain acyl transfer reactions is enforced by the short lifetime of the tetrahedral intermediate.[10]

The available evidence is that aldopyranosyl cations are yet more unstable than $CH_2{=}O^+Me$. The acid-catalyzed hydrolysis of formaldehyde dimethyl acetal[11] is about 10^4 times faster than that of methyl β-D-glucopyranoside,[12] and likewise the spontaneous hydrolysis of methoxymethyl 2,4-dinitrophenolate[8] is ca. 10^2 faster than that of 2,4-dinitrophenyl β-D-glucopyranoside.[12] The spontaneous hydrolysis of $MeOCH_2F$[13] can be estimated to be a similar factor of 10^2 faster than that of the β-glucopyranosyl compound, if this is estimated to react more slowly than its C-4 epimer[14] by the usual[3] factor of 3.

In the light of this instability of aldopyranosyl cations, and the consequent enforced participation of a nucleophile, the fact

0002-7863/80/1502-2026$01.00/0

that various reactions of aldopyranosyl derivatives did not give complete inversion of configuration—even in the absence of nucleophilically participating groups on C-2—was puzzling. A clean S_N2 reaction in the Ingold sense is incompatible with any retention of configuration in the products. It therefore seemed worthwhile to investigate the requirements for nucleophilic "push" in the formation of both inverted and retained products during reactions at C-1 of a series of glucopyranosyl derivatives.

A useful way of doing this is to perform the solvolysis in mixtures of ethanol and trifluoroethanol. The use of this pair of solvents—originally devised for a study of the solvolyses of benzyl derivatives[15]—is based on their similar steric requirements and dielectric constants, but substantially different electrophilic and nucleophilic properties. Relative rates of formation of ethyl and trifluoroethyl benzyl ethers from the bromide are 25:1. The selectivities observed in solvolysis of 1-adamantyl bromide and tosylate—which must give exclusively retained products—are 0.84 and 0.7, respectively.[16] However, the high selectivities (~40:1) obtained in the *p,p'*-dichlorobenzhydryl system were considered to have arisen from the selectivity of a stable, solvent-equilibrated carbonium ion.[17]

Experimental Section

Substrates. α- and β-D-glucopyranosyl fluorides, mp 132–135 °C and decomposition temperature 108 °C, respectively, were made by literature[18] procedures as was 2,4-dinitrophenyl β-D-glucopyranoside.[19] β-D-Glucopyranosyl 3-bromopyridinium bromide was made analogously to the galacto compound;[20] α-D-glucopyranosyl 4-methylpyridinium bromide, mp 125–129 °C, was obtained by deacetylation of the tetra-*O*-acetyl compound[21] with 8% aqueous HBr at 22 °C for 7 days, extraction (to pH 5) with tri-*n*-octylamine in chloroform, and evaporation of solvent at 20 °C. Phenyl α- and β-D-glucopyranosides were commercial materials. β-D-Glucopyranosyl-*p*-nitrophenyltriazene was prepared (as a semisolid residue) from β-D-glucopyranosylamine (mp 128–134 °C dec; lit.[22] 125–127 °C) and *p*-nitrophenyldiazonium tetrafluoroborate exactly analogously to the β-D-galactopyranosylmethyl compound.[23] Ethanol was dried by distillation from magnesium ethoxide and trifluoroethanol was purified by stirring with calcium sulfate and anhydrous sodium carbonate, filtration, and distillation.

Solvolysis Procedure. The substrate (~5 mg) was suspended in the solvent (~1 mL) in an ampule, and, in the case of fluoride, pyridine, and dinitrophenolate leaving groups, 2,6-lutidine (~2 equiv) was added. The ampule was sealed and suspended in a steam bath for the appropriate time, after which the ampule was blown down in a stream of dry nitrogen and derivatized.

The anion associated with the pyridinium salts was changed from bromide to trifluoromethanesulfonate by reaction of aqueous solutions of the bromide and 1.05 equiv of silver trifluoromethanesulfonate, centrifugation, and lyophilization. The acid-catalyzed solvolyses were carried out in mixtures of ethanol (7.51 mL), trifluoroethanol (10.0 mL), and trifluoromethanesulfonic acid (~10 μL). Solvolyses were neutralized with 2,6-lutidine before derivatization.

Gas–Liquid Chromatographic Analyses. To the residue from evaporation of the solvolysis mixture was added *N,O*-bis(trimethylsilyl)acetamide (agent I, ~1 mL) or a 30% (v/v) solution of *N*-trimethylsilylimidazole in dry pyridine (agent II, 1–2 mL). The resulting solution (1–3 μL) was normally analyzed on a 2-m column of 36% SE-13 at 180 °C in a Hewlett-Packard 402 gas chromatograph, with helium as the carrier gas and flame ionization detection. When phenyl glucosides, which were used as internal standards for estimation of recoveries, were analyzed, it proved advantageous to raise the temperature to 190 °C, when no significant loss of resolution occurred. Relative retention times at 180 °C for trifluoroethyl α-, trifluoroethyl β-, ethyl α-, and ethyl β-D-glucopyranosides were 1:1.27:1.42:1.83, respectively. The retention times of ethyl and trifluoroethyl β- and phenyl α- and β-D-glucopyranosides were determined by separate derivatization and analysis of these compounds. The retention times of the alkyl α-glucosides were determined by analyses of the equilibrium mixtures of α- and β-glucopyranosides obtained by the refluxing of glucose and sulfonated polystyrene (H^+ form) in the appropriate alcohol. Peak areas were estimated by triangulation.[24] Products from the α-D-glucopyranosyl 4-methylpyridinium ion were analyzed in a Pye 104 chromatograph on a 2-m column of SE-30 with nitrogen elution at 170 °C.

