Failure of the Antiperiplanar Lone Pair Hypothesis in Glycoside Hydrolysis. Synthesis, Conformation, and Hydrolysis of α-D-Xylopyranosyl- and α-D-Glucopyranosyl-pyridinium Salts

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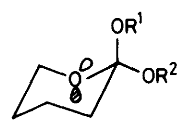
(1) Two series of crystalline α-D-xylopyranosyl- and α-D-glucopyranosyl-pyridinium bromides have been made, by reaction of the acetylated α-bromides with the pyridines in an aprotic solvent in the presence of bromide ion, followed by deacetylation with aqueous HBr at room temperature. (2) 200 MHz ^{1}H N.m.r. spectra in D_2O of representatives of each series show the *xylo*-compounds to adopt the $^1C_4$ conformation, and the *gluco*-compounds the $^1S_3$ conformation. (3) The hydrolyses of α-D-xylopyranosyl- and α-D-glucopyranosyl-3-bromopyridinium ions in 1.0M-$NaClO_4$ at 25.0 °C are described by $k_{obs}/s^{-1} = 4.7 \times 10^{-8} + 1.4 \times 10^{-18}/[H^+]$ and $k_{obs}/s^{-1} = 2 \times 10^{-7} + 1.4 \times 10^{-17}/[H^+]$, respectively. (4) The products of pH-independent hydrolysis of the foregoing ions are the sugars and 3-bromopyridine, whereas at pH 12, 10% of both reactions proceed by attack on the pyridine ring: attack on the sugar yields glucose and 1,6-anhydroglucopyranose, but no xylose. (5) The pH-independent hydrolyses display strongly positive entropies of activation: at 25.0 °C, those of five *xylo*-compounds give a β_{lg} value of -1.27 ± 0.06, and those of four *gluco*-compounds one of -1.06 ± 0.12. (6) Arguments are presented, in the light of the low α:β rate ratios for both *xylo* and *gluco* pyridinium salts (8—23 and 80, respectively, at 25 °C), that departure of a pyridine from C(1) of an aldopyranose ring does not require a conformation in which the leaving group is antiperiplanar to a lone pair of electrons on O(5). (7) The antiperiplanar lone pair hypothesis is shown to be a special case of the principle of least nuclear motion, which is known not to apply to reactions with very product- (or reactant-) like transition states.

The idea that departure of a leaving group from a tetrahedral carbon atom, substituted with one or more heteroatoms, is favoured in an additive way by the presence of antiperiplanar lone pairs of electrons on the heteroatoms and has achieved some currency of late. This antiperiplanar lone pair hypothesis was originally developed to explain products formed at the acyl level of oxidation,[1] as was its theoretical rationale.[2] There are a number of difficulties with even its original formulation:[1] results from the hydrolysis of orthoesters were interpreted on the assumption that the lifetime of a tetrahedral intermediate was short compared with the time of rotation about a carbon–oxygen single bond. In fact hydrogen orthoesters have been directly observed and their lifetimes measured,[3,4] and the antiperiplanar lone pair hypothesis questioned on these grounds.[4] Studies on the hydrolysis of an *E–Z* pair of imidates showed that likewise the lifetime of a tetrahedral intermediate containing nitrogen was long compared with the time of rotation about a C–O or C–N bond.[5] Perrin and Arrhenius[6] analysed the logic behind Deslongchamps' work, and concluded that it contained no unambiguous evidence for the antiperiplanar lone pair hypothesis. One of the crucial findings in the formulation of the hypothesis, the supposed non-production of δ-valerolactone from hydrolysis of orthoesters (**Ia** and **b**), has been shown to be experimentally wrong.[7]

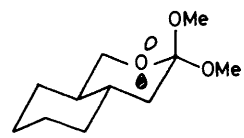
In the gas phase, there is no preference for the loss of a methoxy group from the axial epimer of orthoester (**II**).[8]

Kinetic studies of the acid-catalysed hydrolysis of system (**Ic**) have, however, shown a very modest (2—11 fold), solvent-dependent preference for departure of axial methoxy.[9]

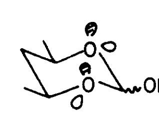
At the aldehyde level of oxidation, in simple systems the antiperiplanar lone pair hypothesis lacks the support of even modest kinetic effects in the right direction: in systems (**III**),[7] and (**IV**)[10,11] the equatorial leaving group is lost the faster. This faster departure of the equatorial leaving groups could be attributed with some plausibility to reaction through boat conformers, which do indeed have antiperiplanar lone pairs of electrons.[12] An elegant series of investigations by Kirby and co-



(I)
a; $R^1 = R^2 =$ Me
b; $R^1 = R^2 =$ Et



(Ic)

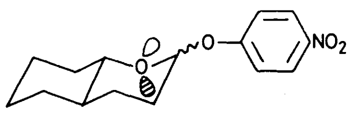


(II)

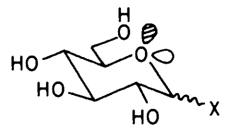
workers attempted to circumvent the conformational ambiguity inherent in systems such as (**III**), and demonstrated dramatic effects in system (**V**)[13] (after correction for ion-pair return), (**VI**)[14] (where the reaction is formally a fragmentation), and (**VII**)[15] (where an 'anti-Bredt' oxocarbonium ion is generated). The problem is clearly the design of an atomic framework sufficiently rigid to restrict conformational preferences, but not so constraining as to introduce uncertainties into the choice of a suitable reference reaction.

We addressed the problem, in a complementary fashion, to Kirby *et al.* by using a leaving group which was also a powerful conformational determinant, *viz.*, pyridine. The bulk and, more importantly, the reverse anomeric effect,* constrains the leaving

* This effect, as originally defined,[23] is the additional tendency of positively charged substituents at C(1) of a pyranose ring to adopt the equatorial orientation. It cannot be accounted for by the frontier orbital picture of the ordinary anomeric effect,[16] and has since been re-defined on theoretical grounds as the additional tendency of groups more electropositive than hydrogen in a σ (S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Am. Chem. Soc.*, 1973, **95**, 3806) or than oxygen in a π (S. Wolfe, M. H. Whangbo, and D. J. Mitchell, *Carbohydr. Res.* 1979, **69**, 1) sense to adopt the equatorial orientation. The effect as so re-defined is wholly without experimental foundation. The experimentally manifested effect is undoubtedly electrostatic in nature, and has nothing to do with any ground-state antiperiplanar lone pair effects.

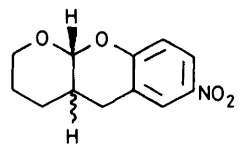


(III)

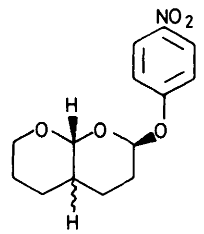


(IV)

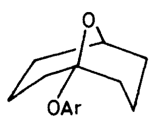
a; $X = H_2PO_4^-$ (ref. 10)
b; X = F (ref. 11)



(V)



(VI)



(VII)

group in the ground state to the equatorial orientation. (Studies with acetylated α-D-glucopyranosyl-[17] and α-D-xylopyranosyl-imidazoles[18] that change their conformational preference on protonation, establish conclusively that the reverse anomeric effect is both powerful, and not trivially caused by the bulk of the pyridine ring.) The ground-state conformational requirements of a pyridinium leaving group, therefore, are directly opposite to the requirements imposed by the antiperiplanar lone pair hypothesis for its departure.

