ACID-CATALYZED HYDROLYSIS OF ALKYL α-D-GLUCOPYRANOSIDES*

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ABSTRACT

Acid-catalyzed hydrolysis of a series of eleven alkyl α-D-glucopyranosides has been effected and compared with that of the corresponding series of alkyl β-D-glucopyranosides. The former were hydrolyzed at a lower rate than the latter, and, as a group, the D-glucopyranosides of primary alcohols were hydrolyzed at a lower rate than those of secondary alcohols. No relationship between rate of hydrolysis and steric or electronic effects of the aglycons was found. The activation parameters partially compensated each other. It is suggested that the rate of hydrolysis is primarily a function of the extent of protonation of the glycosidic oxygen atom, and that heterolysis leads, in each case, to a similar, product-like transition-state. The lower rate of hydrolysis (protonation) of alkyl α-D-glucopyranosides is attributed to the reverse anomeric effect.

INTRODUCTION

Acid-catalyzed hydrolysis of glycopyranosides has been extensively investigated in recent years[1]. However, the glycopyranosides studied have been almost exclusively β-D-glycopyranosides[2]. Further studies of a number of methyl glycopyranosides led to the more general finding that, with anomeric pairs of glycopyranosides, the anomer having an equatorially attached aglycon is hydrolyzed 1.3–3.2 times as rapidly as the anomer in which the aglycon is axially attached[3]. At least three different explanations have been offered for this behavior[1]. It was the purpose of the work now described to make a detailed examination of the hydrolysis of a series of alkyl α-D-glucopyranosides and to compare their hydrolysis with that of a series of alkyl β-D-glucopyranosides.

RESULTS AND DISCUSSION

As did De Bruyne and Van Wijnendaele[4], we have determined the isokinetic relationship for the hydrolysis of alkyl D-glucopyranosides (see Table I) from the data given in Table II. When the results for the alkyl α-D-glucopyranosides were treated by the method of Leffler[5], the values for the glycosides of primary alcohols

*Dedicated to Dr. Nelson K. Richtmyer in honor of his 70th birthday.

fell on one straight line, and those for glycosides of secondary alcohols, on another line. The data for allyl α-D-glucopyranoside fell on the line with the glucopyranosides of other primary alcohols, but were omitted from all calculations. Hence, isokinetic temperatures were separately determined for glucopyranosides of primary and secondary alcohols, respectively, even though two different isokinetic lines were not evident for the alkyl β-D-glucopyranosides.

As found by De Bruyne and Van Wijnendaele for alkyl β-D-xylopyranosides[4], hydrolysis of alkyl D-glucopyranosides involves compensation of the activation parameters according to the Exner classification[6], *i.e.*, both activation parameters are variable in the sense that their effects partially compensate each other. It is interesting that there is a similarity in isokinetic temperatures determined by the two methods (see Table I), and that, as regards the differences in isokinetic temperatures for glucopyranosides of primary and secondary alcohols, the glucopyranosides of secondary alcohols have the lower isokinetic temperature. Two different isokinetic relationships would indicate differences in mechanism or transition state, or the effect of solvent on either.

TABLE I

ISOKINETIC TEMPERATURES FOR THE HYDROLYSIS OF ALKYL D-GLUCOPYRANOSIDES

	Isokinetic temperatures (°C)					
	Alkyl α-D-glucopyranosides			*Alkyl β-D-glucopyranosides*		
Method	*Primary glycosides*[a]	*Secondary glycosides*	*All glycosides*[a]	*Primary glycosides*[a]	*Secondary glycosides*	*All glycosides*[a]
Exner[6] (E_a *vs.* log A)	93 (2)[b]	81 (2)	66 (8)	134 (6)	−23[c]	167 (11)
Leffler[5] ($\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$)	95 (22)	85 (4)	65 (49)	136 (26)	−23[c]	109 (41)

[a]Allyl D-glucopyranoside not included. [b]Numbers in parentheses are sigma values. [c]Only two points.