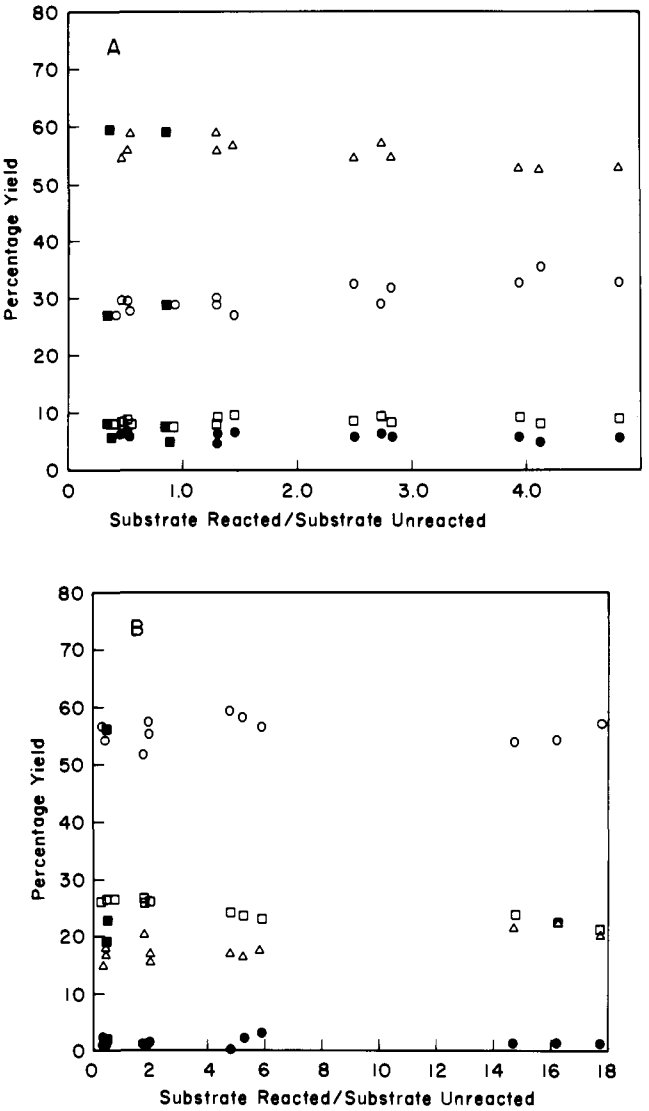


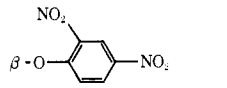
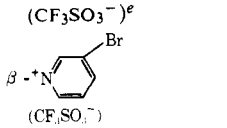
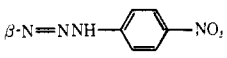
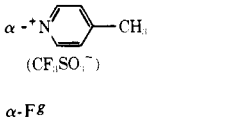
Figure 1. Normalized percentage yields from the solvolysis of (A) α- and (B) β-phenyl D-glucopyranoside in a 1:1 molar ratio of ethanol and trifluoroethanol at 100 °C catalyzed by trace amounts of CF_3SO_3H, displayed as a function of degree of reaction. The products are indicated by (○) ethyl α-D-glucopyranoside; (△) ethyl β-D-glucopyranoside; (□) trifluoroethyl α-D-glucopyranoside; (●) trifluoroethyl β-D-glucopyranoside. For each substrate four solvolyses were performed, and three analyses, each individually displayed, were made on each using bis(trimethylsilyl)acetamide derivatization. Additionally, one solvolysis of each substrate was derivatized with *N*-(trimethylsilyl)imidazole in pyridine; these points are represented (■) for all products, but fall within the clusters of points obtained with bis(trimethylsilyl)acetamide derivatization.

Because ethyl glucosides are hygroscopic, relative response factors were determined after Zemplen[25] deacetylation of known mixtures of the tetra-*O*-acetyl derivatives of ethyl and trifluoroethyl β-D-glucopyranosides[26] (mp 101–104 and 135–137 °C, respectively; lit. mp 106–108[27] and 137–138 °C[28]). No systematic differences in analyses were noted as between derivatization by agents I and II; agent I, indeed, gave flatter base lines. The ratio of the molar response factors of ethyl and trifluoroethyl β-D-glucopyranosides was 1.00 ± 0.06, and that for phenyl β-D-glucopyranoside relative to either was 1.15 ± 0.07. Response factors for anomers were assumed to be identical.

Results

Figure 1 (A,B) shows the normalized percentage yields of solvolysis products from phenyl α- and β-D-glucopyranosides

Table I. Products from Solvolyses, Expressed as Normalized Percentage Yields,[a] of D-Glucopyranosyl Derivatives in an Equimolar Mixture of Ethanol and Trifluoroethanol at 100 °C

leaving group	recovery, %	trifluoroethyl α-D-glucopyranoside	trifluoroethyl β-D-glucopyranoside	ethyl α-D-glucopyranoside	ethyl β-D-glucopyranoside	nucleophilic[b] selectivity (inversion)	nucleophilic[b] selectivity (retention)	stereoselectivity[c] (trifluoroethyl glycosides)	stereoselectivity[c] (ethyl glycosides)	gross[d] stereoselectivity
β-F	71	13.9 ± 2.2	8.1 ± 1.6	65.0 ± 1.1	13.0 ± 0.9	4.7 ± 0.7	1.6 ± 0.3	1.7 ± 0.4	5.0 ± 0.4	3.7 ± 0.3
	74 ± 5	13.4 ± 1.2	2.1 ± 0.4	73.6 ± 2.1	10.8 ± 0.9	5.5 ± 0.5	5.1 ± 1.1	6.4 ± 1.3	6.8 ± 0.6	6.7 ± 0.6
β-OPh, H^+ ($CF_3SO_3^-$)[e]	(100)	25	1.5	55	18	2.2	12	17	3.1	4.1
	94 ± 4	14.6 ± 1.0	1.3 ± 0.6	65.6 ± 4.3	17.2 ± 3.8	4.5 ± 0.4	13 ± 7	11 ± 3	3.8 ± 0.9	4.3 ± 0.9
		24.2 ± 1.3	3.2 ± 0.6	45.5 ± 3.0	28.2 ± 1.6	1.9 ± 0.2	8.8 ± 1.7	7.6 ± 1.5	1.6 ± 0.15	2.2 ± 0.16
α-F	66	16.7 ± 2.0	3.2 ± 0.5	15.2 ± 1.5	64.8 ± 2.9	20 ± 3	0.91 ± 0.14	0.19 ± 0.04	4.2 ± 0.5	2.1 ± 0.2
α-OPh, H^+ ($CF_3SO_3^-$)[e]	(100)	8	6	28	59	10	3.5	0.75	2.1	1.8
	50 ± 7	8.7 ± 0.6	7.2 ± 1.0	17.5 ± 1.0	67.0 ± 1.3	9.3 ± 1.3	2.0 ± 0.2	0.83 ± 0.13	3.8 ± 0.2	2.8 ± 0.1
α-F[g]		14.3 ± 0.5	detected (1.7 ± 1.1)	10.8 ± 0.9	41.8 ± 2.6	phenyl α-D-glucopyranoside 29.9 ± 3.4	phenyl β-D-glucopyranoside detected (1.4 ± 1.7)			

