Alkyl–Oxygen *versus* Glycosyl–Oxygen Fission in the Acid-catalysed Hydrolyses of Some Alkyl β-D-Glycopyranosides

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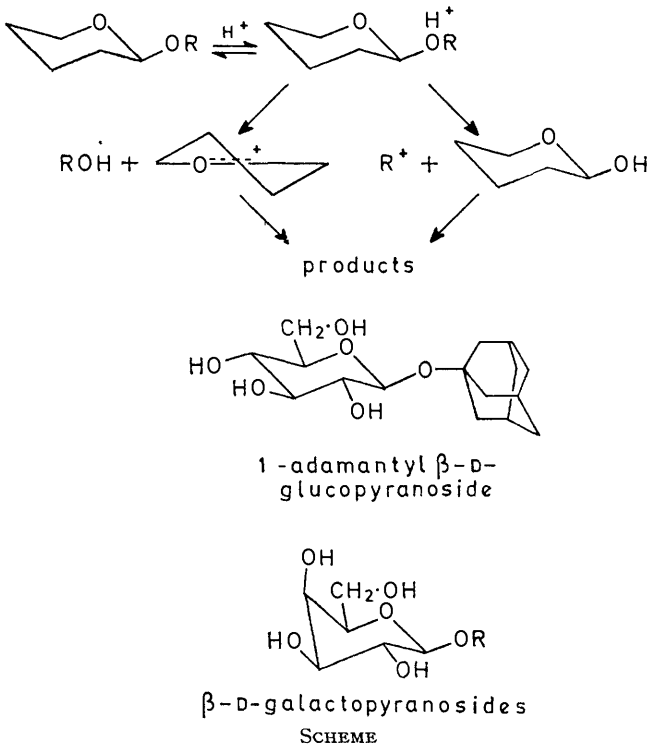
The rates of hydrolysis of 1-adamantyl β-D-glucopyranoside, and of t-butyl, 1,1-diethylpropyl, and diphenylmethyl β-D-galactopyranosides in 0·500M-aqueous sulphuric acid indicate steric acceleration is the major driving force for the accelerated rates of hydrolysis of tertiary glycopyranosides: generation of planar tertiary cations is, however, predominant in the *gluco*-series and important in the *galacto*-series. Product-analytical studies and the rate of acetolysis of 2,4-dinitrophenyl β-D-galactopyranoside relative to those of the dinitrophenolates of the aglycons confirm this.

ACID-catalysed hydrolyses of alkyl β-D-glycopyranosides are considered to take place by equilibrium protonation of the exocyclic oxygen atom, followed by slow unimolecular heterolysis to yield a glycopyranosyl or alkyl cation, depending on the relative stability of these species (see Scheme) [1] (thermodynamic and kinetic



SCHEME

criteria of stability are interchangeable in the interpretation of gross effects [2]). The greatly accelerated rates of hydrolysis of tertiary glycosides (t-butyl and 1,1-diethylpropyl glucosides are hydrolysed 550 and 30,600 times faster than their methyl analogue) are considered to arise from the ' great stability of (tertiary alkyl cations) which is far greater than that of the (glycosyl cation),' and steric effects of the aglycon on glycosyl–oxygen fission are thought to be small.[3] This picture of the hydrolysis of tertiary glycosides has the following necessary consequences.

(1) Hydrolysis of t-butyl β-D-glucopyranoside should yield 2-methylpropan-2-ol in which all the oxygen has arisen from solvent. This has been demonstrated.[4]

(2) Hydrolysis of 1,1-diethylpropyl glycopyranosides should yield products from the 1,1-diethylpropyl cation, *i.e.* substantial quantities of 3-ethylpent-2-ene.[5]

(3) Hydrolysis of a β-D-glucopyranoside of an aglycon with the same steric requirements as the t-butyl group, but which will give rise to a less stable cation, should be non-accelerated. Such a group is the 1-adamantyl system, for the virtually strain-free framework [6] will have nearly the same steric requirements as the t-butyl group, but the bridgehead 1-adamantyl cation is much less stable than the planar t-butyl cation (*e.g.* by 10^3 in rate of formation from the halides in 80% aqueous ethanol [7]).