By working with aldopyranose derivatives in aqueous solution, for which there exist a reasonably reliable set of empirical conformational energies,[19] it is possible to make predictions as to what the ratio of S_N1 hydrolysis of anomeric pairs of aldopyranosylpyridinium salts would be, if the antiperiplanar lone pair hypothesis were correct. The ground-state conformational preference of the pyridine leaving group is exactly opposite to the supposed requirement for its departure. Therefore we assume that the most accessible conformation of the pyranose ring of a pyridinium salt that has a lone pair of electrons antiperiplanar to the leaving pyridine is the ground-state conformation of the pyranose ring in the pyridinium salt of opposite anomeric configuration.

The further advantage of carbohydrate systems is that they are directly relevant to biological glycosyl-transferring systems, which have been subjected to theoretical consideration in the light of the antiperiplanar lone pair hypothesis.[20] A disadvantage of using aldopyranosyl derivatives is that in ethanol or trifluoroethanol certainly,[21] the intermediate oxocarbonium ions are too unstable to exist[22] and the reactions are therefore bimolecular. However, in water, although there are salt effects on the hydrolysis of glycosyl derivatives, these parallel basicity rather than the nucleophilicity of the salt. Rates in 1.0M salt, for instance, are in the order NaF > NaCl > NaI. Moreover, the neutral nucleophile thiourea has no effect.[12] This provides reassurance that the reactions are indeed unimolecular in water, even if only just so; therefore the trajectory of approach of a nucleophile does not have to be considered.

Experimental

Tri-O-acetyl-α-D-xylopyranosylpyridinium Bromides.—Generally, tri-*O*-acetyl-α-D-xylopyranosyl bromide (5 g) was dissolved in a mixture of dry acetone (10 ml), dry *m*-cresol (1.0 ml), and the pyridine (5 g) and allowed to stand overnight at room temperature. The product was isolated by pouring the reaction mixture into ether. Yields, characterisation data, and recrystallisation solvents are given in Table 1. The conditions were slightly altered for the unsubstituted pyridine [glycosyl halide (2.0 g), acetone (75 ml), and pyridine (25 ml); product crystallised out of the reaction mixture] and nicotinamide [glycosyl halide (5 g), dry nicotinamide (2.0 g), in dry acetone (125 ml); after 3 h the abundant precipitate of nicotinamide hydrobromide was filtered off, and the mixture allowed to stand overnight at room temperature: on lowering the temperature to 4 °C the product crystallised].

Tri-O-acetyl-β-D-xylopyranosylpyridinium Bromides.—Generally, the pyridine (3 g) was warmed with tri-*O*-acetyl-α-D-xylopyranosyl bromide (5 g) and *m*-cresol (4.5—6.5 ml) until a homogeneous melt was obtained, then left overnight at room temperature. The product was isolated by pouring the reaction mixture into ether. Yields, characterisation data, and recrystallisation solvents are given in Table 1. However, the unsubstituted pyridine compound was prepared by reaction of the glycosyl halide (2.0 g) with pyridine (25 ml) in dry ethanol (75 ml) at room temperature.

Tetra-O-acetyl-α-D-glucopyranosylpyridinium Bromides.—These were prepared by the method of Lemieux and Morgan[23] for the 4-methylpyridinium salt, and were isolated by pouring into ether. Yields, characterisation data, and recrystallisation solvents are given in Table 1.

De-O-acetylation of Labile (Largely α) Glycopyranosylpyridinium Salts.—The fully acetylated compounds (1.0 g) were dissolved in 8% aqueous hydrogen bromide (10 ml) and left at room temperature in the dark for 6 days. Any small amount of insoluble material was removed by filtration through Celite, and the hydrogen bromide was removed from the filtrate by extraction with a 33% (v/v) solution of tri-n-octylamine in dichloromethane until the pH of the aqueous layer increased to between 5 and 6 (no higher). The aqueous layer was then extracted with dichloromethane (3 × 10 ml), and was evaporated to a pale yellow syrup. Portions of dry ethanol (3 × 10 ml) were evaporated from the syrup to give a very stiff white gum which, on trituration with a 3:1 (v/v) mixture of ethanol and methanol (3.5 ml) gave a crystalline product. The comparatively stable 2,3,4-tri-*O*-acetyl-β-D-xylopyranosylpyridinum salt was taken to pH 8 after deacetylation: in this case the acetate salt of the β-D-xylopyranosylpyridinium ion was isolated. De-*O*-acetylation of some of the more robust tri-*O*-acetyl-α- and β-xylopyranosylpyridinium salts was achieved by the method of Lemieux and Morgan.[23]

Kinetic Measurements.—The changes in absorbance were followed at the wavelengths of maximum absorbance for the stated aglycones: pyridine and 4-methylpyridine, 265 nm; 4-bromoisoquinoline, 344 nm; 3-carbamoylpyridine, 275 nm; and 3-bromopyridine, 280 nm. Runs below 80 °C were followed in 1 cm cells in the thermostatted cell block of a Unicam SP 1800 spectrometer system, the temperature of the cell block being kept constant by a Techne C-100 closed-system water-bath. The temperature in the cell was measured by means of Radiospares miniature bead thermistors enclosed in glass capillaries (sealed at one end), inserted through holes drilled in the Teflon stoppers of the cells and glued in with epoxy resin. The thermistor resistances were calibrated by immersing them in a water-bath maintained at a constant temperature by a circulating thermostatic pump.

At temperatures above 90 °C, the reactions were followed by immersing sealed ampoules in a Tamson thermostatic oil-bath, withdrawing them at suitable invervals, cooling, and taking the optical density reading on a Unicam SP 1800 or Perkin-Elmer 555 spectrometer.

In general, rate constants were calculated from linear least-squares treatments of $\ln(A - A_\infty)$ *versus* time plots using experimental infinity points. However, degradative browning reactions at high pH or above 90 °C made these values unreliable, so in these cases A_∞ values calculated from Kezdy–Swinbourne [24] plots were used.

All data pertain to 50mM-buffer solutions in 1.0M-sodium perchlorate: pH values were measured at room temperature. The following buffer systems were used: pH 3.5—5.5, acetic acid–sodium hydroxide; pH 5.5—8.5, disodium hydrogen phosphate–sodium dihydrogen phosphate; pH 8.5—10.5, EDTA–sodium hydroxide; pH 11—12.5, disodium hydrogen phosphate–sodium hydroxide; pH 12.95 was obtained using sodium hydroxide alone. Buffers were made up to the pH values and measured with a standard combination electrode, used in conjunction with a Radiometer PHM 62 pH meter, which had been freshly calibrated with BDH standard buffers.

Note on the Use of Standard Combination Electrodes and $NaClO_4$ *Solutions.*—After a period of time a standard combination pH electrode immersed in 1.0M-sodium perchlorate will become sluggish, owing, no doubt, to the precipitation of potassium perchlorate in the porous plug of the potassium chloride bridge. On soaking in dilute buffer, a quick response is re-established, and the electrode, when calibrated with standard buffer, reads correctly in dilute solutions and in 1.0M-sodium perchlorate. Insidiously, however, in 1.0M-potassium chloride solutions the electrode can now read up to 0.8 pH units too low.

^{1}H *N.m.r. Spectra.*—For the determination of conformations, these were measured on a JEOL 200 MHz Fourier transform instrument in D_2O with 3-trimethylsilylpropane-1-sulphonate as internal standard. Signals were assigned by irradiation at H(1), H(2), H(3), and H(4) in the case of α-D-xylopyranosyl-4-methylpyridinium ion, H(1) and H(5) (*pro-R*) in the case of β-D-xylopyranosylpyridinium ion, and at H(1) and H(2) in the case of the α-glucosylpyridinium ions. The H(3), H(4), H(5), H(6), H(6′) region of α-D-glucopyranosyl-4-bromoisoquinolinium ion was simulated using the NUMARIT program. Analysis of inversion:retention ratios in the reaction of acetylglycopyranosyl bromides with pyridine were made on a JEOL PMX60 continuous wave instrument.