In a search for a relationship between the electronic (σ^* values)[7] or steric (E_s values)[8] effects of the aglycon and the rate constants or enthalpies or entropies of activation for either the α-D- or β-D-glucopyranosides (see Table II), no simple relationship was apparent. However, it is evident that there is more variation in the activation parameters among the α-D-glucopyranosides than among the β-D-glucopyranosides. The variations may be due to apparently random deviations from a perfect isokinetic relationship[5], rather than to changes in an activation parameter, because the temperature range used in the determination of rate constants for the hydrolysis of alkyl α-D-glucopyranosides is near the isokinetic temperature; alternatively, activation parameters for the hydrolysis of alkyl α-D-glucopyranosides might have a much wider range than the corresponding values for the hydrolysis of the alkyl β-D-glucopyranosides (see Table II), as the former are more dependent on

TABLE II

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF ALKYL D-GLUCOPYRANOSIDES IN 0.5M SULFURIC ACID

D-*Glucopyranosides*	*Alkyl α-D-glucopyranosides*							*Alkyl β-D-glucopyranosides*[7]				
	10^6k (sec^{-1})			E_a (*kcal.* mol^{-1})	$\Delta H^{\ddagger}$ (*kcal.* $mole^{-1}$)	$\Delta S^{\ddagger}$ (85°) (*cal.*mol^{-1} .deg^{-1})	$\Delta F^{\ddagger}$ (*kcal.* mol^{-1})	10^6k (sec^{-1}) (80°)	E_a[a] (*kcal.* mol^{-1})	$\Delta H^{\ddagger}$[a] (*kcal.* mol^{-1})	$\Delta S^{\ddagger}$ (70°)[b] (*cal.*mol^{-1}. deg^{-1})	$\Delta F^{\ddagger}$ (*kcal.* mol^{-1})
	80°	85°	90°									
Primary												
Ethyl	10.0	20.0	38.1	34.1	33.4	+16.9	27.4	28.0	33.9	32.2	+18.4	26.7
Propyl	11.6	22.7	38.6	30.7	29.9	+ 7.4	27.3	31.2	33.2	32.5	+16.7	26.6
Butyl	12.5	22.9	41.8	30.8	30.1	+7.8	27.2	27.9	33.3	32.6	+16.7	26.7
Pentyl	8.34	17.6	33.7	35.6	34.9	+20.8	27.6	—	—	—	—	—
2-Methyl-1-propyl (Isobutyl)	9.20	17.2	32.8	32.5	31.7	+11.8	27.5	34.4	33.8	33.2	+18.7	26.6
2,2-Dimethyl-1-propyl (Neopentyl)	9.81	18.6	34.7	32.2	31.5	+11.4	27.5	39.9	32.8	32.1	+16.1	26.4
Benzyl	11.6	19.8	35.7	28.6	27.9	+1.65	27.3	28.3	33.9	33.2	+18.4	26.7
Av.	10.4	19.8	36.5	32.1	31.3	+11.1	27.4	31.6	33.5	32.8	+17.5	26.6
Secondary												
2-Propyl (Isopropyl)	21.4	40.8	96.4	38.3	37.6	+30.3	26.9	44.5	33.0	32.3	+16.7	26.4
2-Butyl (*sec*-Butyl)	21.4	48.5	96.8	38.5	37.8	+30.8	26.9	—	—	—	—	—
Cyclohexyl	21.8	41.3	82.6	33.9	33.2	+18.0	26.8	56.4	33.4	32.7	+18.3	26.2
Av.	21.5	43.5	91.9	36.9	36.2	+26.4	26.9	50.4	33.2	32.5	+17.5	26.3
Other												
Allyl	9.86	23.7	49.1	40.9	40.2	+36.2	27.4	32.8	33.7	33.0	+18.3	26.5

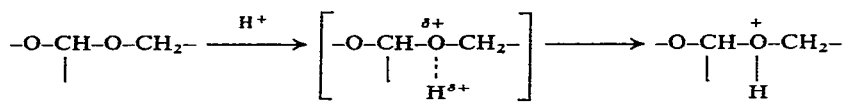
[a]Recalculated from the kinetic data published by Timell[7] by using our own computer program, which fits a straight line by the method of least squares. Minor variations are thereby made in the values originally published, except for the values for the 2,2-dimethyl-1-propyl (neopentyl) β-D-glucopyranoside, which are in error in the original paper. [b]Recalculated for the kinetic data published by Timell, by using $H_0 = +0.13$, as reported by M. A. Paul and F. A. Long, *Chem. Rev.*, 57 (1957) 1.

steric factors. However, this work, like other work on the hydrolysis of glycopyranosides, suffers from the fact that kinetic measurements are made over a very narrow (10°) range of temperature. With these limited data, the significance of small differences in enthalpies or entropies of activation between members of a group is open to question, and, if it is real, it may only reflect differences in solvation of reactant, transition state, products, or all three.