(4) A glycoside, the aglycon of which is sterically less demanding than the t-butyl group, but which can give rise to a more stable cation, should be hydrolysed at an accelerated rate. The diphenylmethyl group fits these requirements adequately, since it is secondary, yet gives rise to a cation which is more stable than the t-butyl cation.[8]

(5) Hydrolyses of primary alkyl β-D-galactopyrano-

[1] B. Capon, *Chem. Rev.*, 1969, **69**, 407.
[2] D. Bethell and V. Gold, ' Carbonium Ions,' Academic Press, London and New York, 1967, ch. 4, pp. 59—116.
[3] T. E. Timmell, *Canad. J. Chem.*, 1964, **42**, 1456.
[4] C. Armour, C. A. Bunton, S. Patai, L. H. Sehman, and C. A. Vernon, *J. Chem. Soc.*, 1961, 412.
[5] H. C. Brown and R. S. Fletcher, *J. Amer. Chem. Soc.*, 1950, **72**, 1223.
[6] P. von R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, 1970, **92**, 2377.
[7] P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, 1961, **83**, 2700.
[8] S. Winstein, A. H. Fainberg, and E. Grunwald, *J. Amer. Chem. Soc.*, 1957, **79**, 4146.

sides are *ca.* 4 times faster than those of their C(4) epimers: this is ascribed to the axial C(4) hydroxy-group predisposing the galactopyranose ring to adopt the half-chair conformation of the pyranosyl cation.[1] This accelerating factor should be absent in processes involving alkyl–oxygen fission, and therefore t-butyl and 1,1-diethylpropyl β-D-*gluco*- and *galacto*-pyranosides should be hydrolysed at virtually identical rates.

(6) Solvolytic generation of a glycopyranosyl cation should be much slower than that of a t-butyl or 1,1-diethylpropyl cation. This approach was formerly precluded by the difficulty of finding a suitable leaving group (unprotected glycosyl halides—except the fluorides—are not known), but the recent availability of kinetic data for the acetolysis of 2,4-dinitrophenolates [9] and of a ready synthesis of 2,4-dinitrophenyl β-D-galactopyranoside [10] made possible a direct solvolytic measurement of relative cation stability, at least in acetic acid.

EXPERIMENTAL

2,4-Dinitrophenyl β-D-galactopyranoside was made by the method of Capon and Sutherland;[10] m.p. 160—161°, $[\alpha]_D^{25}$ −143° (*c* 0·5, acetone) {lit.,[11] 150—151°, $[\alpha]_D^{25}$ −105° (*c* 1, MeOH)}.

Alkyl 2,3,4,6-Tetra-O-acetyl-β-D-hexopyranosides.—These compounds were made by reaction of the alcohol with the acetobromosugar [12] in dry acetonitrile (1 mol; 20% w/v) with mercuric cyanide (0·5 mol) as a base and mercuric bromide (0·5 mol) as an electrophilic catalyst.[13] 1 Mol quantities of diphenylmethanol and adamantanol but 3—5 mol of the volatile 3-ethylpentan-3-ol and 2-methylpropan-2-ol were used: reaction times at 22° were, with adamantan-1-ol 3 h, with diphenylmethanol 20 h, and with 3-ethylpentan-3-ol and 2-methylpropan-2-ol 15 min. 3M-Aqueous sodium carbonate (5—10% v/v) was added to the mixture to destroy acidic impurities which reduced the yield, and the acetonitrile was evaporated ($t < 25°$). The residue was dissolved in chloroform, filtered, washed with saturated aqueous potassium bromide, dried ($MgSO_4$), and evaporated to yield the crude glycoside tetra-acetates as yellow gums.

1-Adamantyl β-D-Glucopyranoside.—Trituration of the crude tetra-acetate with methanol induced crystallisation: *1'-adamantyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (48%), m.p. 155—157°, $[\alpha]_D^{25}$ −7° (*c* 1·0, $CHCl_3$) was obtained after two further crystallisations (Found: C, 59·65; H, 7·05. $C_{24}H_{34}O_{10}$ requires C, 59·75; H, 7·05%). The tetra-acetate (20% w/v) was deacylated with 0·17% sodium methoxide in methanol for 1 h at 22° to yield, after recrystallisation from water and ethanol, the *product* (80%), m.p. 226—227°, $[\alpha]_D^{25}$ −18° (*c* 1·0, EtOH) (Found: C, 61·0; H, 8·2. $C_{16}H_{26}O_6$ requires C, 61·1; H, 8·35%).