[a] Errors are standard deviations from (minimally) six analyses from two solvolyses. [b] Ethanol-derived product/trifluoroethanol-derived product. [c] Inverted/retained. [d] Total inverted products/total retained products. [e] From the intercepts in Figures 1 and 2. [f] Not stereochemically pure—see text. [g] Solvolysis in an equimolar mixture of ethanol, trifluoroethanol, and phenol.

as a function of the degree of reaction. The product compositions from the two substrates are different; hence the reaction mixture is not at equilibrium. Further, both distributions change only slowly with extent of reaction. We therefore conclude that extrapolated values of normalized percentage yields represent the distribution of the initial products formed on departure of phenol from the α or β positions of a glucopyranosyl moiety. The lesser sensitivity of alkyl glucosides to acid, as compared to phenyl glucosides, and the predominantly inverted products obtained confirm the results of Vernon et al. in methanol.[29] No products other than the four alkyl glucosides are formed, since first-order rate coefficients, calculated from the proportion of residual phenyl glucoside to solvolysis products in the reaction mixture, are accurately constant over the period over which the reaction was followed. (The very small concentrations of acid are not accurately reproducible, but with one batch the rate coefficient for phenyl β-D-glucopyranoside was $7.3 \pm 0.4 \times 10^{-4}$ s^{-1} and for its anomer $4.6 \pm 0.2 \times 10^{-4}$ s^{-1}).

Table I shows the product distributions resulting from the departure of various leaving groups from both anomeric positions of the D-glucopyranosyl residue. The anion associated with cationic substrates was in all cases $CF_3SO_3^-$, since this anion is essentially nonnucleophilic, although capable of participating in the formation of ion pairs. (When the β-D-glucopyranosyl 3-bromopyridinium ion was solvolyzed with the nonpairing BPh_4^- as anion, nonsolvolytic decomposition occurred.) Table II shows the products obtained from solvolysis of glucopyranosyl fluorides in mixtures of ethanol and trifluoroethanol of various compositions.

Even though β-D-glucopyranosyl-*p*-nitrophenyltriazene was made from pure β-D-glucopyranosylamine, this could have mutarotated during the reaction with diazonium salt, resulting in a small proportion of the α stereoisomer in the triazene solvolyzed. In view of the availability in principle of formally similar pathways for mutarotation of amine and triazene (involving ring opening with concomitant formation of a -CH=N- grouping at C-1[30]) in this case stereochemical purity of substrate was not pursued. The reproducibility of results from several preparations of triazene, however, argues against products being derived from a stereoisomeric mixture of uncontrolled composition.

In those solvolyses of β-glucopyranosyl derivatives which were buffered with 2,6-lutidine, there is in principle the possibility that apparently "retained" products could have arisen by the double-displacement mechanism that holds[3] for the base-catalyzed reactions of those glycosides possessing a vicinal trans hydroxyl (Scheme I). This possibility can be discounted on two grounds:

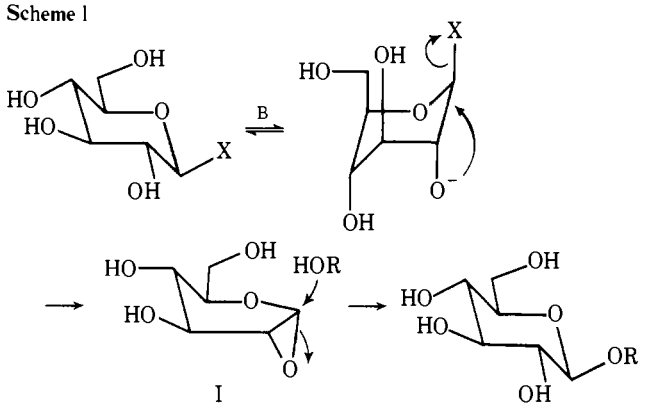
1. The ratio of ethyl to trifluoroethyl β-glucopyranosides formed from a series of β-D-glucopyranosyl derivatives varies over a factor of 8 as the leaving group is varied. The intermediate 1,2-anhydro-α-D-glucopyranose (I) is not likely to have such a short lifetime as to enforce the presence of X in the

