Steric Acceleration in the Acid-catalysed Hydrolysis of 1-Adamantyl β-D-Glucopyranoside. The Origin of the High Rates of Hydrolysis of Tertiary Glycosides

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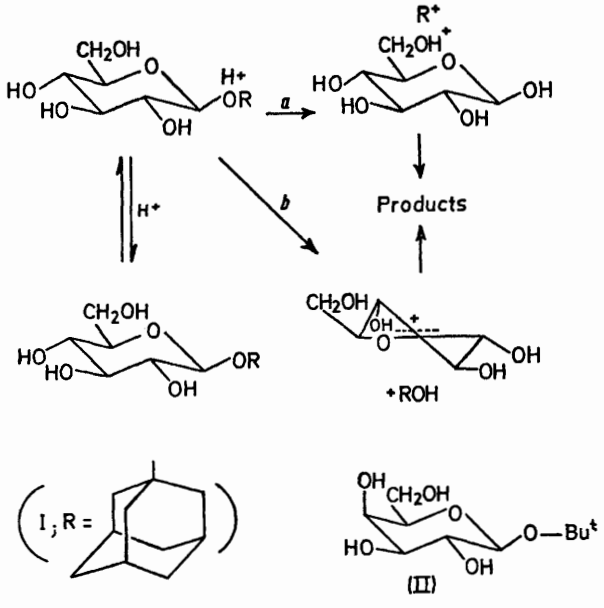
Summary 1-Adamantyl β-D-glucopyranoside is hydrolysed by 0·5M-sulphuric acid at 60·0° 49 times faster than the methyl compound, with >95% glucosyl–oxygen fission; steric acceleration is thus considered to be a major driving force for the high rates of hydrolysis of tertiary glycosides, even though alkyl–oxygen fission to planar cations is probably taking place, as shown *inter alia* by the close similarity of the hydrolysis rates of t-butyl β-D-*gluco*- and *galacto*-pyranosides.

ACID-CATALYSED hydrolyses of alkyl β-D-glucopyranosides are considered to take place by equilibrium protonation of the exocyclic oxygen atom, followed by unimolecular heterolysis to yield a glucosyl or tertiary alkyl cation[1] (Scheme). Steric effects of the aglycon on glucosyl–oxygen fission are considered to be small,[2] and the accelerated rates of hydrolysis of tertiary glucosides to be a reflection of the stability of the tertiary alkyl cations.[2,3]

To test these latter hypotheses, we synthesised the title compound (I), m.p. 226—227°, $[\alpha]_D^{20}$ − 18°, (*c* 1% EtOH) by standard procedures,[4] and measured its rate of hydrolysis in 0·5M-aqueous sulphuric acid polarimetrically. The data in the Table indicate that at 60·0° it hydrolyses 49 times faster than its methyl analogue, and only 11 times slower than the t-butyl compound. Hydrolysis yields D-glucose (96% measured enzymically with glucose oxidase[5])



SCHEME. *Path* a *is operative for* R = Me_3C, $EtMe_2C$, Et_3C, *path* b *for* R = *primary or secondary alkyl.*

and adamantan-1-ol (96% by g.l.c.) in 0·5M-aqueous sulphuric acid; in a 1:1 (v/v) mixture of this medium and absolute ethanol only 0·8 ± 0·2% of 1-ethoxyadamantane was obtained (g.l.c.); incubation of adamantan-1-ol under the same conditions of aqueous ethanolysis gives 0·6 ± 0·2% of 1-ethoxyadamantane. The ethoxyadamantane from the glycoside thus arises substantially from subsequent acid-catalysed etherification of the adamantan-1-ol.

TABLE

Hydrolysis of β-D-glycopyranosides in 0·5M-aqueous sulphuric acid

Glycoside	10^5k/(s^{-1}) at 60·0°[b]	$\Delta H^{\ddagger}$/kcal[a]	$\Delta S^{\ddagger}$/(cal deg mol^{-1})[a]
Methyl glucoside[c]	0·138	32·5	+11
Methyl galactoside[d]	0·587	31·3	+12
Ethyl glucoside[c]	0·154	33·8	+15
t-Butyl glucoside[c]	76·7	30·4	+17
t-Butyl galactoside	115	30·0 ± 0·3[e]	+17·5 ± 0·8[e]
1-Adamantyl glucoside	6·7	32·1 ± 0·6[e]	+19 ± 2[e]

[a] J = 4·185 joules/cal. [b] Extrapolated or interpolated. [c] Ref. 2. [d] T. E. Timmell, W. Enterman, J. Spencer, and E. J. Soltes, *Canad. J. Chem.*, 1965, **43**, 2296. [e] Calculated from 3 duplicate rate measurements over a 20° range.

The steric demands of the virtually[6] strain-free 1-adamantyl system will not be greater than those of the t-butyl group, but the bridgehead 1-adamantyl cation is markedly 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]). A process exhibiting a t-butyl:1-adamantyl rate ratio of only 11 is unlikely to involve generation of the 1-adamantyl cation. That the hydrolysis of glycoside (I) proceeds without alkyl–oxygen fission was confirmed by the failure to trap a 1-adamantyl cation in aqueous ethanol. The 1-adamantyl cation,[8] like the more stable t-butyl cation,[9] is largely non-specific with respect to capture by the two components of aqueous ethanol; generation of the 1-adamantyl cation from various sources in 50% aqueous ethanol yields minimally 13% of 1-ethoxyadamantane,[10] whilst acid-catalysed equilibration of alcohol and ether gives 20% of the latter.[10]

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 compound (I). The bulk of the 1-adamantyl system—possibly magnified by the region of ordered solvent necessary round this strongly hydrophobic group—must therefore be responsible. The occurrence of strain in the glycoside can be confirmed from space-filling models.

This result does not necessarily mean that t-butyl-β-D-glucopyranoside also hydrolyses *via* a glucosyl cation; indeed ^{18}O labelling work militates against this.[3] Further evidence for alkyl–oxygen fission comes from the similarity of hydrolysis rates of t-butyl β-D-*galacto*- and *gluco*-pyranosides. Processes involving generation of a glycosyl cation, such as the acid-catalysed hydrolyses of primary glycosides, proceed *ca.* 4 times faster in the *galacto*- than in the *gluco*-series. The axial hydroxy-group at C(4) of the galactopyranose ring is considered to predispose it to adopt the half-chair conformation of the galactopyranosyl cation. Such an accelerating factor should be absent in processes involving alkyl–oxygen fission. t-Butyl β-D-galactopyranoside (II) was obtained as a colourless glass (giving a 90% yield of NADH on incubation with NAD^+, β-galactosidase, and β-D-galactopyranose dehydrogenase[11]) by standard procedures.[4] It hydrolyses 1·5 times faster than the *gluco*-compound. Thus it seems likely that from t-butyl β-D-galactopyranoside generation of the t-butyl and glycosyl cations is competitive. However, in the case of the tertiary glycosides of both series, the driving force for the accelerated rates of hydrolysis is substantially relief of steric crowding by either alkyl–oxygen or glycosyl–oxygen fission, rather than generation of a "stable" tertiary cation.

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