ACID-CATALYZED HYDROLYSIS OF METHYL 4-*O*-ALKYL-D-GLUCOPYRANOSIDES

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ABSTRACT

Methyl 4-*O*-alkyl-α- and β-D-glucopyranosides having both primary and secondary alkyl groups have been hydrolyzed in water–*p*-dioxane solutions. In general, the larger the substituent group, the larger the rate constant for acid-catalyzed hydrolysis; but, regardless of whether etherification at O-4 was with a primary or a secondary alkyl group, hydrolysis was slowed and the free energy of hydrolysis was increased over that obtained under similar conditions with glycosides unsubstituted at O-4. The values of the free energy of hydrolysis of the methyl 4-*O*-alkyl-β-D-glucopyranosides were consistently lower than those for the hydrolysis of the α-D anomers. These differences have been explained on the basis of a complete, free energy–reaction coordinate diagram.

INTRODUCTION

It has been generally accepted that the acid-catalyzed hydrolysis of polysaccharides is non-random. Non-random hydrolysis is found even with homopolysaccharides having a single kind of linkage. Evidence for non-random hydrolysis is indirect. For example, when the theoretical amounts of D-glucose and the oligosaccharides which should be liberated by random hydrolysis of starch or cellulose are compared with the actual amounts formed, it is found that there are more products of low degree of polymerization and fewer intermediate-sized products than would be expected from a completely random hydrolysis, for any extent or duration of hydrolysis[1].

The initial rate of hydrolysis of the cycloamyloses (which have no ends) is much lower than the rate for the corresponding malto-oligosaccharides[2,3]; and, whereas the hydrolysis of maltose and other disaccharides follows normal, *pseudo*-first-order kinetics, the rate constant for the hydrolysis of amylose increases with time until it becomes the same as that of maltose, which has only an end bond[4,5]. Such information has been used to suggest that the rate of hydrolysis of terminal bonds is higher than that of internal bonds. All possible differences have been suggested[1]. More recently, direct experimental evidence has suggested that hydrolysis of the glycosidic bond at the nonreducing terminus is favored[6–8]. This favored hydrolysis

at the nonreducing end is explicable by the mechanism of acid-catalyzed hydrolysis, which predicts, in general, that a glycosidic unit having a bulky substituent group will undergo hydrolysis more slowly than would an unsubstituted unit[1].

In an investigation of this hypothesis, Hook and Lindberg[9] hydrolyzed the eight mono-(2-propyl) ethers of methyl α- and β-D-glucopyranoside. To their surprise, they found that all except the methyl 6-*O*-(2-propyl)-D-glucopyranosides were hydrolyzed more rapidly than the respective, parent methyl D-glucopyranoside. Later, they hydrolyzed the eight mono 2-(hydroxyethyl) ethers of methyl α- and β-D-glucopyranoside and found that each was hydrolyzed more slowly than the parent compound[10].

De and Timell[11] found that methyl 3-*O*-methyl-β-D-glucopyranoside is hydrolyzed slightly more slowly than methyl β-D-glucopyranoside.

It was the purpose of the present investigation to examine the effect of the size of a substituent on O-4 of a D-glucopyranosyl unit on the hydrolysis of the bond to that unit.

RESULTS AND DISCUSSION

Favored hydrolysis at the nonreducing end has been explained on the basis of the mechanism of acid-catalyzed hydrolysis[1] by employing the reasoning of Feather and Harris[12].

As originally suggested by Edward[13], the cyclic carbonium–oxonium ion intermediate will have charge dispersal and stabilization when the compound is in the $^3H_4$ conformation. Transformation of the $^4C_1$ conformation to this half-chair conformation involves rotation of the C-2–C-3 and C-3–C-4 bonds until C-1, C-2, C-5, and O-5 are in the same plane. In this transformation, the groups on C-2 rotate counter-clockwise to the groups on C-3 when viewed down the C-2–C-3 bond, and the groups on C-4 rotate counter-clockwise to the groups on C-5 when viewed down the C-4–C-5 bond. Hence, in D-glucose, the larger groups on each pair of adjacent carbon atoms move away from each other and towards a position in which there will be 1,3-interactions. Edward[13] explained differences in rates of hydrolysis on differences in stability of the ground state due to non-bonded interactions *vis-à-vis* that of a transition state. Feather and Harris[12], however, found that rates of hydrolysis could be correlated with the resistance to rotation in the opposite direction.