Table II. Normalized Percentage Yields from Solvolyses of D-Glucopyranosyl Fluorides in Mixtures of Ethanol and Trifluoroethanol

mole fraction trifluoro-ethanol	trifluoroethyl α-D-gluco-pyranoside	trifluoroethyl β-D-gluco-pyranoside	ethyl α-D-gluco-pyranoside	ethyl β-D-gluco-pyranoside	nucleophilic[a] selectivity (inversion)	nucleophilic[a] selectivity (retention)	stereo-selectivity[b] (trifluoroethyl glycosides)	stereo-selectivity[b] (ethyl glycosides)	gross stereo-selectivity[b]
				β					
1.00	64.4	35.5					1.8		1.8
0.80	35.4	19.5	36.4	8.6	4.1	1.8	1.8	4.2	2.6
0.75	27.8	15.5	46.3	10.4	5.0	2.0	1.8	4.5	2.9
0.67	25.2	8.6	55.8	10.4	4.4	2.4	2.9	5.4	4.3
0.50	13.9 ± 2.2	8.1 ± 1.6	65.0 ± 1.1	13.0 ± 0.9	4.7 ± 0.7	1.6 ± 0.3	1.7 ± 0.4	5.0 ± 0.4	3.7 ± 0.3
0.33	7.5	3.1	78.0	11.4	5.2	1.8	2.4	6.8	5.9
0.25	5.4	2.2	81.6	10.9	5.0	1.7	2.5	7.5	6.6
0			91.9	8.1				11.3	11.3
mean values					(4.7 ± 0.4)	(1.9 ± 0.3)	(2.1 ± 0.5)	(6.4 ± 2.5)	
				α					
1.00	88.5	11.5					0.13		0.13
0.80	51.4	7.0	7.8	33.8	19.0	0.61	0.14	4.3	0.69
0.75	44.3	7.6	9.7	38.4	15.1	0.66	0.17	4.0	0.86
0.67	33.6	5.8	13.5	47.2	16.3	0.80	0.17	3.5	1.12
0.50	16.7 ± 2.0	3.2 ± 0.5	15.2 ± 1.5	64.8 ± 2.9	20 ± 3	0.91 ± 0.14	0.19 ± 0.04	4.2 ± 0.5	2.1 ± 0.2
0.33	11.0	1.8	17.5	69.7	19.7	0.80	0.16	4.0	2.85
0.25	7.5	1.6	18.5	72.5	15.1	0.82	0.21	3.9	2.85
0			20.2	79.7				3.9	
mean values					(17.5 ± 2.3)	(0.77 ± 0.11)	(0.17 ± 0.03)	(4.0 ± 0.3)	

[a] Ethyl glycoside/trifluoroethyl glycoside × [trifluoroethanol]/[ethanol]. [b] For definition of these terms see footnotes to Table I.

Scheme I



product-forming step: the 3,4,6-tri-*O*-acetyl derivative ("Brigl's anhydride"[31]) is a comparatively stable, crystalline compound.

2. The importance of any pathway via compound I would be expected to increase as the basicity of the solvent increased, making initial deprotonation of the C-2 hydroxyl easier. The data in Table II for the β fluoride show the precisely opposite trend, the proportion of retention decreasing as the proportion of ethanol increases.

A number of the leaving groups used are themselves significant nucleophiles; it is therefore in principle possible that apparently "retained" products are in reality the consequence of a double-displacement reaction, the leaving group liberated in the initial stages of a clean S_N2 reaction epimerizing the substrate. For example, β glucosides could have arisen from β-glucosyl fluoride by S_N2 attack on α-glucosyl fluoride, which was itself the product of attack, in the later stages of the reaction, by F^- on β-glucosyl fluoride. For this mechanism to hold, however, the discrimination between the two solvent components in formation of "retained" product from one anomer would be the same as that for formation of inverted product from the other anomer. Table I shows that 1.6 times as much ethyl β-D-glucopyranoside as trifluoroethyl β-D-glucopyranoside is formed from solvolysis of the β fluoride, but 20 times as much in the solvolysis of the α fluoride, and similar differences are observed with pyridine leaving groups. The data in Table I therefore represent the distribution of initial, kinetic products from the stated substrate.

Discussion

The data in Tables I and II leave no room for doubt that the products from solvolysis of D-glucopyranosyl derivatives are formed via transition states which still contain the leaving group. When differing leaving groups (fluoride, 2,4-dinitrophenolate, phenol, nitrogen, and 3-bromopyridine) leave from the same anomeric position, different products are formed; likewise, when either the same leaving group—fluoride or phenol—or closely related ones (3-bromo and 4-methylpyridine) depart from the two different anomeric positions, a different product distribution is observed.

However, at least in equimolar ethanol-trifluoroethanol, products of predominantly inverted anomeric configuration are produced from all substrates. It could therefore be argued that these products had arisen in a classical S_N2 reaction, even though retained products arose from some S_N1-type reaction. This proposal of competing reactions is, however, inconsistent with the persistence of essentially constant behavior as the solvent is changed. The nucleophilic selectivity and stereoselectivity ratios remain remarkably constant (Table II). The free-energy differences—using a mole fraction standard state—among the four transition states leading from α-D-glucopyranosyl fluoride to the four alkyl glucoside products do not alter detectably as the solvent is changed from one pure solvent to the other, or indeed if a third solvent (phenol) is added (Table I). There is some detectable alteration in the free-energy differences among the transition states leading from the β fluoride, that leading to ethyl α-D-glucopyranoside possibly falling in relation to the others. The effect is, however, small ($\leq RT$). By comparison, both E_T and the Winstein-Grunwald Y value show large changes over this range,[17] and a solvolysis which is in principle nucleophilically unassisted—that of 1-adamantyl bromide—changes in rate by a factor of 10^5.[32] It is, therefore, unlikely that competing S_N1 and S_N2 reactions could maintain such relative constancy over such a wide range of ionizing power.

General Features of Observed Specificities. From the data in Table I, four phenomena are apparent.

1. As the leaving group gets better in the β series, from 2,4-dinitrophenolate to nitrogen, so the selection between nucleophiles in forming inverted products decreases. The range is not dramatic ($\sim RT$ in $\Delta\Delta G^{\ddagger}$) but is nonetheless present. This is consistent with an earlier transition state that gives lower selectivity with a better leaving group.