Product Analyses.—The glycones were analysed by g.l.c. of their trimethylsilyl ethers using 1,6-anhydrogalactose as an internal standard for products from glucosylpyridinium salts and 1,6-anhydro-D-glucose as an internal standard for xylosylpyridinium salts. Analyses were performed on a 2 m column of 5% Dexsil 300SC (on 100—20 mesh Gas Chrom Q) at 170 °C for xylose and 190 °C for glucose. Relative retention times were 1,6-anhydrogalactose:1,6-anhydroglucose:α-glucose:β-glucose, 1:1.26:1.97:2.96, and 1,6-anhydroglucose:α-xylose:β-xylose, 1:0.84:1.16; the number of theoretical plates was 1 520 (β-glucose) and 1 280 (β-xylose).

Portions (5 ml) of a solution of the pyridinium salt in the appropriate buffer were heated for 6 half-lives at 100 °C, neutralised (where appropriate), and extracted with ether (3 × 2 ml). The ethereal solution was blown down with nitrogen, the residue taken up in pH 6.0 buffer, and the pyridine estimated from its u.v. absorbance. To the aqueous layer was added an internal standard, the solution was shell-frozen and freeze-dried, and then derivatised for g.l.c. with a pyridine–hexamethyldisilazane–trimethylchlorosilane mixture (5:1:2 v/v).

Aglycones liberated in alkaline solution were also analysed without ether extraction.

Results and Discussion

Reaction of Acetylglycopyranosyl Bromides with Pyridines.—This work partly has its origin in our finding that conditions for reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl [25] or 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl [26] bromides with pyridines, which gave pyridinium salts of inverted anomeric configuration, when applied to 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide, gave 2,3,4-tri-*O*-acetyl-α-D-xylopyranosylpyridinium salts. A previous, related, preparative observation had been that 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-4-bromoisoquinolinium bromide, prepared in the same way as its C(4) epimer,[25] was, as a crude material, contaminated with the α-anomer.[27] Some quantitation of these preparative impressions can be obtained from the inversion:retention ratio, as measured by n.m.r. integration of the anomeric hydrogen resonance, of the pyridinium salt products formed when acetylglycopyranosyl bromide (0.2 g) was dissolved in dry deuteriopyridine (0.5 ml) and left overnight at room temperature: α-D-*galacto*, 8; α-D-*gluco*, 3.6; α-D-*xylo*, 0; and β-L-*arabino*, 3.

The basic proposition, advanced by Lemieux and Morgan to explain their results in the *gluco*-series,[23] that apparently retained pyridinium salts arise from S_N2 reactions of the pyridine on inverted acylglycopyranosyl bromide, itself the product of S_N2 attack by bromide ion on the original halide, is clearly correct. The halide-ion-catalysed anomerisation of glycosyl halides, discovered in that investigation,[23] was subsequently used to develop one of the few successful and widely applied α-glycoside syntheses.[28] This synthesis, and the original reactions with pyridine, have been rationalised in terms of a complex reaction pathway, under stereoelectronic control, involving ion pairs and ion triplets.[29] It is, however, difficult to reconcile this pathway, complex though it is, with either the qualitatively different results obtained with acylglycopyranosyl bromides epimeric at C(4), or with recent evidence against intimate ion pairs as intermediates in glycosyl transfer reactions.[21] We now suggest that our results, and those of Lemieux and Morgan,[23] can be rationalised by a series of classical S_N2 reactions, on two supplementary hypotheses. The first is that 'naked' bromide ion is a better nucleophile than a pyridine unless its approach is opposed by the negative end of the dipole of an acyloxy group, when the neutral nucleophile is favoured. The second is that the anomerised, thermodynamically less stable glycopyranosyl halides are the more susceptible to nucleophilic attack.

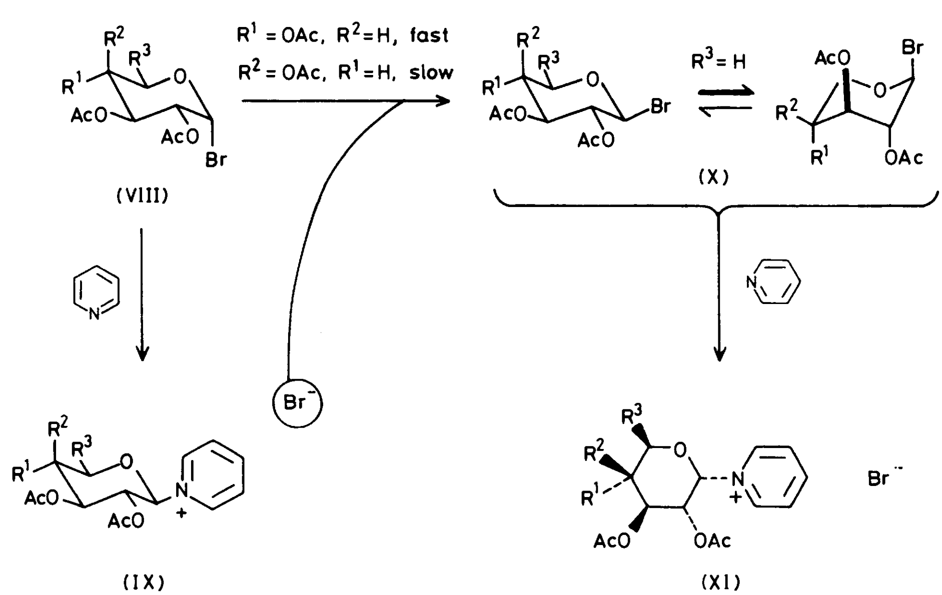
Our proposals are set out in Scheme 1. Initial nucleophilic attack by pyridine on starting bromide (**VIII**) gives 'inverted' pyridinium ion (**IX**) and bromide ion, this last serving to anomerise (**VIII**) to (**X**) rapidly unless opposed by an axial acetoxy group at C(4). (**X**) reacts competitively with bromide ion to re-form (**VIII**) and pyridine to form (**XI**): because of opposition from the acetoxy dipole on C(2), pyridine is a better nucleophile than bromide ion: this is particularly pronounced in the xylose case since it is likely that tri-*O*-acetyl-β-D-xylopyranosyl bromide, like the chloride,[30] adopts the $^1C_4$ conformation as shown. Addition of bromide ion thus favours production of compound (**X**) and hence pyridinium salt (**XI**); addition of hydrogen-bonding solvents, such as phenols or alcohols, solvates the bromide ion and decelerates the anomerisation of the glycosyl bromide.