Previous consideration of the higher rate of hydrolysis of terminal bonds as compared with those of internal bonds has resulted in the conclusion that a bulky substituent would simply inhibit any transformation from one conformation to another. However, according to Edward[13], if, on going to the transition state, steric strain caused by non-bonded interactions is relieved, the rate of hydrolysis should be increased.

In an investigation of the acid-catalyzed hydrolysis of alkyl α-D-glucopyranosides, BeMiller and Doyle[14] pointed out that a complete, free energy–reaction coordinate diagram containing the free energies of the ground state, the transition

state for the formation of the conjugate acid, and the transition state for heterolysis needs to be considered.

As stated previously[14], investigations of the hydrolysis of glycosides suffer from the fact that kinetic measurements can be readily made over only a very narrow range of temperature. With these limited data, the significance of small differences in enthalpies or entropies of activation is open to question; and, as compensation is involved, values of the free energy of activation ($\Delta G^{\ddagger}$) are better related to rate constants than are either $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$, and are preferable for use when groups of glycosides are compared.

The values of $\Delta G^{\ddagger}$ for hydrolysis of the methyl 4-*O*-alkyl-β-D-glucopyranosides are consistently lower than the corresponding values for hydrolysis of the α-D anomers (see Table I). This difference has been attributed to strain introduced by the reverse anomeric effect when α-D-glycosides are protonated[14]. Also consistent with previous results is the fact that there is more variation in the activation parameters among the α-D-glucopyranosides than among the β-D-glucopyranosides. In addition, the results given in Table I reveal that etherification on O-4 with a secondary alkyl group increases the rate of hydrolysis and lowers the $\Delta G^{\ddagger}$ value, compared to those shown by the analogs etherified with a primary alkyl group. In both cases, hydrolysis is slowed and the $\Delta G^{\ddagger}$ value is increased over that obtained[15] under similar conditions with methyl D-glucopyranosides unsubstituted on O-4.

The effect of a substituent group situated on O-4 of a D-glucopyranoside may be viewed as follows. As with unsubstituted compounds, protonation of α-D-glucopyranosides (axially attached aglycon) should be more difficult than protonation of β-D-glucopyranosides (equatorially attached aglycon) because of the reverse anomeric effect, and should result in a transient, high-energy species which might become an abortive complex in the context of hydrolysis[14]. Thus, in forming the reactant for the rate-determining step (protonation of an exocyclic oxygen atom), β-D-glycopyranosides undergo change from a less to a more stable species, with a corresponding decrease in conformational changes (entropy) of the ring. The reverse is true for α-D-glucopyranosides. Thus, in 4-*O*-substituted D-glucopyranosides, protonation of the α-D anomer would be even more difficult (higher $\Delta H^{\ddagger}$), owing to increased difficulty of "inversion" of the chair conformation of the compound.

The transition state for cleavage of D-glucopyranosides is also believed to be largely product-like, *i.e.*, a $^3H_4$ carbonium–oxonium ion[14]. As the chair conformer of the α-D anomer is moving towards "inversion", its conversion into the transition state would require less input of energy and would result in a large gain in entropy. Formation of the $^3H_4$ conformer from the β-D anomer would require more energy, and result in a smaller gain in entropy.