Given that triazene decomposition is a typical deamination reaction,[33,34] the persistence of selectivity between nucleophiles is unexpected. Heterolytic decomposition of alkyl aryl triazenes is promoted by proton donation, a proton being in flight in the

transition state,[35] although in water *p*-nitrophenyl alkyl triazenes undergo a pH-independent decomposition above pH 7.[36] Evidently, the developing positive charge on the 1-carbon and 5-oxygen atoms is sufficient to give a greater stabilization of the transition state by ethanol than by trifluoroethanol, with a resulting increase in the ethyl glucoside produced.

2. The ratio of retained to inverted product varies little with leaving group. For uncharged leaving groups, selection between the two solvent components to form retained products is similar to the selection that yields inverted products. These latter selectivities are large, and comparable to those for unambiguous S_N2 reactions. The pK_a of CH_3CH_2OH is 16 and of CF_3CH_2OH is 12.4; it is reasonable to assume that the pK_as of $CH_3CH_2O^+H_2$ and $CF_3CH_2O^+H_2$ will differ by a similar amount. A 20-fold preference for ethanol rather than trifluoroethanol, such as occurs with inversion from the α fluoride, can then be converted into a β_{nuc} value of 0.36 (based on pK_a values in water[37]). However, if the difference in pK_a of protonated ethanol and trifluoroethanol is assumed to be the same as that between $CF_3CH_2NH_3^+$ and $CH_3CH_2NH_3^+$ (5.2 pK units),[38] then the estimation of β_{nuc} is 0.25. These values may be compared to the value of $\beta_{nuc} = 0.51$ for the reaction of substituted pyridines with methyl iodide in nitrobenzene.[39]

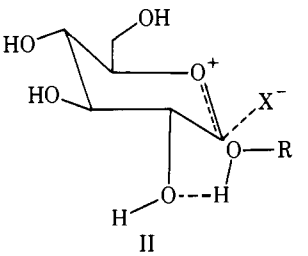
3. Anionic leaving groups—particularly fluoride—lower the selectivity between nucleophiles to form retained products. This may be attributed to hydrogen bonding between the fluoride ion and the hydroxyl group of the alcohol. Such hydrogen bonding to the relatively acidic trifluoroethanol molecule is expected to facilitate both fluoride ion departure and formation of the trifluoroethyl product. Departure of fluoride ion in S_N reactions is known to be assisted by proton donation, the unbuffered solvolyses of alkyl fluorides being strongly autocatalytic;[40] likewise, hydrolysis of glycosyl fluorides in water is acid catalyzed.[41]

Formation of retained product from $F^-\cdots HOR$ can be regarded as a type of "internal return", the nucleophilic atoms of the ambident leaving group being connected by hydrogen bonds. This interpretation receives support from the results of solvolysis of α-D-glucopyranosyl fluoride in an equimolar mixture of ethanol, trifluoroethanol, and phenol (Table I). The phenyl glucoside produced is overwhelmingly retained—as is the trifluoroethyl glucoside—indicating that "internal return" from $CF_3CH_2OH\cdots F^-$ is comparable to that from $PhOH\cdots F^-$.

4. With a constant leaving group, there is a greater tendency for overall inversion with β rather than α derivatives. This is in the reverse sense to that anticipated on simple steric grounds; nucleophilic assistance to the departure of leaving groups which are equatorial in a six-membered ring is less ready than such assistance to the departure of axial leaving groups.[42] The ground-state conformation of the neutral substrates, and of the β-3-bromopyridinium salt, is the $^4C_1$ chair, but in the case of the α-4-methylpyridinium salt analogy with its tetra-*O*-acetyl derivative[43] makes it likely that the reverse anomeric effect will constrain it to the $^{2,5}B$ boat conformer. These considerations apply only to the ground state of the pyranose ring; the conformation in which the glycon-aglycon bond is broken is not known with confidence, and it could be argued that, if departure of the leaving group requires an antiperiplanar lone pair of electrons on oxygen, then the β compounds must solvolyze through nonchair conformers. However, the proportionality observed with leaving groups which are equatorial in the $^4C_1$ conformation between rates of pH-independent hydrolyses of glycosyl 2,4-dinitrophenolates and rates of acid-catalyzed hydrolyses of the corresponding methyl glycosides[12] makes it likely that the reactive conformations with neutral and anionic leaving groups, at least in the β series in water, are the same. This conformation resembles the $^4C_1$ chair since the lesser solvolytic reactivity of glucosyl derivatives as compared with their tetrahydropyranyl analogues is accounted for by the inductive effect of the hydroxyl groups, whereas were high-energy conformers to be involved an additional decelerating effect would be expected by virtue of these groups acting as "equatorial anchors".[44]

We therefore consider most of the substrates studied to be reacting through the $^4C_1$ chair, and therefore the preference for α-attack is contrary to steric expectation. This preference for α-attack is associated with a lower selectivity between nucleophiles. If allowance is made for the effect of anionic leaving groups on observed selectivities for retention, this lowered selectivity is manifested irrespective of whether the attack is on the same side or the opposite side of the leaving group.

A probable explanation is that the oxygen atom of the C-2 hydroxyl group acts as a partial proton acceptor for the approaching alcohol (II). Such partial proton acceptance would



II

assist the attack of alcohols from the same side as the hydroxyl and would lower discrimination between them on the basis of pK_a. This proposal has precedent in the observed faster reactions of carbocations with hydrogen-bonded aggregates of alcohols than with the monomeric species.[47] It might be regarded as an "internal solvation", analogous to that proposed in order to account for small rate accelerations by neighboring hydroxyl groups in the hydrolysis and alcoholysis of esters,[48] or as general base catalysis of the proton removal that must take place from the entering alcohol. Nucleophilic reactions of water with carbonium ions[49] and (intramolecularly) of alcohols in S_N2 displacement reactions[50,51] are known to be subject to general base catalysis.