A similar argument with alcohols (or a hydrogen-bonded complex of alcohol and amine base) explains the success of the halide-ion-catalysed α-glycosylation reaction;[29] in this case

Table 1. Yields, characterisation data, and recrystallisation data

Sugar residue	Aglycone	Yield (%)	Recrystallisation solvent	M.p. (°C)	$[\alpha]_D^{25}$ (°)	Empirical formula	Required (%) C	Required (%) H	Required (%) N	Required (%) Br	Found (%) C	Found (%) H	Found (%) N	Found (%) Br	Anomeric proton δ (solvent) (*J*/Hz)
2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl	3-Bromopyridine	71	Me_2CO	114—115 (dec.)		$C_{16}H_{19}O_7NBr_2$	38.65	3.85	2.8	32.15	38.5	4.0	2.8	32.3	7.50 ($CDCl_3$) s
	4-Methylpyridine	37	Me_2CO–Et_2O	156—158	−38.9 (*c* 1 in $CHCl_3$)	$C_{17}H_{22}O_7NBr$	47.25	5.15	3.25	18.5	47.05	5.05	3.35	18.45	7.32 ($CDCl_3$) s
	Isoquinoline	30	Me_2CO	138—143	−46.0 (*c* 0.8 in $CHCl_3$)	$C_{20}H_{22}O_7NBr$	51.3	4.75	3.0	17.05	51.20	5.3	2.55	17.1	7.50 ($CDCl_3$) s
	4-Bromoisoquinoline	50		122—126		$C_{20}H_{21}O_7NBr_2$	43.9	3.85	2.55	29.2	43.5	3.85	2.6	29.75	7.72 ($CDCl_3$) s
	Pyridine	42		169—170	−45.7 (*c* 0.8 in $CHCl_3$)	$C_{16}H_{20}O_7NBr$	45.95	4.8	3.35	19.1	46.25	5.05	3.4	20.25	7.41 ($CDCl_3$) s
	3-Carbamoylpyridine	16		114—118 (dec.)		$C_{17}H_{21}O_8N_2Br \cdot 0.5Me_2CO$	45.3	4.95	5.7	16.3	44.9	5.6	4.95	17.7	6.62 (D_2O) s
	3-Methylpyridine	24	Me_2CO	131—133	−41.7 (*c* 1 in $CHCl_3$)	$C_{17}H_{22}O_7NBr$	47.25	5.15	3.25	18.5	47.0	5.25	3.3	18.4	7.40 ($CDCl_3$) s
	3,4-Dimethylpyridine	61	Et_2O–Me_2CO	164—168 (dec.)	−36.6 (*c* 1 in $CHCl_3$)	$C_{18}H_{24}O_7NBr$	48.45	5.4	3.15	17.9	48.4	5.7	3.05	17.9	7.40 ($CDCl_3$) s
	3,5-Dimethylpyridine	39	Et_2O–Me_2CO	159—161		$C_{18}H_{24}O_7NBr$	48.45	5.4	3.15	17.9	48.45	5.6	3.1	17.8	7.52 ($CDCl_3$) s
2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl	Isoquinoline	23	EtOH	185—186 (dec.)	−39.8 (*c* 1 in $CHCl_3$)	$C_{20}H_{22}O_7NBr$	51.3	4.75	3.0	17.05	51.45	5.1	2.95	16.95	6.29 (D_2O) (8)
	4-Bromoisoquinoline	19	EtOH	169—171 (dec.)	−71.7 (*c* 1 in $CHCl_3$)	$C_{20}H_{21}O_7NBr_2$	43.9	3.85	2.55	29.2	43.4	4.3	2.55	29.25	6.38 (CD_3OD) (8)
	3-Carbamoylpyridine	21		144—147 (dec.)		$C_{17}H_{21}O_8N_2Br$	44.25	4.6	6.05	17.3	44.4	4.8	6.15	17.2	6.18 (D_2O) (8)
	Pyridine	21	Me_2CO	167—169 (dec.)	−21.9 (*c* 1 in $CHCl_3$)	$C_{16}H_{20}O_7NBr$	45.95	4.8	3.35	19.1	45.0	4.9	3.3	19.3	7.41 ($CDCl_3$) (8)
	3-Bromopyridine	20	EtOH	155—156 (dec.)		$C_{16}H_{19}O_7NBr_2$	38.65	3.85	2.8	32.15	38.85	3.85	2.95	31.85	6.16 (D_2O) (8)
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl	4-Methylpyridine	24	Et_2O–Me_2CO	168—169	+25.3 (*c* 1 in $CHCl_3$)	$C_{20}H_{26}O_9NBr$	47.65	5.15	2.75	15.85	47.0	5.8	2.8	15.5	7.42 ($CDCl_3$) (3)
	Isoquinoline	12	Et_2O–Me_2CO	154—155	+21.0 (*c* 1 in $CHCl_3$)	$C_{23}H_{26}O_9NBr$	51.1	4.85	2.6	14.8	51.05	5.1	2.35	14.85	7.74 ($CDCl_3$) (3)
	3,5-Dimethylpyridine	41	Et_2O–Me_2CO	177	+21.2 (*c* 1 in $CHCl_3$)	$C_{21}H_{28}O_9NBr$	48.65	5.45	2.7	15.4	48.3	5.7	2.45	15.4	7.67 ($CDCl_3$) (3)
	3-Bromopyridine	18	Me_2CO–Et_2O	137—138	+31.0 (*c* 0.8 in $CHCl_3$)	$C_{19}H_{23}O_9NBr_2$	40.05	4.05	2.45	28.1	39.9	4.15	1.95	28.5	7.7 ($CDCl_3$) (2.8)
	4-Bromoisoquinoline	43	Et_2O–Me_2CO	161—162	+25.1 (*c* 1 in $CHCl_3$)	$C_{23}H_{25}O_9NBr_2$	44.6	4.05	2.25	25.8	44.0	4.35	1.9	25.55	7.9 ($CDCl_3$) (1.7)
	Pyridine	14	Et_2O–Me_2CO	127—128	+19.2 (*c* 1 in $CHCl_3$)	$C_{19}H_{24}O_9NBr$	46.55	4.9	2.85	16.3	45.0	4.85	2.65	14.1	7.5 ($CDCl_3$) (2.6)
	3-Carbamoylpyridine	36	Et_2O–Me_2CO	162—165	+21.1 (*c* 1.0 in H_2O)	$C_{20}H_{25}O_{10}N_2Br$	45.05	4.75	5.25	15.0	45.05	4.85	5.6	15.1	6.78 (D_2O) (2.4)