Diphenylmethyl β-D-Galactopyranoside.—Trituration of the crude tetra-acetate with methanol yielded bis(diphenylmethyl) ether (20%), m.p. 110—113° (lit.,[14] 108—109°), broad singlet at δ 7·2 p.p.m., 10H sharp singlet at δ 5·8 p.p.m., 1H ($CHCl_3$/Me_4Si), ν(CH) 3080, 3060, 3030s, 2870m, δ(CH) 1600 cm^{-1}; no ν(C=O) (CCl_4). Diphenylmethanol is stable indefinitely at 22° to mercuric cyanide–mercuric bromide in acetonitrile. Evaporation of the mother liquors yielded a gum, a sample (50 mg) of which was subjected to preparative t.l.c. [0·25 mm unactivated silica gel on a 20 × 20 cm^2 glass plate, benzene–ethyl acetate (2 : 1 v/v) as eluant]. The tetra-acetate (R_F = 0·7) was eluted with hot ethyl acetate, evaporation of which yielded a *pale yellow gum*, δ(CCl_4–Me_4Si) 7·23 and 7·28 (10H, d), and 1·92, 1·98, 2·05, and 2·10 (12H, complex), which was deacylated 20 h at 22° with 0·07M-magnesium methoxide in methanol; evaporation, extraction of the residue with hot water, and concentration of the extract, yielded, after 8 weeks at 5°, with intermittent agitation, seed crystals of *diphenylmethyl β-D-galactopyranoside hydrate.* The bulk of the crude tetra-acetate was then deacylated as above. The aqueous extract was, however, extracted with ether to remove diphenylmethanol before concentration; seeding of the concentrate gave a 3·5% yield of the glycoside hydrate, m.p. 85—87°, resolidification 100—110°, m.p. 159—165°, $[\alpha]_D^{25}$ +42° (*c* 0·3, water) (Found: C, 63·2; H, 6·5. $C_{19}H_{22}O_6,H_2O$ requires C, 62·65; H, 6·6%) [Found (after 20 h at 100°/0·1 mmHg): C, 66·2; H, 6·25. $C_{19}H_{22}O_6$ requires C, 65·5; H, 6·35%].

1,1-Diethylpropyl β-D-Galactopyranoside.—The crude tetra-acetate was purified by chromatography on 15% deactivated silica gel with benzene–ethyl acetate (2 : 1 v/v) as eluant: the tetra-acetate fraction showed δ(CCl_4; Me_4Si) 0·7—1·1 (9H, distorted t), 1·3—1·7 (6H, distorted t), 2·0—2·4 (12H, sharp complex), and 4·0—5·3 (7H, complex). Deacylation with 0·03M-sodium methoxide in methanol 1·2 h at 22°, evaporation, and trituration with water yielded, after a further recrystallisation, the *product hydrate*, m.p. 122—123°, $[\alpha]_D^{25}$ 0° ($[\alpha]_{578}^{25}$ +4°) (*c* 0·5, H_2O) (Found: C, 53·45; H, 9·55. $C_{13}H_{26}O_6,H_2O$ requires C, 52·7; H, 9·45%). This product gives a 100 ± 5% yield of 3-ethylpentan-3-ol with β-galactosidase and shows a perturbed A_2X_3 system (D_2O) with J_{AX} = 7 Hz.

t-Butyl β-D-galactopyranoside was obtained similarly: the pure tetra-acetate showed δ(CCl_4; Me_4Si) 1·2 (9H, sharp s), 2·0—2·4 (12H, sharp complex), and 4·0—5·3 (7H, complex). The deacylated compound failed to crystallise and so was chromatographed on silica gel with absolute ethanol as eluant. Evaporation of the ethanol, and drying over phosphorus pentoxide (22°/15 mmHg/3 weeks) gave the *product* as a colourless, hygroscopic glass which gave a 90% yield of NADH on incubation with NAD^+, β-galactosidase, and β-galactopyranose dehydrogenase.[6]