In the case of the α fluoride, the effect of a strongly hydrogen-bonded leaving group and of preference for α-attack reinforce one another to the extent that solvolysis in pure trifluoroethanol yields 88.5% retention. This fraction of α product is marginally higher than that in the equilibrium mixture of the two glycosides (78%).[52]

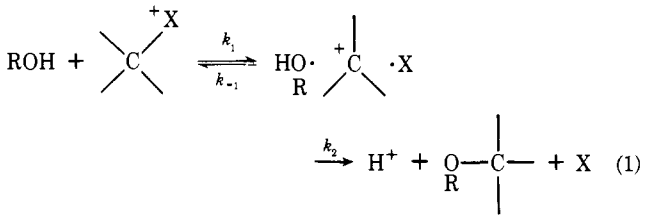
A Model for Solvolysis at Carbon Centers Next to Oxygen. Reactions through solvent-equilibrated oxocarbonium ions are readily detectable and present no conceptual difficulties—in the limit (pyrylium salts[53]) these ions are stable, isolable species. Likewise classical Ingold S_N2 reactions involving clean second-order kinetics and exclusive inversion of the stereochemistry of the reaction center are well recognized. Problems arise when a reaction is S_N1 by one criterion and S_N2 by another. In simple alkyl systems the clash of criteria usually occurs in the sense that the reactions are kinetically unimolecular but give exclusively inverted products. The present data present precisely the converse paradox: the reactions are unimolecular by the stereochemical criterion, since 8.1-88.5% retention of configuration is observed, yet by a kinetic criterion—dependence of relative rates of product formation on nucleophilicity—they are bimolecular. There are four possible resolutions of this paradox.

1. The observed selectivities of product formation represent, not nucleophilic efficacy in promoting the departure of the leaving group, but preferential solvation of the substrate in its ground state. The observed selectivities for inverted products are not consistent with this view, which would envisage them as arising from the preferential solvation of the pyranose ring

by ethanol, and hence being invariant with respect to change in leaving group or—maximally—showing a small dependence on its charge. In fact the selection between ethanol and trifluoroethanol approaching from the α face is experimentally the same for β-2,4-dinitrophenolate and β-3-bromopyridine as leaving groups, but selectivities for inversion do change with leaving group, with selection decreasing as the leaving group gets better. Moreover, there is no evidence for preferential ground-state solvation in the case of solvolyses of 1-adamantyl bromide and tosylate,[16] where all the product is necessarily of retained configuration. Finally, the observed selectivities *must* be a measure of the relative stabilities of transition states, regardless of ground-state solvation; if preferential solvation by ethanol existed in the ground state but was lost in the transition state no selectivity would be observed.

2. The reactions could proceed by way of ion pairs or, in the case of reactions with electrically neutral leaving groups, ion-dipole encounter complexes. If this concept is to be distinguished from an extended transition state, there must be negligible covalent interaction between the cationic fragment and the leaving group. Discrimination among solvent molecules in the formation of product could then arise in two ways: there could be attack on rapidly and reversibly formed ion pairs or encounter complexes in an activated process, or the encounter complex could be formed essentially irreversibly, but the carbonium ion therein could discriminate among the available components of the solvent shell.

The rapid, reversible formation of an ion pair or an encounter complex[54] (eq 1, $k_{-1} > k_2$) cannot account for the



(1)

observed specificities in the solvolyses of the phenyl glucosides or of β-D-glucopyranosyl-*p*-nitrophenyltriazene, since the leaving groups are less nucleophilic than the solvent. Once the R-X bond is broken, it is more likely that the components of the solvent shell—particularly ethanol—will react with the glucosyl cation than that the newly departed leaving group will, so that, if this mechanism were followed, $k_2 > k_{-1}$. Since there is no time for diffusion, the discrimination must therefore take place before C-X bond cleavage is complete. The experiments on solvolysis of α-D-glucopyranosyl fluoride in a phenolic medium confirm that phenol is comparably nucleophilic to trifluoroethanol, around 2% each of inverted phenyl and trifluoroethyl product being formed in a 1:1:1 molar ratio of ethanol, trifluoroethanol, and phenol, as compared with 42% inverted ethyl product. Molecular nitrogen is barely nucleophilic, and is known to be captured with only low efficiency even by the highly energetic phenyl cation.[55] The different product ratios with different leaving groups provide further evidence against an ion-pair or encounter-pair mechanism.

The idea of a pool of solvent molecules, possessing essentially equal probabilities of combining with a carbonium-ion center, was advanced by Grunwald et al.[56] on the basis of concurrent measurements of the acid-catalyzed racemization and ^{18}O exchange of 1-phenylethanol in water. They found that racemization was faster than exchange by less than the factor of 2 predicted by a simple Ingold S_N2 mechanism. The data were quantitatively accounted for by the proposal that the protonated alcohol decomposed into $PhCH^+CH_3$ and a water molecule, which became essentially indistinguishable from two or three other water molecules on the same side as the leaving water, and, except by virtue of its chirality, from the three or

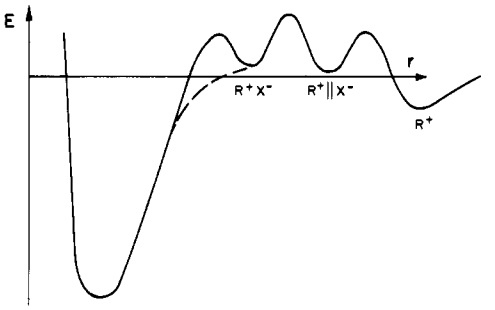


Figure 2.

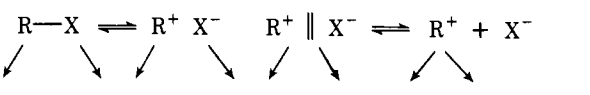
four molecules on the other side. Analogous measurements in methanol or ethanol indicated similar pools, containing fewer of these bigger molecules, in reactions in these solvents.