Sugar residue	Aglycone	Yield (%)	Recrystallisation solvent	M.p. (°C)	$[\alpha]_D^{25}$ (°)	Empirical formula	Required (%) C	Required (%) H	Required (%) N	Required (%) Br	Found (%) C	Found (%) H	Found (%) N	Found (%) Br	Anomeric proton δ (solvent) (J/Hz)
α-D-Xylopyranosyl	3-Bromopyridine	60	See text	108—111	−38.7 (c 0.9 in H_2O)	$C_{10}H_{13}O_4NBr_2$	32.35	3.55	3.8	43.05	32.45	3.6	3.45	43.3	6.25 (D_2O) s
	4-Bromoisoquinoline	76		107—115 (dec.)	−40.6 (c 1.0 in H_2O)	$C_{14}H_{15}O_4NBr_2$–$0.5C_2H_5OH \cdot H_2O$	39.0	4.35	3.05	34.6	38.8	4.35	3.0	34.1	6.33 (D_2O) s: 1/2 mole Equivalent of ethanol detected
	3-Carbamoylpyridine	52		127—129	−43.4 (c 0.9 in H_2O)	$C_{11}H_{15}O_5N_2Br$	39.4	4.5	8.35	23.85	39.8	4.6	7.9	23.8	6.34 (D_2O) s
	Pyridine	79		157—159 (dec.)	−58.5 (c 1.4 in H_2O)	$C_{10}H_{14}O_4NBr$	41.1	4.85	4.8	27.35	41.15	5.0	4.95	27.7	6.19 (D_2O) s
	Isoquinoline	41		146—149	−39.4 (c 1.5 in H_2O)	$C_{14}H_{16}O_4NBr$	49.15	4.7	4.1	23.35	48.85	4.9	4.05	23.15	6.29 (D_2O) s
	4-Methylpyridine	68		155—157	−52.6 (c 0.9 in H_2O)	$C_{11}H_{16}O_4NBr$	43.15	5.25	4.55	26.1	43.45	5.45	4.6	25.7	6.09 (D_2O) s
β-D-Xylopyranosyl	4-Bromoisoquinoline	50		148—150 (dec.)	−8.4 (c 0.8 in H_2O)	$C_{14}H_{15}O_4NBr_2$	39.95	3.6	3.35	37.95	40.35	3.65	3.35	37.5	5.84 (D_2O), 8.5 (+ virtual coupling)
	3-Carbamoylpyridine	74		157—160		$C_{11}H_{15}O_5N_2Br$	39.4	4.5	8.35	23.85	40.1	5.05	7.9	23.65	5.79 (D_2O) (8)
	Pyridine	92		149—150	−5.6 (c 1.0 in H_2O)	$C_{10}H_{14}O_4NBr$	41.1	4.85	4.8	27.35	41.15	5.0	4.75	27.2	5.70 (D_2O) (8)
	Isoquinoline	51		142—145	−1.7 (c 1.2 in H_2O)	$C_{14}H_{16}O_4NBr$	49.15	4.7	4.1	23.35	49.15	5.0	3.9	23.25	5.87 (D_2O) (8.3)
α-D-Glucopyranosyl	3-Bromopyridine	28		121—122	+40.2 (c 1 in H_2O)	$C_{11}H_{15}O_5NBr_2$	32.95	3.8	3.5	39.85	32.75	3.9	3.2	40.05	6.39 (D_2O) (3.8)
	4-Bromoisoquinoline	40		140—143	+48.9 (c 0.9 in H_2O)	$C_{15}H_{17}O_8NBr_2$	39.95	3.8	3.1	34.45	39.75	3.95	2.9	35.05	6.60 (D_2O) (3.9)
	Pyridine	54		145—147	+52.5 (c 1 in H_2O)	$C_{11}H_{16}O_5NBr$	41.0	5.01	4.35	24.8	40.7	5.3	4.1	25.25	6.28 (D_2O) (3.8)
	Isoquinoline	21		138—140	+51.5 (c 0.9 in H_2O)	$C_{15}H_{18}O_5NBr$	48.4	4.85	3.75	21.5	48.25	5.05	3.55	21.65	6.6 (D_2O) (3)
	4-Methylpyridine	46		127—128	+57.3 (c 0.8 in H_2O)	$C_{12}H_{18}O_5NBr$	42.85	5.4	4.15	23.75	43.1	5.35	4.1	23.45	6.32 (D_2O) (3.9)



R^1 = OAc, R^2 = R^3 = H, D-*xylo*
R^2 = OAc, R^1 = R^3 = H, L-*arabino*
R^1 = OAc, R^2 = H, R^3 = CH_2OAc, D-*gluco*
R^2 = OAc, R^1 = H, R^3 = CH_2OAc, D-*galacto*

Scheme 1.

Table 2. Chemical shifts and coupling constants (D_2O)

	Chemical shifts (δ)		
	α-D-Xylopyranosyl-4-methylpyridinium bromide	β-D-Xylopyranosyl-pyridinium acetate	α-D-Glucopyranosyl-4-bromoisoquinolinium bromide
H(1)	6.19	5.70	6.60
H(2)	4.01	3.63	4.49
H(3)	4.23	3.72	4.19
H(4)	3.86	3.91	3.90
H(5) (*pro-R*)	4.35	4.32	
H(5) (*pro-S*)	4.25	3.65	
	Coupling constants (Hz)		
H(1)–H(2)	1.4	8.3	3.7
H(2)–H(3)	2.7	10.0	6.8
H(3)–H(4)	2.5	8.9	6.2
H(4)–H(5) (*pro-R*)	1.8	5.4	
H(4)–H(5) (*pro-S*)	1.5	10.4	8.3
H(5)–H(5)	13.4	11.2	
H(1)–H(3)	0.9		
H(2)–H(4)	1.2		
H(3)–H(5) (*pro-S*)	1.2		

however the 2-acetoxy group of halide (**X**) competes favourably as an intramolecular nucleophile with alcohol as an external nucleophile, and orthoesters are eventually produced unless non-participating protecting groups are used.

Conformation of Deprotected α-D-Xylopyranosyl- and α-D-Glucopyranosyl-pyridinium Salts in Water.—Chemical shifts and coupling constants of protons attached to the pyranose rings of representative α- and β-D-xylopyranosyl- and α-D-glucopyranosyl-pyridinium salts are given in Table 2. These indicate that the α-D-xylopyranosyl-4-methylpyridinium ion adopts the $^1C_4$ conformation in D_2O. Indeed, the coupling constants quoted by Paulsen *et al.*[18] for the tri-*O*-acetylpyridinium chloride in deuterionitromethane can be used to give coupling patterns that correspond to the observed spectrum, if an additional 0.9 Hz coupling between H(1) and H(3) is assumed. A slight change in the shape of the pyranose ring is expected on deacetylation, since acylation is known to reduce the repulsion between 1,3-diaxial hydroxy groups.[13,31]

This additional four-bond coupling makes the anomeric

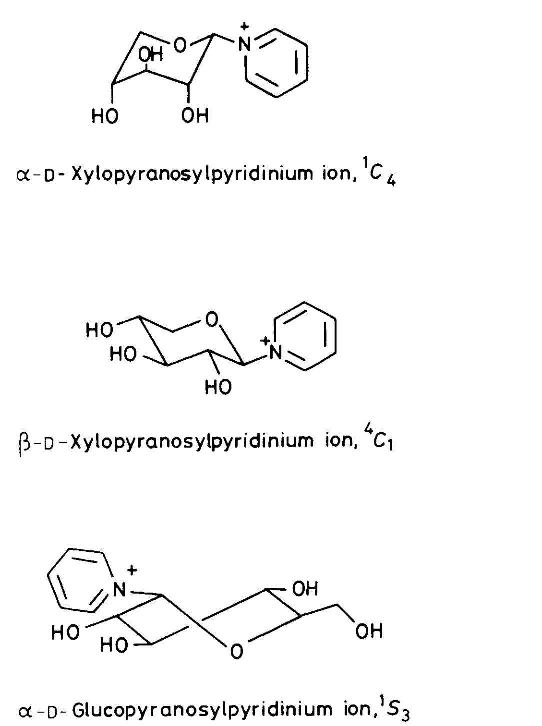


Figure 1. Preferred conformations of glycopyranosylpyridinium salts

protons of α-D-xylopyranosylpyridinium salts appear as broad singlets.

The β-D-xylopyranosylpyridinium salts are clearly in the $^4C_1$ conformation; the $^4C_1$ and the $^1C_4$ conformations are illustrated in Figure 1. The conformation of the α-D-glucopyranosylpyridinium salts is less obvious. Lemieux[17] examined the ^{1}H n.m.r. spectrum of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-4-methylpyridinium bromide in D_2O, found $J_{1,2}$ 2.8, $J_{2,3}$ 3.1, $J_{3,4}$ 3.2, and $J_{4,5}$ 5.7 Hz, and concluded that the same $B_{2,5}$ conformation was adopted as in the crystal.[32] A full analysis of the deacetylated compound in D_2O was not possible because of chemical shift coincidences, but we find $J_{1,2}$ 3.9, $J_{2,3}$ 7.1, and $J_{3,4}$ 5.6 Hz: with the 4-bromoisoquinolinium salt $J_{4,5}$ is also determinable (Table 2). It is clear that dihedral angles are radically different from those of the tetra-*O*-acetyl derivative, a possible consequence of the apparent attraction between acyloxy groups mentioned earlier.[31] Comparison with the data for α- and β-xylopyranosylpyridinium salts (Table 2) shows that the deacetylated compound is neither in the $^4C_1$ nor the $^1C_4$ conformation, nor an equilibrating mixture of just those two conformations. Clearly, as with the acetylated compound, the axial substituent at C(5) makes the $^1C_4$ conformation prohibitively energetic, and boat conformations are adopted. [The full positive charge on the nitrogen of the pyridinium salt thus has a bigger effect than the half positive charge on N(1) of protonated α-D-glucopyranosylimidazole, which remains in the $^4C_1$ conformation.[33]]

Although the possibility that observed coupling constants are a time average of several different conformations cannot be ruled out, one single conformation at an energy minimum on the twist-boat pseudorotational itinerary can account for the observed coupling constants in a general way (*cf.* ref. 34). In this, the $^1S_3$ conformation (Figure 1), all substituents are in energetically favourable positions. The C(1)–N bond is pseudoequatorial exactly eclipsing a line bisecting the two oxygen lone pair orbitals, thus allowing maximum operation of the reverse anomeric effect. The hydroxymethyl group and 2-OH are isoclinal, and the remaining substituents pseudo-equatorial. This is thus likely to be the most populated conformation of α-D-glucopyranosylpyridinium salts.