Mean values of the individual activation-parameters for a group of glucopyranosides are, at this time, the best values to use for a discussion of the effect of structure on rate of hydrolysis. An examination of these parameters reveals that changes in E_a, $\Delta H^{\ddagger}$, or $\Delta S^{\ddagger}$ alone are not sufficient to explain the differences in hydrolysis rates of α-D- and β-D-glucopyranosides (see Table II). As compensation is involved, the values of $\Delta G^{\ddagger}$ are better related to the rate constants than are either $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$, and show little variation within a group. Their similarity may indicate a common transition-state which could only occur were it largely product-like.

In order to understand the relationship of these gross thermodynamic parameters to hydrolysis rates, the reaction must be dissected into its component parts, *viz.*, (*a*) protonation of the exocyclic oxygen atom to form the conjugate acid, and (*b*) heterolysis of the conjugate acid to form an alcohol and a carbonium–oxonium ion, the former being a rapid, equilibrium process and the latter the slow, rate-determining step.

Protonation of glycopyranosides of primary alcohols is shown in equation *1*. (The ring-oxygen atom, C-1, the exocyclic atom, and the first carbon atom of the aglycon are shown in this and subsequent equations; the transition state is in brackets). In this reaction, protonation of α-D-glucopyranosides (axial aglycon) should be more difficult than protonation of β-D-glucopyranosides (equatorial aglycon), because



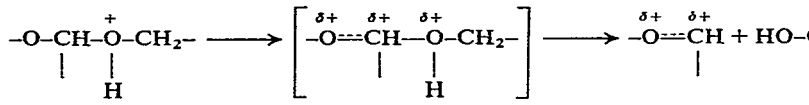
(*1*)

of the reverse anomeric effect, a phenomenon whereby a positive charge in the axial position causes conformational destabilization[9]. Although protonation of β-D-glucopyranosides may result in some gain of entropy because proton-transfer reactions are often characterized by positive values of $\Delta S^{\ddagger}$, protonation on the glycosidic oxygen atom of α-D-glucopyranosides could result in a species having a higher energy-level. For example, it is known that the forces that destabilize the α-D anomer, in which the exocyclic atom bears a positive charge, are strong enough to force such compounds as *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)pyridinium bromide into the *1C*(D) conformation, having the pyridinium group in the equatorial orientation[9]. This may mean, as speculated by Lemieux and Morgan[9], that the favored point of protonation for α-D-glucosides is the ring-oxygen atom. However, as the hydrolysis of alkyl α-D-glucopyranosides seems to be more, rather than less, dependent on the nature of the aglycon than the hydrolysis of alkyl β-D-glucopyranosides, and as the same empirical relationship is found for the rates of hydrolysis of either anomer and

C-2–C-3 and C-4–C-5 diequatorial interactions (*viz.*, hydrolysis rates as follows: methyl α-D-glucopyranoside <methyl α-D-mannopyranoside <methyl α-D-galactopyranoside[3,cf.10]), it is unlikely that α-D-glucopyranosides are hydrolyzed by a different mechanism. Rather, it is suggested that protonation of the ring-oxygen atom makes an abortive complex and that there is less protonation of the glycosidic oxygen atom (less reactant for the rate-determining step), thus resulting in a lower rate of hydrolysis.

In this kind of reaction, in which only a very small fraction of either oxygen atom is protonated at any one time, it is unlikely that competitive protonation[11,12] would affect the rate, but it is suggested that the extent of protonation of the glycosidic oxygen atom at any one time is an important factor in determining the rate of hydrolysis.