Kinetics.—Techniques for the acetolysis of 2,4-dinitrophenolates have been described, as has the system of temperature measurement; [9] the acetic acid used contained 210 p.p.m. of water. The hydrolyses of 1-adamantyl β-D-glucopyranoside and t-butyl β-D-galactopyranoside were followed polarimetrically in a Perkin-Elmer 114 photoelectric polarimeter connected to an A.E.I. pen recorder. A wavelength of 346 nm was used to maximise the observed rotation: solutions (*ca.* 0·5% w/v) of the glycoside in the acid were placed in a 1-ml, 1-dm cell provided with a jacket through which water from a bath thermostatted to ±0·1° by a Tecam 'Tempunit' was circulated. The temperature of the jacket was taken as the median of both exit and re-entry temperature (the difference was always <0·5°).

This technique appeared inadequate when applied to the

[9] I. D. Page, J. R. Pritt, and M. C. Whiting, *J.C.S. Perkin II*, 1972, 906.
[10] D. B. Sutherland, Ph.D. Thesis, Glasgow, 1972.
[11] W. Hengstenberg and K. Wallenfels, *Carbohydrate Res.*, 1969, **11**, 85.
[12] M. Bárczai-Marcos and F. Körösy, *Nature*, 1950, **165**, 319.
[13] B. Helferich and W. Ost, *Chem. Ber.*, 1962, **95**, 2612.
[14] H. Wieland, C. Schopf, and W. Hermsen, *Annalen*, 1925, **444**, 55.

acid-catalysed hydrolysis of 1,1-diethylpropyl β-D-galactopyranoside; consequently the hydrolysis was followed by monitoring the just accessible u.v. absorption of the 3-ethylpent-2-ene formed in the reaction in a Unicam SP1800 spectrophotometer (at 207 nm, band width 3 nm). Although this olefin is not formed stoicheiometrically, its concentration is a linear function of the degree of reaction. As the Guggenheim [15] method of calculation was used in this and other cases so far discussed, rate constants being obtained from a least-squares treatment of at least 14 points which gave a standard error on the slope of $<4\%$, the rate constant obtained is that for the disappearance of glycoside. Screw-capped 10-mm silica cells with PTFE-coated septa were used to avoid evaporation of olefin: solid glycoside was added to pre-equilibrated acid on the end of a polystyrene stirrer-rod. Reproducibility between runs was only fair, probably due to the slow hydration of the olefin, evidenced by loss of chromophore at *ca.* 1/40th the rate of the hydrolysis, and product analysis (see below) (Table 1); related to the ready 1-electron oxidation of diphenylmethyl derivatives.[18]

Products.—D-Glucose was estimated by the commercially available kit for estimating blood-sugar (' GOD-Perid method ', ex Boehringer, Ltd.), *cf.* ref. 19. The reaction solution, appropriately diluted, was added directly to the buffered assay medium.

Products from aglycons were estimated by g.l.c. on Perkin-Elmer F11 instruments. Peak areas were estimated by triangulation, and relative response factors calculated on the basis of carbon number: aqueous solutions were extracted with ether before injection, aqueous ethanol was injected directly. Extraction of products from the aglycons, and of the two internal standards, adamantan-2-ol (for adamantan-1-ol) and octan-2-ol (for 3-ethylpentan-3-ol), into ether from water was assumed to be quantitative. Acid solutions were neutralised before extraction, except with the volatile C_7 compounds, the ethereal extracts of which were kept over anhydrous sodium carbonate, to