Such a pool of solvent molecules could account for some of the observed selectivities. A pool of four solvent molecules in equimolar ethanol and trifluoroethanol would have a probability of 0.0625 ($(1/2)^4$) of containing no ethanol. Thus, the nucleophilic selectivity available on the assumption that the cation in the irreversibly formed ion pair reacts exclusively with ethanol if it gets the chance is 15 with a pool of this maximum size. However, the persistence of such high selectivities into the region of high concentrations of trifluoroethanol is not predicted by the model. In 4:1 molar ratio trifluoroethanol-ethanol, a pool of four solvent molecules has a probability of 0.41 ($(0.8)^4$) of containing no ethanol. Therefore the maximum selectivity obtainable on a molar basis is 5.8, compared with one of 19 observed for inversion with α-glucosyl fluoride.

Therefore neither a reversibly formed nor an irreversibly formed ion pair or encounter complex can explain the present data.

3. There is always the possibility that the oxygen atom attached to the reaction center has a sufficiently perturbing influence as to modify the quantum-mechanical prohibitions that are widely assumed to exist for a syn S_N2 process, or even that there are no such prohibitions. Our natural reluctance to call into question such fundamental dogma as Walden inversion is reinforced by the observation by Rhind-Tutt and Vernon[4] of the classical Ingoldian S_N2 reaction of thiophenoxide ion and 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride, which shows second-order kinetics but no detectable retention of configuration; however, the same result could be explained by an unfavorable electrostatic interaction between the leaving and entering anions.

4. Some form of "push" must be coming from the solvent molecules in the common rate- and product-determining step of these reactions, yet a conceptually well-defined ion-pair model is inadequate, and the "push" is exerted equally for retention as for inversion. In order to define precisely where this "push" is being exerted, it is useful to consider the widely quoted Winstein solvolysis scheme.[57]

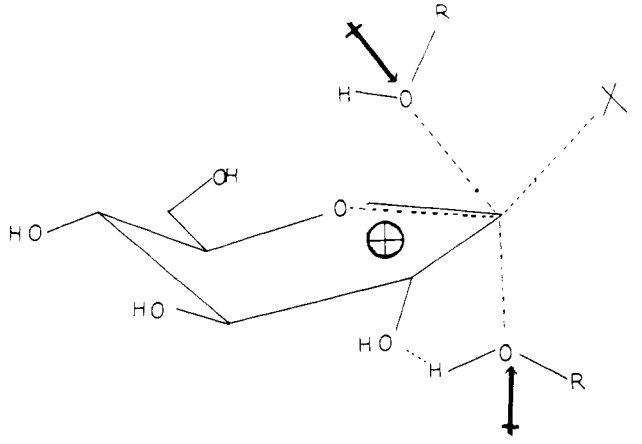


This corresponds in its horizontal direction to the potential energy curve shown in Figure 2.

There is little or no evidence in support of this scheme that distinguishes between the solid reaction profile and the dashed line. There is evidence, including the special salt effect, common ion rate depression, and anion exchange, for "solvent-separated" and solvent-equilibrated ion pairs, but it is difficult to distinguish the intimate ion-pair "intermediate" from a transition state with the available evidence. For example, the observation of "internal return" in a system with an ambident

carbonium ion or an ^{18}O-labeled ambident leaving group does not distinguish between a true intermediate and a plateau on the many-dimensional energy surface where all these reaction pathways have very similar energies. There are similar objections to the use of product stereochemistries and elimination/substitution ratios as probes for the presence of the intimate ion pair as a discrete intermediate. Thus, some of the experimental phenomena ascribed to intimate ion pair "intermediates" may represent concerted reaction mechanisms, according to the definition used here, and other phenomena ascribed to solvent-separated ion pairs may, in fact, proceed through intimate ion pair intermediates that do have a significant lifetime.

The data reported here require a transition state in which there is some specific but weak interaction with both the leaving group and the incoming solvent molecule in the transition state for product formation. This would result if the separation of the leaving group from the oxocarbonium-ion-like center were facilitated by an interaction of the entering solvent molecule with the positive charge on the reaction center that helps to prevent reversion to starting materials, in a transition state which resembles that for diffusion-controlled separation of the leaving group (III). This interaction may be predominantly or entirely electrostatic.



III

If it were not for the formation of products with retention of configuration, however, there would be no sharp line separating this kind of interaction from that in the transition state of a classical S_N2 displacement reaction. The results suggest that, when a transition state is sufficiently open, with weak interactions of the central atom with both entering and leaving groups, these interactions can be significant on the same as well as on the opposite side of the central atom as the leaving group.

Acknowledgment. We thank Mr. Philip J. Marshall for the syntheses of α-D-glucopyranosyl-4-methylpyridinium bromide.