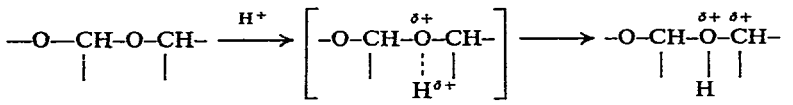
Cleavage (rate-determining step) of glycosides of primary alcohols is believed to proceed as depicted in equation *2*. (Here, and throughout the remainder of the paper, it is assumed that the conjugate acid involving the exocyclic oxygen atom is the reactant in the heterolysis step.) The stretching of the C-1–glycosidic oxygen



(*2*)

bond and the change in enthalpy in going to the transition state are probably almost equal for α-D- and β-D-glucopyranosides, although the ground states are at different energy-levels; both should show an increase in entropy, with the greatest increase shown for the α-D-glucopyranosides as the strain due to the reverse anomeric effect is relieved.

Because of the higher rate of hydrolysis of β-D-xylopyranosides of secondary alcohols (compared with glycosides of primary alcohols), De Bruyne and Van Wijnendaele[4] suggested that, during their hydrolysis, there may be some glycosidic oxygen–aglycon bond-cleavage leading to a secondary carbonium ion. This is unlikely, as cyclohexyl D-glucopyranoside is hydrolyzed at the same rate as the D-glucopyranosides of other secondary alcohols, although it is quite difficult to form a carbonium ion on a cyclohexyl ring[13]. Although there may not be any actual bond-cleavage of this type with the formation of an aglycon carbonium ion, it is likely that protonation of the glycosidic oxygen atom of glycosides of secondary alcohols results in a more stable conjugate acid, because of the ability of the aglycon to share the positive charge (a displacement of the electrons towards the oxygen atom) (see equation *3*).

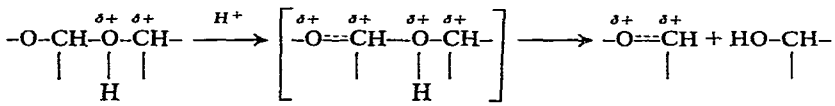


(*3*)

With β-D-glucopyranosides of secondary alcohols, the energy of activation for protonation of the glycosidic oxygen atom should be slightly less than that of gluco-

sides of primary alcohols because of the dispersal of charge. α-D-Glucopyranosides of secondary alcohols must be at a higher energy-level in the ground state, with little entropy due to axial–axial interaction and a restriction of rotation around the glycosidic bond. Protonation of these α-D-glucopyranosides of secondary alcohols would result in much less loss in entropy (or, perhaps, a gain in entropy) than is found with protonation of α-D-glucopyranosides of primary alcohols, due to dispersal of the positive charge; but it would still require more energy to protonate α-D-glucopyranosides than to protonate β-D-glucopyranosides, because of the reverse anomeric effect; and both ought to require less energy for their protonation than is required for the corresponding glycosides of primary alcohols. Hence, the concentration of substrate for the rate-determining step (conjugate acid), and, therefore, the rate of hydrolysis, should be in the order β-D-glucopyranosides of secondary alcohols > α-D-glucopyranosides of secondary alcohols > β-D-glucopyranosides of primary alcohols > α-D-glucopyranosides of primary alcohols.

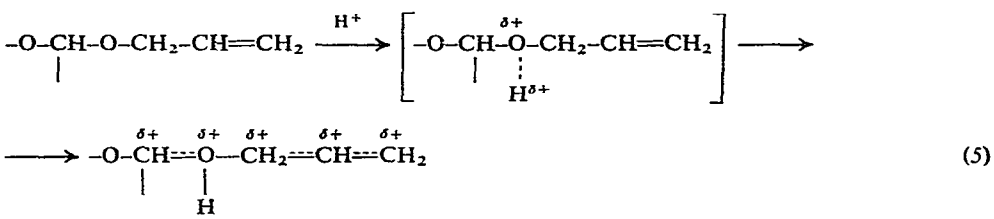
Both anomers of glycosides of secondary alcohols would require more energy to achieve the transition state in bond cleavage than is required for the glycosides of primary alcohols. With glycosides of primary alcohols, bond stretching would result in a separation of like charges (see equation *2*) that would aid in bond cleavage. Because of dispersal of charge in protonated glycosides of secondary alcohols, the bond would have to be stretched farther in the transition state and, hence, would result in a greater gain in entropy (see equation *4*).