TABLE 1

Rates of hydrolysis of β-D-glycopyranosides in 0·50M-aqueous sulphuric acid

Glycoside	t/°C	10^5k/s^{-1}	Average deviation from mean	No. of determinations	$\Delta H^{\ddagger} \pm$ S.E. / kcal mol^{-1} (no. of points)	$\Delta S^{\ddagger} \pm$ S.E. / cal deg^{-1} mol^{-1} (no. of points)
Methyl glucoside [a]	60·0	0·138 [c]			32·5	+11
Ethyl glucoside [a]	60·0	0·154 [c]			33·8	+15
t-Butyl glucoside [a]	60·0	76·7 [c]			30·4	+17
1,1-Diethylpropyl glucoside [a]	60·0	4280 [d]			25·4 [e]	+11 [e]
1-Adamantyl glucoside	60·0	6·7 [c]				
	69·7	27·6	0·2	2	32·1 ± 0·6(7)	+19 ± 2(7)
	79·25	100·6		1		
	79·65	114·9	3·4	2		
	88·9	359	9	2		
Methyl galactoside [b]	60·0	0·587 [c]			31·3	+12
t-Butyl galactoside	60·0	115 [c]				
	60·9	129	0	2	30·0 ± 0·3(6)	+17·5 ± 0·8(6)
	51·3	33·9	0·5	2		
	42·3	8·55	0·17	2		
1,1-Diethylpropyl galactoside	60·0	9000 [c]				
	23·5	91	11	3		
	32·0	329		1	24·0 ± 0·8(12)	+9 ± 3(12)
	33·8	388				
	35·1	487	24	3		
	45·15	1570	190	4		
Diphenylmethyl galactoside	60·0	15	2	6		

[a] Ref. 3. [b] T. E. Timmell, W. Enterman, J. Spencer, and E. J. Soltes, *Canad. J. Chem.*, 1965, **43**, 2296. [c] Extrapolated or interpolated from data at other temperatures. [d] Calculated assuming same acidity-dependence as t-butyl glucoside. [e] For rates in ' 0·01N ' H_2SO_4.

for the purposes of comparison, however, this accuracy was adequate.

Activation parameters were obtained from least-squares treatment of plots of log k *vs.* $1/T$; n determinations at the same temperature were treated as n points.

Diphenylmethanol precipitated out from the hydrolysis of diphenylmethyl β-D-galactopyranoside at polarimetrically useful concentrations: u.v. analysis of remaining glycoside after extraction of liberated diphenylmethanol with ether, or analysis of galactose enzymically [16] or by the reducing sugar method of Hagedorn and Jensen,[17] gave rates of *ca.* $1{\cdot}5 \times 10^{-4}$ s^{-1} at 60·0°, but attempts to obtain more accurate data by any of these methods failed. This failure with the Hagedorn and Jensen method, even after extraction of benzhydrol with benzene, is surprising and may be avoid acid-catalysed dehydration of the alcohol on the injection port. Conditions of g.l.c. analysis were (relative retention times in brackets): 3-ethylpent-2-ene/3-ethylpentan-3-ol/octan-2-ol, 1 or 2 m Phasepak at 150° or 175° (1 : 2·3 : 3·6); 1-ethoxyadamantane/adamantan-1-ol/adamantan-2-ol, 1 m Geo 100 at 140° (1 : 2 : 3).

RESULTS AND DISCUSSION

Some, but not all, of the consequences of the picture of the acid-catalysed hydrolysis of tertiary glycosides outlined in the introduction are observed.

Thus, hydrolysis of 3-ethyl-3-pentyl-β-D-galactopyranoside in 0·50M-aqueous sulphuric acid at 22° yields 3-ethylpentan-3-ol and 3-ethylpent-2-ene in an 11 : 1 ratio after 2 half-lives and a 12 : 1 ratio after 8 half-

[15] E. A. Guggenheim, *Phil. Mag.*, 1926, **7**(2), 538.
[16] K. Wallenfels and G. Kurz, *Biochem. Z.*, 1963, **335**, 559.
[17] H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, 1923, **135**, 46.
[18] W. J. Hickinbottom in ' Chemistry of Carbon Compounds,' ed. E. H. Rodd, Elsevier, Amsterdam, 1956, ch. 17, vol. IIIB.
[19] W. Werner, H.-G. Rey, and H. Weilinger, *Z. Analyt. Chem.*, 1970, **252**, 224.

lives. This is consistent with the slow hydration of the olefin observed by u.v. spectroscopy, and conclusively demonstrates that the olefin has not arisen from the 3-ethylpentan-3-ol. Alkyl–oxygen fission is thus taking place in the hydrolysis of the glycoside. t-Butyl, 1,1-dimethylpropyl, and 1,1-diethylpropyl chlorides in 80% aqueous ethanol yield the following respective percentages of olefin: 16, 34, and 40;[20] in pure water the first two substrates yield 5 ± 1 and 8·8 ± 0·4% olefin,[21] all at 25.* Thus a reasonable supposition is that were 1,1-diethylpropyl chloride sufficiently soluble in water to be studied, it would yield 10—11% olefin. Since elimination from tertiary cations in pure water takes place through the free ions, and is independent of leaving group,[21] 10—11% olefin would be expected for 100% alkyl–oxygen fission in the hydrolysis of the glycoside. It is possible, therefore, that *some* glycosyl–oxygen fission is taking place.