References and Notes

(1) Supported by grants from the National Science Foundation (PCM-7708369) and the National Institutes of Health (GM20888 and GM20168).
(2) On leave from the University of Bristol, School of Chemistry.
(3) Capon, B. *Chem. Rev.* **1969,** *69,* 407–498.
(4) Rhind-Tutt, A. J.; Vernon, C. A. *J. Chem. Soc.* **1960,** 4637–4644.
(5) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975,** *97,* 4056–4062.
(6) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 8238–8248.
(7) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978,** *100,* 7031–7036.
(8) Craze, G. A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978,** 357–368.
(9) Knier, B. L.; Jencks, W. P., submitted for publication in *J. Am. Chem. Soc.*
(10) Jencks, W. P. *Acc. Chem. Res.* **1976,** *9,* 425–432.
(11) Skrabal, A.; Eger, H. H. *Z. Phys. Chem. (Leipzig)* **1926,** *122,* 349–356.
(12) Cocker, D.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1975,** 1391–1395.
(13) Kokesh, F. C.; Hine, J. *J. Org. Chem.* **1976,** *41,* 1976–1979.
(14) Jones, C. C.; Sinnott, M. L. *J. Chem. Soc., Chem. Commun.* **1977,** 767–768.
(15) da Roza, D. A.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1973,** *95,* 7003–7009.
(16) Ando, T.; Tsukamoto, S. *Tetrahedron Lett.* **1977,** 2775–2778.
(17) Rappoport, Z.: Ben-Yacov, H.; Kaspi, J. *J. Org. Chem.* **1978,** *43,* 3678–3684.
(18) Micheel, F.; Klemer, A. *Adv. Carbohydr. Chem.* **1961,** *16,* 85–103.
(19) Ballardie, F.; Capon, B.; Sutherland, J. D. G.; Cocker, D.; Sinnott, M. *J. Chem. Soc., Perkin Trans 1* **1973,** 2418–2419.
(20) Wither, S. G. Ph.D. Thesis, Bristol, 1977. Cf. Sinnott, M. L.; Withers, S. G. *Biochem. J.* **1974,** *143,* 751–762.
(21) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965,** *43,* 2205–2213.
(22) Isbell, H. S.; Frush, H. L. *J. Org. Chem.* **1958,** *23,* 1309–1319.
(23) Sinnott, M. L.; Smith, P. J. *Biochem. J.* **1978,** *175,* 525–538.
(24) See, for example, Pecsok, R. L.; Shields, L. D.; Cairms, T.; McWilliam, I. G. "Modern Methods of Chemical Analysis", 2nd ed.; Wiley: New York, 1976; p 103.
(25) Zemplen, G.; Pacsu, E. *Chem. Ber.* **1929,** *62,* 1613–1614.
(26) Made by the method of: Helferich, B.; Ost, W. *Chem. Ber.* **1962,** *95,* 2612–2615.
(27) Ferguson, J. H. *J. Am. Chem. Soc.* **1932,** *54,* 4086–4090.
(28) Poretz, R. D.: Goldstein, I. J. *Biochemistry* **1970,** *9,* 2890–2896.
(29) Banks, B. E.C.; Meinwald, Y.; Rhind-Tutt, A. J.; Sheft, I.; Vernon, C. A. *J. Chem. Soc.* **1961,** 3240–3246.
(30) For glycosylamines, see: Capon, B.; Connett, B. E. *J. Chem. Soc.* **1965,** 4492–4497, 4497–4502.
(31) Brigl, P. *Hoppe-Seyler's Z. Physiol. Chem.* **1922,** *122,* 245–262.
(32) Raber, D. J.; Neal, W. C., Jr.; Dukes, M. D.; Harris, J. M.; Mount, D. L. *J. Am. Chem. Soc.* **1978,** *100,* 8137–8146.
(33) White, E. H.; Scherrer, H. *Tetrahedron Lett.* **1961,** 758–762.
(34) Maskill, H.; Southam, R. M.; Whiting, M. C. *Chem. Commun.* **1965,** 496–498.
(35) Isaacs, N. S.; Rannala, E. *J. Chem. Soc., Perkin Trans. 2* **1974,** 899–902.
(36) Jones, C. C.; Sinnott, M. L., unpublished.
(37) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959,** *81,* 1050–1053; **1960,** *82,* 795–798.
(38) Perrin, D. D. "Dissociation Constants of Organic Bases in Aqueous Solution", Supplement 1972; Butterworths: London, 1972.
(39) Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964,** 3596–3599. The dielectric constants of nitrobenzene (34) and the present solvolysis medium (~25) are similar.
(40) Chapman, N. B.; Levy, J. L. *J. Chem. Soc.* **1952,** 1677–1682.
(41) Barnett, J. E. G. *Carbohydr. Res.* **1969,** *9,* 21–31.
(42) Fry, J. L.; Lancelot, C. J.; Lam, L. K. M.; Harris, J. M.; Bingham, R. C.; Raber, D. J.; Hall, R. E.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1970,** *92,* 2538–2540.
(43) Lemieux, R. U. *Pure Appl. Chem.* **1971,** *27,* 527–547.
(44) At 39 °C, the rate of hydrolysis of 3,4-dinitrophenyl β-D-galactopyranoside is estimated to be 8×10^{-8} s^{-1},[45] compared with 2.3×10^{-2} s^{-1} for the tetrahydropyranyl derivative.[46] Of this 300 000-fold rate reduction, a factor of ~2000 can be attributed to the inductive effect of the 2-OH,[3] and a further factor of 3–5 to that of the C-6 OH.[12] The hydrolysis rates of xylosides and 6-deoxyglucosides are similar,[12] showing that the effect of the C-5 substituent in the pyranose ring is indeed electronic and not steric.
(45) Sinnott, M. L.; Withers, S. G.; Viratelle, O. M. *Biochem. J.* **1978,** *175,* 539–546.
(46) Craze, G. A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978,** 354–356.
(47) Sujdak, R. J.; Jones, R. L.; Dorfman, L. M. *J. Am. Chem. Soc.* **1976,** *98,* 4875–4879.
(48) Bruice, T. C.; Benkovic, S. J. "Bioorganic Mechanisms", Vol. 1; W. A. Benjamin: New York, 1966; pp 148–166.
(49) Ritchie, C. D.; Wright, D. J.; Huang, D.-S.; Kamego, A. A. *J. Am. Chem. Soc.* **1975,** *97,* 1163–1170.
(50) Capon, B.; McManus, S. P. "Neighboring Group Participation", Vol. 1; Plenum Press: New York, 1976; p 163.
(51) Coward, J. K.; Lok, R.; Takagi, O. *J. Am. Chem. Soc.* **1976,** *98,* 1057–1059.
(52) This figure is derived from the time-invariant products from acid-catalyzed trifluoroethanolysis of phenyl α-glucoside.
(53) See, for example, Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 3rd ed.; Wiley: New York, 1976; p 282.
(54) Sneen, R. A. *Acc. Chem. Res.* **1973,** *6,* 46–53.
(55) Hashida, Y.; Landells, R. G. M.; Lewis, G. E.; Szele, I.; Zollinger, H. *J. Am. Chem. Soc.* **1978,** *100,* 2816–2823.
(56) Grunwald, E.; Heller, A.; Klein, F. S. *J. Chem. Soc.* **1957,** 2604–2613.
(57) See, for example, Harris, J. M. *Prog. Phys. Org. Chem.* **1974,** *11,* 89–173.