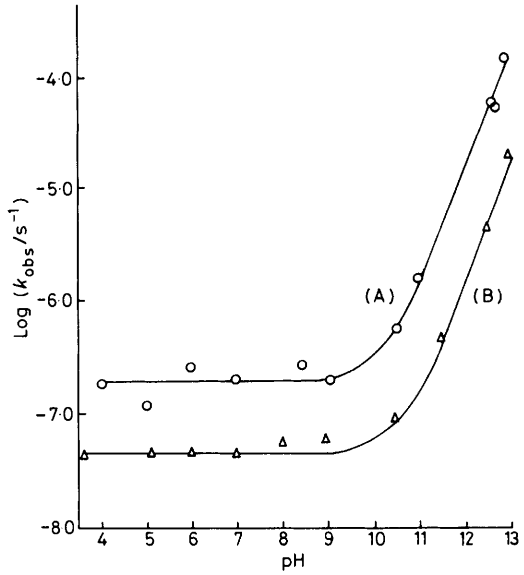


Figure 2. Dependence of rate of hydrolysis of (A) α-D-glucopyranosyl- and (B) α-D-xylopyranosyl-3-bromopyridinium ions on pH. Conditions: 25.0 °C, 1.0M-sodium perchlorate. Rate constants $< 10^{-5}$ s^{-1} were estimated from extrapolation of two rate constants obtained at two higher temperatures. The solid lines describe the following equations, for the α-D-xylopyranosylpyridinium salts:

$$k_{obs}/s^{-1} = 4.7 \times 10^{-8} + \frac{1.4 \times 10^{-18}}{[H^+]}$$

and for the α-D-glucopyranosylpyridinium salts:

$$k_{obs}/s^{-1} = 2 \times 10^{-7} + \frac{1.4 \times 10^{-17}}{[H^+]}$$

Hydrolysis of α- and β-, D-Glucopyranosyl- and D-Xylopyranosylpyridinium Ions.—Figure 2 shows the dependence on pH of the first-order rate constant for disappearance of α-D-xylopyranosyl- and α-D-glucopyranosyl-3-bromopyridinium ions. It is clear that there are two pathways for these hydrolyses, a pH-independent and a base-catalysed one.

The pH-independent pathway is a simple unimolecular heterolysis of the glycosyl–pyridine bond, as is shown by the positive entropies of activation (15 ± 1 for the α-*xylo*- and 13 ± 2 cal mol^{-1} K^{-1} for the α-*gluco*-compound) and, in the *xylo*-case, the absence of a detectable rate enhancement in the presence of the neutral nucleophile thiourea.[12] At pH 6.0, glucose (80%) and 3-bromopyridine (78%) or xylose (45%) and 3-bromopyridine (92%) are the products. The low yield of xylose is almost certainly due to degradation of the labile pentose: products were isolated after six half-lives, and from β-D-xylopyranosyl-3-carbamoylpyridinium ion, a slower substrate, only 17% xylose could be detected, despite a 67% yield of aglycone. Heating D-xylose and nicotinamide under the conditions, and at the concentrations used for product isolation, results in extensive degradation, browning, and 70% loss of optical activity; the nicotinamide is not affected. The degradation of reducing sugars under the fairly drastic conditions used for complete hydrolysis of the pyridinium salts (pH 6 at 100 °C for several hours) is well recognised: the process is acid- and base-dependent, having a minimum at pH 3.5,[35] and gives complex, non-carbohydrate products.[36]

We assume that the β-D-glucopyranosyl-4-bromoisoquinolinium salt gives the sugar and the aglycone, by analogy

Table 3. Kinetic data for hydrolysis of glycosylpyridinium salts in 50mM-NaH_2PO_4–Na_2HPO_4, buffer 1.0M-$NaClO_4$, pH 6.0

Pyridine	T/°C	10^5 k/s^{-1}	$\Delta H^{\ddagger}$/ kcal/mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1}K^{-1}
(i) α-D-Xylopyranosylpyridinium salts				
3-Bromopyridine	89.8	74.3	31.2 ± 0.8	13.0 ± 2.8
	80.5	26.9	(31.7 ± 0.4)	(14.6 ± 1.2)[a]
	50.2	0.35		
4-Bromoisoquinoline	100.1	85.7	33.1 ± 0.3	15.5 ± 0.9
	89.9	23.1		
	80.7	6.98		
Nicotinamide	100.1	126.2	32.9 ± 0.9	15.8 ± 3.1
	89.9	33.6		
	80.6	10.5		
Pyridine	130	111.6	38.9 ± 1.7	24 ± 6
	120	28.9		
	110	8.56		
4-Methylpyridine	140	77.8	39 ± 2	21 ± 7
	130	26.1		
	120	6.66		
(ii) β-D-Xylopyranosylpyridinium salts				
4-Bromoisoquinoline	109.8	116.9	39 ± 2	30 ± 7
	100.1	24.5		
	81.1	1.621		
Nicotinamide	104.7	75.0	37.6 ± 1.0	25 ± 3
	100.1	36.8		
	80.8	2.58		
	79.4	1.88		
Pyridine	136	119.4	42.3 ± 0.8	31 ± 3
	131	59.3		
	116	7.81		
(iii) β-D-Glucopyranosyl-4-bromoisoquinolinium ion				
	127	164		
	118	62.9	36.5 ± 1.8	18 ± 6
	108	16.7		
(iv) α-D-Glucopyranosylpyridinium salts				
3-Bromopyridine	80.4	59.7		
	80.4	62.0		
	80.8	64.4	29.5 ± 0.2	9.9 ± 0.8
	65.7	9.98	(30.4 ± 0.8)	(13.0 ± 2.4)[a]
	65.8	10.67		
	65.7	10.00		
	65.75	10.22		
	49.9	1.017		
	50.2	1.20		
4-Bromoisoquinoline	89.9	57.6		
	89.9	56.1		
	81.3	17.6	33.2 ± 0.9	17.6 ± 3.1
	81.4	16.9		
	66.8	2.14		
	66.8	2.14		
	67.0	2.61		
	66.6	2.44		
Pyridine	120.0	102.5		
	119.5	88.5	34.6 ± 1.0	15.2 ± 3.3
	110.0	27.4		
	110.5	30.0		
	100.2	9.43		
	100.2	8.58		
4-Methylpyridine	136.0	80.1		
	136.0	89.5		
	128.0	36.5	35.6 ± 1.5	13.9 ± 5.1
	126.7	33.0		
	115.0	10.0		
	118.0	11.9		

[a] Mean and S. D. of data used to construct pH-rate profile, pH 3—9.

with the *galacto*-compounds, where this was demonstrated [37] in a representative case.