1-Adamantyl β-D-glucopyranoside hydrolyses 49 times faster than the methyl compound, and only 11 times slower than its t-butyl analogue (Table 1). The products are the expected ones, D-glucose (96%) and adamantan-1-ol (96%). That alkyl–oxygen fission was not taking place in the 1-adamantyl case was confirmed by solvolysing the glycoside in a 1 : 1 (v/v) mixture of ethanol and 0·50M-aqueous sulphuric acid. Only 0·8 ± 0·2% 1-ethoxyadamantane was obtained, and even this arose largely by subsequent acid-catalysed etherification of adamantan-1-ol, since this compound, on incubation under the same conditions of aqueous ethanolysis, yields 0·6 ± 0·2% 1-ethoxyadamantane. The 1-adamantyl cation,[23] like the more stable t-butyl cation,[24] is largely nonspecific with respect to capture by the two components of aqueous ethanol; generation of the 1-adamantyl cation from various sources in this solvent yields minimally 13% of 1-ethoxyadamantane, whilst acid-catalysed equilibration of alcohol and ether yields 20% of the latter. Since methyl and ethyl β-D-glucopyranosides hydrolyse at near identical rates, inductive effects on the pre-equilibrium cannot account for the high rate of hydrolysis of 1-adamantyl β-D-glucopyranoside. The bulk of the 1-adamantyl system must therefore be responsible: the occurrence of strain in the glycoside can be confirmed by space-filling models.

It is therefore necessary to revise the picture of the hydrolysis of tertiary glycosides outlined in the introduction. Alkyl–oxygen fission does take place—at least to a significant extent—in the acid-catalysed hydrolysis of non-bridgehead tertiary pyranosides, but the driving force for the accelerated rates is largely steric in origin. Relief of *F* strain [22] can be achieved by either glycosyl–oxygen or alkyl–oxygen fission. Application of criteria 4, 5, and 6, outlined in the introduction, confirms this view.

Whereas a diphenylmethyl : t-butyl rate ratio of 11 : 1 is obtained for the acetolysis of the 2,4-dinitrophenolates at 100·0° (Table 2), and one of *ca.* 30 : 1 for the hydrolysis of the chlorides at 25°, if data are extrapolated to pure water by the Winstein–Grunwald equation,[8] a rate ratio of 1 : 8 is obtained for the acid-catalysed hydrolyses of the β-D-galactopyranosides. This demonstrates the importance of steric crowding in accelerating the rates of hydrolysis of tertiary glycosides, but also that alkyl–oxygen fission still takes place, since the diphenylmethyl galactoside still hydrolyses *ca.* 30 times faster than the methyl compound.

TABLE 2

Rates of acetolysis of 2,4-dinitrophenolates

Parent system	*t*/°C	10^5k/s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1} (±S.E.)	$\Delta S^{\ddagger}$/e.u. (±S.E.)
t-Butyl [a]	100·0	28·6 ± 0·6	27·5 ± 0·3	−1·4 ± 0·9
1,1-Diethylpropyl	100·0	*ca.* 400		
Diphenylmethyl [a]	100·0	316 ± 3	24·9 ± 1·4	−2·1 ± 0·4
β-D-Galactopyranosyl	100·0	89		
	103·3	112 ± 6	23 ± 1	−11 ± 3
	89·4	34·1 ± 0·5		
	80·4	11·5 ± 0·5		
	69·0	4·7 ± 0·3		

[a] Ref. 9. [b] I. D. Page, unpublished results.