Thus, if the conjugate acid is considered to be the reactant species in the rate-determining step, the methyl 4-*O*-alkyl-α-D-glucopyranosides would start at a much higher ground-state than would the corresponding β-D anomers. With the α-D-glucopyranosides, the energy level of the ground state would increase with increasing size of the substituent group on O-4, and, as no change in conformation is involved,

TABLE I

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF METHYL 4-*O*-ALKYL-D-GLUCOPYRANOSIDES IN 0.5M SULFURIC ACID IN 3:1 (v/v) WATER–*p*-DIOXANE

4-O-Alkyl substituent	*Methyl α-D-glucopyranosides*						
	10^6k (sec^{-1})			E_a ($kcal \cdot mol^{-1}$)	$\Delta H^{\ddagger}$ ($kcal \cdot mol^{-1}$)	$\Delta S^{\ddagger}$ ($cal \cdot mol^{-1} \cdot deg^{-1}$)	$\Delta G^{\ddagger}$ ($kcal \cdot mol^{-1}$)
	80°	*85°*	*90°*				
Primary alkyl groups							
Methyl	—	—	—	—	—	—	—
Ethyl	3.38	9.29	22.8	48.6	47.9	+51.9	29.3
Propyl	4.13	10.1	22.9	43.6	42.9	+38.1	29.3
Butyl	5.37	12.0	27.0	41.1	40.4	+31.5	29.1
Secondary alkyl groups							
2-Butyl (*sec*-butyl)	6.95	14.0	29.8	36.9	36.2	+20.0	29.0
2-Propyl (isopropyl)	8.43	15.5	27.5	30.1	29.4	+1.25	29.0
4-O-Alkyl substituent	*Methyl β-D-glucopyranosides*						
	10^6k (sec^{-1})			E_a ($kcal \cdot mol^{-1}$)	$\Delta H^{\ddagger}$ ($kcal \cdot mol^{-1}$)	$\Delta S^{\ddagger}$ ($cal \cdot mol^{-1} \cdot deg^{-1}$)	$\Delta G^{\ddagger}$ ($kcal \cdot mol^{-1}$)
	80°	*85°*	*90°*				
Primary alkyl groups							
Methyl	11.7	20.9	46.0	34.9	34.2	+15.2	28.8
Ethyl	12.7	25.4	45.2	32.4	31.7	+8.39	28.7
Propyl	11.3	25.9	42.6	33.9	33.1	+12.4	28.7
Butyl	15.0	31.6	73.3	40.4	39.7	+31.4	28.6
Secondary alkyl groups							
2-Butyl (*sec*-butyl)	14.5	28.0	64.8	38.1	37.4	+24.9	28.5
2-Propyl (isopropyl)	12.9	29.3	57.6	38.1	37.4	+24.8	28.5

the size of the substituent group would have much less influence on the ground state of the β-D anomers. If the transition state for heterolysis is, indeed, largely product-like, it will be essentially the same for the hydrolysis of either anomer. Thus, with relatively small hydrophobic groups on O-4, the rate of hydrolysis roughly increases with the size of the group (which is determined by hydrophobic hydration and by the ordering of water molecules around the group)[16]; greater differences are observed with the α-D-glucopyranosides than with the β-D-glucopyranosides.

Such, however, is not the case when a D-glucopyranoside is substituted at O-4 with another glycosyl group. Available evidence[7,8] suggests that such substitution lowers the rate of hydrolysis by a factor of 0.6–0.7. It can merely be speculated that the explanation here given holds only for substituents up to a certain size and that, when the substituent is a large, highly solvated group, with, perhaps, interunit hydrogen-bonding, the entropy of the ring is very low, and the change in conformation needed for forming the transition state for bond cleavage is inhibited.

EXPERIMENTAL

The methyl 4-*O*-alkyl-D-glucopyranosides were prepared from methyl 2,3,6-tri-*O*-benzyl-α- and β-D-glucopyranosides as previously described[17]. Solutions of the glucosides in 1:1 (v/v) water–*p*-dioxane were added to an equal volume (2 ml) of M sulfuric acid. After thorough mixing for ~1 min, the resulting solution was placed in a preheated, water-jacketed, polarimeter cell of a Bendix ETL-NPL Automatic Polarimeter equipped with a 546-nm (mercury green line) interference filter. The change in optical rotation as the reaction progressed was recorded, and rate constants were determined by Guggenheim's method[18] by use of a computer to give a least-squares fit of the data.

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