The base-catalysed pathways are more complex, since in principle attack can occur either on the pyridinium ring or at the anomeric centre, and attack at either of these sites can be by either hydroxide ion or by one of the sugar hydroxy groups, ionised in a pre-equilibrium process. Attack at the anomeric centre is predominant; at pH 12.2 both α-D-glucopyranosyl- and α-D-xylopyranosyl-3-bromopyridinium bromides give an 80% yield of free pyridine, and the glucosyl salt gives 35% 1,6-anhydro-D-glucopyranose and 17% glucose. This last figure is almost certainly a lower limit; glucose, like all reducing sugars is destroyed in alkali, and indeed from the *xylo* salt no xylose could be detected (although a fast-moving peak on the g.l.c. could conceivably be the trimethylsilylated 1,3-anhydro-D-xylopyranose). However, attack on the pyridine also takes place: both the α-D-glucopyranosyl- and α-D-xylopyranosyl-3-bromopyridinium ions at pH 12.2 give an intense, non-ether-extractable absorbance at $\lambda_{max.}$ 366, probably due to the sodium salt of bromoglutaconic dialdehyde: its intensity, and the literature extinction coefficient,[38] indicates about 8% of the reaction goes this way in both cases. Since the absolute rates of the α-*gluco*- and α-*xylo*-salts in alkali differ by an order of magnitude (Figure 2), and since the rate of attack of hydroxide ion on the pyridinium ring in the two ions should be approximately the same, the attack on the pyridine ring is probably initiated by intramolecular attack of an ionised sugar hydroxy group.[39]

Kinetic data for the hydrolyses of various glycosylpyridinium salts in 1.0M-sodium perchlorate at pH 6.0, in the clearly pH-independent region, are given in Table 3. Rates, extrapolated from these data to 25.0 °C, correlate with the pK_a of the departing pyridine as shown in equations (1), (2), and (3) for the α-D-xylopyranosylpyridinium salts, the three β-D-xylopyranosylpyridinium salts, and the α-D-glucopyranosylpyridinium salts, respectively. It has been shown previously[37] that for pH-independent hydrolysis of β-D-galactopyranosylpyridinium salts in 1.0M-potassium chloride equation (4) results.

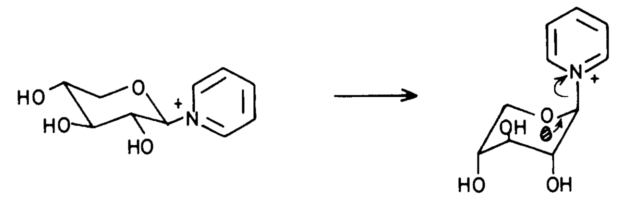
$$\log(k/\text{s}^{-1}) = -(3.67 \pm 0.26) - (1.28 \pm 0.06)\,pK_a \quad (1)$$

$$\log(k/\text{s}^{-1}) = -(5.2 \pm 0.9) - (1.2 \pm 0.2)\,pK_a \quad (2)$$

$$\log(k/\text{s}^{-1}) = -(3.88 \pm 0.53) - (1.06 \pm 0.12)\,pK_a \quad (3)$$

$$\log(k/\text{s}^{-1}) = -(4.33 \pm 0.49) - (1.26 \pm 0.12)\,pK_a \quad (4)$$

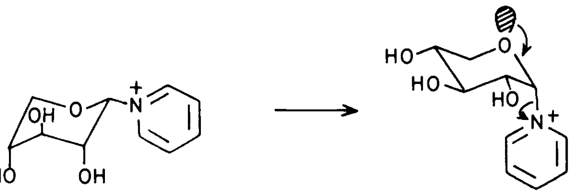
The ratio of rates of departure of pyridines from α- and β-xylopyranosyl residues is very modest, about an order of magnitude if the data are extrapolated to 25 °C (24 for the 4-bromoisoquinolinium, 13 for the 3-carbamoylpyridinium, and 8 for the pyridinium salts), and 3.5 if measured rates for the first two compounds are directly compared at 100.1 °C. It is what would have been expected before the advent of the antiperiplanar lone pair hypothesis for conversion of three equatorial to three axial substituents: it was then considered that relief of strain on going to the half-chair conformation of the glycosyl cation resulted in about a three-fold increase in the rate of hydrolysis of glycopyranosyl derivatives with one axial hydroxy group, compared with the corresponding all-equatorial derivative.[40] The calculations set out in Figure 3, using Angyal's instability factors,[19] indicate that, according to the antiperiplanar lone pair hypothesis, the α-xylosyl salts should hydrolyse at least 150 times faster than their anomers, even in the unlikely event that repulsive 1,3-interactions between a pyridine and a hydroxy group were no greater than between a pyridine and a hydrogen. It could doubtless be argued that the structure of the



2 vicinal diequatorial OH interactions = 0.7 kcal

1 1–3 OH–OH diaxial interaction = 1.5 kcal
1 1–3 OH–H diaxial interaction = 0.45 kcal
1 axial pyridine = X
1 1–3 OH–pyridine diaxial interaction = Y

Total change in conformational energy on going from $^4C_1$ to $^1C_4$ conformation = 1.25 + X + Y



2 1–3 OH–H diaxial interactions = 0.9 kcal
1 1–3 OH–OH diaxial interaction = 1.5 kcal

2 vicinal diequatorial OH interactions = 0.7 kcal
1 axial pyridine = X

Total change in conformational energy on going from $^1C_4$ to $^4C_1$ conformation = X − 1.7 kcal

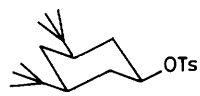
Difference in energy required to provide an antiplanar lone pair = 2.95 + Y kcal

Figure 3. Estimation of the ratio of hydrolysis rates of α- to β-xylopyranosylpyridinium salts, if the antiperiplanar lone pair hypothesis were correct

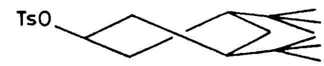
transition state is different for the two sets of anomeric pyridinium salts: there is no evidence from β_{lg} values * that this is so. (Strictly, the difference in conformational energies between ground state and transition states, rather than reactive ground state conformations, should be estimated: however, the antiperiplanar lone pair hypothesis as formulated[1] is a statement about reactive ground state conformations and thus, *strictu sensu*, violates the Curtin–Hammett principle. As the chair conformation with an oxygen lone pair antiperiplanar to the leaving group moves towards the half-chair of the oxocarbonium ion, the disfavouring of axial OH groups will decrease somewhat, but Y will still be substantial.)

Similar considerations apply to the *gluco*-series. The α:β rate ratio here, determined on the 4-bromoisoquinolinium salts,[27] is 80 at 25.0 °C. It is highly unlikely that the β_{lg} value for the β salts will vary as between glucose and galactose, and so the value of -1.26 ± 0.12 from equation (4) can be compared with the value of -1.06 ± 0.12 for the α-glucosyl salts [equation (3)]: there is little evidence for a substantial change of transition state structure in the two sets of compounds. A similar calculation to that of Figure 3 can be performed, but conformational energies for substituents in boat-form pyranose rings are not available. A value of 5.5 kcal mol^{-1} for the chair-twist boat conformational enthalpy difference in cyclohexane has been estimated.[41] If we assume that a β-glucopyranosylpyridinium salt has to adopt the $^1S_3$ conformation to present the leaving group with an antiperiplanar lone pair, whereas the α salt has to adopt a $^4C_1$

* β_{lg} is the gradient of the plot of $\log_{10}$ (rate) against the pK_a of the leaving group.