^{18}O Labelling experiments indicate that, within experimental error, all the oxygen in the 2-methylpropan-2-ol formed on hydrolysis of the β-D-glucopyranoside arises from solvent.[4] If it is accepted that the *F*-strain in 1-adamantyl β-D-glucopyranoside is not greater than that in the t-butyl glucoside, then the mere 11-fold rate difference between the two compounds implies that the conjugate acid of the t-butyl glucoside reacts by glycosyl–oxygen fission to the extent of at least 10%. This is just compatible with the ^{18}O labelling work. However, galactopyranosyl cations are generated *ca.* 4 times faster than their C(4) epimers (Table 1): therefore alkyl–oxygen fission should be comparable with glycosyl–oxygen fission in the hydrolysis of t-butyl β-D-galactopyranoside, which should therefore be between 1 and 4 times as fast as the corresponding glucoside. A ratio of 1·5 is in fact observed (Table 1).

* The temperature difference of 3° will have a negligible effect on the proportion of olefin.[22]

[20] H. C. Brown and R. S. Fletcher, *J. Amer. Chem. Soc.*, 1950, **72**, 1223.

[21] M. Cocivera and S. Winstein, *J. Amer. Chem. Soc.*, 1963, **85**, 1702.

[22] G. S. Hammond in 'Steric Effects in Organic Chemistry', ed. M. S. Newman, Wiley, New York, 1956, p. 454.

[23] J. MacMillan and R. J. Pryce, *J. Chem. Soc.* (*B*), 1970, **337**.

Relative rates of generation of t-butyl and 1,1-diethylpropyl cations in 80% aqueous ethanol at 35° are from the chlorides 1 : 2·6 and from the iodides 1 : 4·4; the bigger ratio from iodides is probably a reflection of *F* strain with the larger leaving group.[25] Thus the further (80-fold) rate enhancement in the hydrolysis of β-D-galactopyranosides on changing the aglycon from 2-methylpropan-2-ol to 3-ethylpentan-3-ol is wholly due to increase in *F* strain. This is confirmed by a galacto/gluco ratio of *ca.* 2 for the acid-catalysed hydrolyses of the 1,1-diethylpropyl hexopyranosides, consistent with competitive alkyl–oxygen and glycosyl–oxygen fission. *F* Strain must therefore account for nearly all of the rate acceleration of over 4 orders of magnitude of 1,1-diethylpropyl β-D-hexapyranosides compared to their methyl analogues.

Conclusive confirmation of the comparable stabilities of the galactopyranosyl and tertiary alkyl cations comes from the acetolysis data of Table 2. Generation of cations by acetolysis of the 2,4-dinitrophenolates at 100° is in the ratio 14 : 3 : 1 for the 1,1-diethylpropyl, β-D-galactopyranosyl, and t-butyl systems, *i.e.* at least in acetic acid, the galactopyranosyl and tertiary cations are of comparable stability. Since the steric demands of the 2,4-dinitrophenolate leaving group are not negligible, the high 1,1-diethylpropyl : t-butyl ratio is probably caused by an increase in *F* strain.

[24] L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1938, 331.

Therefore we can conclude the following. (i) Tertiary β-D-hexopyranosides have considerable *F* strain. (ii) In acid-catalysed hydrolysis, relief of this strain, by either alkyl–oxygen or glycosyl–oxygen fission, accounts for accelerated rates. (iii) In the absence of *B* strain, alkyl–oxygen fission in the hydrolysis of non-bridgehead tertiary glycosides is predominant in the *gluco*-series [4] and significant in the *galacto*-series (see above).

de Belder *et al.*[26] have presented evidence that ferrocenylmethyl β-D-glucopyranoside hydrolyses predominantly by glycosyl–oxygen fission in spite of its 10^6 rate acceleration compared to the methyl compound. The previously unsuspected importance of steric acceleration in glycoside hydrolysis would make this not so questionable [1] were there some way of envisaging steric strain in this primary glycoside. The isolation of di(ferrocenylmethyl) ether in the Koenigs–Knorr step in its synthesis [26] parallels our isolation of bis(diphenylmethyl) ether in the synthesis of diphenylmethyl β-D-galactopyranoside, and indicates alkyl–oxygen fission is occurring in the glycosidation reaction at least.

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[25] J. Shorter and C. N. Hinshelwood, *J. Chem. Soc.*, 1949, 2412.
[26] A. N. de Belder, E. J. Bourne, and J. B. Pridham, *J. Chem. Soc.*, 1961, 4464.