(4)

Cyclohexyl α-D-glucopyranoside would have little entropy in the ground state, would lose some upon protonation of the glycosidic oxygen atom (because there would be no partial charge on the cyclohexyl ring), and would gain less upon going to the transition state for bond cleavage (because this bond would be stretched less, similarly to that for glycosides of primary alcohols), and, hence, would have a lower value of E_a. It was found that the activation parameters for cyclohexyl α-D-glucopyranoside are more like those of the alkyl α-D-glucopyranosides of primary alcohols than those of the D-glucopyranosides of secondary alcohols.

Allyl D-glucopyranosides constitute a third case. Protonation of the glycosidic oxygen atom of allyl D-glucopyranosides would result in an even greater dispersal of charge (see equation *5*).



(5)

Like the α-D-glucopyranosides of secondary alcohols, protonated allyl α-D-glucopyranoside would have some of the charge on the carbon atoms of the aglycon and, hence, would have less reverse anomeric effect. However, because of less steric hindrance, it would have more entropy in the ground state than would α-D-glucopyranosides of secondary alcohols, so there would be little change upon protonation. Therefore, the concentration of the conjugate acid and the rate of hydrolysis would be like that of glycosides of primary alcohols. Also, like the D-glucopyranosides of secondary alcohols, there would have to be greater bond-stretching to achieve the transition state for bond cleavage than occurs with glycosides of either primary or secondary alcohols, with the corresponding increases in both E_a and $\Delta S^{\ddagger}$.

The arguments presented here are based on the assumption that both transition states are largely product-like. In the case of the bond-cleavage step, this means that the transition state for the hydrolysis of either anomer is largely like the proposed half-chair (H_4^3) carbonium–oxonium ion. The lower E_a value and the smaller increase in entropy for alkyl β-D-xylopyranosides[4], as compared to alkyl β-D-glucopyranosides[7], is consistent with this viewpoint, for, in the former, there would be less resistance to rotation about the C-4–C-5 bond.

It is also consistent with other aspects of the acid-catalyzed hydrolysis of glycosides, as, for example, the hydrolysis of glycosiduronic acids. Capon and Ghosh[14] found that the relative rates of hydrolysis of ionized 2-naphthyl β-D-glucopyranosiduronate, 2-naphthyl β-D-glucopyranoside, and 2-naphthyl β-D-glucopyranosiduronic acid are 1580:78:1, correlating well with the inductive effects of the groups. If the transition state for cleavage is largely product-like, with considerable positive charge on the ring-oxygen atom, it is clear why the hydrolysis rates correlate well with the inductive effects of the substituents at C-5. The low increases in E_a and $\Delta S^{\ddagger}$ found for hydrolysis of glycosides of D-glycopyranuronic acids may be due to the fact that there is little bond-stretching in the transition state for cleavage. This condition would be brought about were most of the positive charge on C-1 (orbital overlap with the ring-oxygen atom, to form a carbonium–oxonium ion, being prevented by the electron-withdrawing, un-ionized carboxyl group on C-5). Such a transition state could explain the observation that hydrolysis of alkyl D-glucopyranosiduronic acids proceeds at a higher rate than that of the corresponding alkyl D-glucopyranosides and is more dependent on the electronic nature of the aglycon[15]. Likewise, with other derivatives, an inverse relationship between the rate of hydrolysis and the electron affinity of the substituent at C-5 has been found[16]. However, further experimentation with these compounds will be necessary before a detailed discussion of their hydrolysis can be presented.

EXPERIMENTAL

Alkyl α-D-glucopyranosides were prepared by alcoholysis of β-D-glucopyranose pentaacetate, followed by hydrolysis, in the presence of β-D-glucosidase, of the alkyl β-D-glucopyranoside present in the reaction mixture, and removal of the D-glucose and the alcohol formed by this hydrolysis, as described by Wing and BeMiller[17].

Hydrolyses were monitored by recording the change in optical rotation, as the reaction progressed, by means of a Bendix ETL-NPL Automatic Polarimeter equipped with a 546-nm (mercury green line), interference filter and a water-jacketed, polarimeter cell. Rate constants were determined by the method of Guggenheim[18] by using a least-squares fit of the data by means of a computer.

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