(XII)



(XIII)

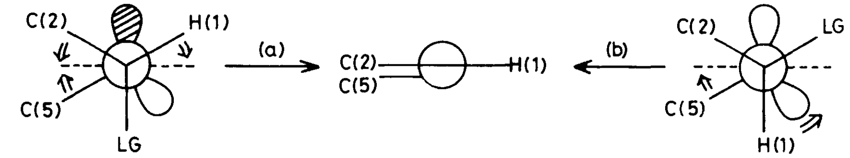
chair from the $^1S_3$ conformation, this value alone, neglecting any additional steric interactions of substituents in the $^1S_3$ conformation, predicts a rate ratio of around 10^8. This is clearly not observed: indeed, the α:β rate ratio, corresponding to departure of a leaving group from a boat, or from the equatorial position of a chair, is surprisingly close to that observed by Hanack and Heinz[42] for ethanolysis of toluene-*p*-sulphonates **(XII)** and **(XIII)** (137 at 50 °C).

The possibility that α:β ratios in either the *gluco*- or the *xylo*-series arise from the selective operation of eliminative pathways or of neighbouring group participation by OH is unlikely. Eliminative pathways would not give any reducing sugar at all, and pH-independence of the reaction would require H_2O to act as a base towards unactivated C–H bonds. Participation in reactions at C(1) of a sugar by un-ionised OH groups in water has never been observed. In the most favourable case, the α-glucopyridinium salts, it would have produced 1,6-anhydroglucose, which was not detected.

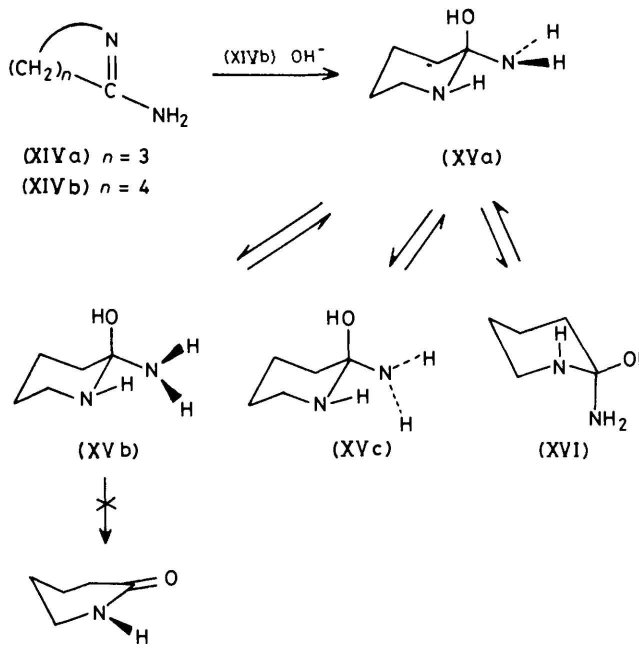
We conclude that the antiperiplanar lone pair hypothesis has no predictive value in the area of glycosyl transfer. In order to clarify the reasons for the failure of the hypothesis in this area, it is instructive to consider its predictions in terms of *nuclear* motion. Chemical reactions necessarily involve nuclear motion, and, in accord with the Born–Oppenheimer approximation, the motions of nuclei can be considered independently of the motion of electrons.[43] As applied to S_N1 reactions of aldopyranosyl derivatives, the antiperiplanar lone pair hypothesis predicts trajectory (a) to be favoured over trajectory (b) (Scheme 2). If we discuss motion along these pathways relative to the plane defined by C(2), O(5), C(5), C(1), and H(1) of the oxocarbonium ion, the only difference in motion of the glycone portion of the molecule is a 90°, rather than a 30°, rotation of the C(1)–H(1) bond. In this case, then, the predictions of the antiperiplanar lone pair hypothesis are equivalent to the predictions of the principle of least nuclear motion.[44]

Least motion effects are recognised to be of variable importance.[44] In particular, because of the variation of internal energy as (approximately) the square of nuclear displacement, they are of limited importance for very reactant-like or very product-like transition states. A substantial body of evidence indicates that the transition state in glycosyl transfer reactions is very late:[40,45] in the case of the glycosylpyridinium salts, the hydrolyses of which are considered here, this is shown by β_{lg} values of less than −1. Therefore, since the transition state for glycosyl transfer strongly resembles the immediate product, a glycosyl cation, least motion effects are not expected to be important; indeed they are not.

The failure of the antiperiplanar lone pair hypothesis in glycosyl transfer is therefore in accord with the re-interpretation of the hypothesis as a special case of the principle of least nuclear motion. This principle also accounts for the 'first unambiguous evidence for stereoelectronic control',[6] published by Perrin and Arrhenius in 1982. This was the production of ω-amino amides as kinetic products, and lactams as thermodynamic products, in the base-catalysed hydrolysis of cyclic amidines **(XIV)** (Scheme 3). The tetrahedral intermediate was considered to have a lifetime that was short compared with the time of inversion about nitrogen, but long compared with ring inversion or rotation about C–O or C–N bonds.[6] Under these conditions least motion arguments also predict the observed results, in the following way. The tetrahedral intermediate will



Scheme 2. LG = leaving group



Scheme 3.

be generated in conformation (**XVa**) first, since this conformation alone is accessible by only 30° rotations of bonds out of the plane defined by the amidine function. This species has various rotamers [*e.g.* (**XVb** and **c**)] and the ring-flipped conformation (**XVI**) and its rotamers, available to it, but does not live long enough for nitrogen inversion to convert the ring NH of (**XV**) or (**XVI**) into the equatorial orientation. Consequently, there is no accessible conformation that can give lactam without a 90° motion, similar to that of H(1) in pathway (b) in Scheme 2, either of the OH group in conformation (**XV**) or of the hydrogen bound to the ring nitrogen in conformation (**XVI**). However, opening of the ring from either conformation (**XVb** or **c**) is possible with only 30° bond motions. Therefore, least motion predicts the exclusive formation of ω-amino amide.

Re-interpretation of the corpus of data held to support the antiperiplanar lone pair hypothesis in terms of least motion removes a puzzling feature of this supposedly electronic phenomenon, namely, that it is more readily observed with compounds at the acyl level of oxidation than at the aldehyde level. The electronic interactions with a developing cationic centre are of decreasing importance in the presence of another electron-donating conjugating group.[46] By contrast, the transition state for reactions of acetals is more oxocarbonium-ion like than the transition state for the hydrolysis of orthoesters,[47] and this is consistent with the greater importance of least motion effects in the latter case. However, if molecules, such as acetal (**VII**), are constructed in which motion analogous to that of H(1) in pathway (b) of Scheme 2 is made wholly impossible, least motion predictions of reactivity are necessarily fulfilled.

Conclusion

The antiperiplanar lone pair hypothesis has been promoted as a fundamental chemical principle, of widespread application.[48] Our results with glycosyl derivatives show unambiguously that such large claims are unwarranted: a theory that claims to be fundamental need only fail once to be disproved, no matter how useful it is as a rule-of-thumb. The predictions of the antiperiplanar lone pair hypothesis are in fact equivalent to the predictions of the principle of least nuclear motion; this principle accounts, for example, for the positive result of 'the first unambiguous test of the theory of stereoelectronic control'.[6] The limitations of the principle of least nuclear motion are well known.[44]

Whatever value the antiperiplanar lone pair hypothesis may have as the simple pictorial illustration of a rule-of-thumb, its limitations must be recognised. Its application, as dogma, to the interpretation of ambiguous preparative experiments (*cf.* the discussion in ref. 6) or mechanistically inaccessible steps in enzymic reactions,[49] can only hinder proper understanding.

Acknowledgements

We thank the S.E.R.C. for research studentships (to L. H. and P. J. M.), Dr. M. Murray for running n.m.r. spectra, and Dr. R. W. Alder for helpful discussions.

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Received 24th March 1983; *Paper* 3/465