Carbohydrate Research, 70 (1979) 319–322

Note

Acid-catalyzed hydrolysis of alkyl β-D-glucofuranoside 5,6-carbonates*

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(Received October 11th, 1978; accepted for publication in revised form, December 26th, 1978)

The relatively rapid, acid-catalyzed hydrolysis of glycofuranosides was the first property used for differentiating them from glycopyranosides[1]. Reported values of the energy of activation (E_a) for the acid-catalyzed hydrolysis of glycofuranosides from early investigations range from 19.2 to 23.1 kcal/mol, whereas reported E_a values for hydrolysis of the corresponding glycopyranosides range from 32.3 to 34.3 kcal/mol[2–4]. Reported $\Delta S^{\ddagger}$ values for the hydrolysis of glycofuranosides are negative and range from –7.1 to –11.1 entropy units (e.u.), whereas reported $\Delta S^{\ddagger}$ values for the hydrolysis of the corresponding glycopyranosides are positive and range from 11.2 to 17.7 e.u.[2–4].

The mechanism of the acid-catalyzed hydrolysis of glycofuranosides has not been established. Four hypotheses have been proposed. Overend *et al.*[2] proposed an A-2 (SN2) mechanism that involves an entropically unfavorable transition-state. Capon and Thacker[4] proposed two additional A-2 mechanisms both of which involve an entropically unfavorable, crowded transition state, one as a result of a bimolecular reaction between an acyclic carbonium ion and a water molecule, and the other as a result of the attack by a water molecule at C-1, concerted with ring opening. BeMiller[5] proposed an A-1 (SN1) mechanism involving a transition state that was entropically unfavorable because of its carbonium–oxonium ion character.

The purpose of this investigation was to obtain rate constants for the acid-catalyzed hydrolysis of alkyl β-D-glycofuranoside 5,6-carbonates, to use these rate constants to determine activation parameters, and to use these activation parameters to evaluate the proposed mechanisms. D-Glucofuranoside 5,6-carbonates were chosen because the rates of hydrolysis were to be determined by means of changes in optical rotation; and the relatively acid-stable carbonate diester was expected to maintain the furanose configuration during and after hydrolysis and, therefore, prevent any change in optical rotation through conversion of the furanose to the pyranose ring-form, a conversion ignored in previous studies. The rate constants determined in this investigation and reported in Table I indicate that the

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*Dedicated to Professor Roy L. Whistler.

TABLE I

RATE CONSTANTS FOR THE ACID-CATALYZED HYDROLYSIS OF ALKYL β-D-GLUCOFURANOSIDE 5,6-CARBONATES

Alkyl	*Acid normality*[a]	*Temperature (°C)*	10^6 k *(sec^{-1})*
Methyl (1)	0.025	50	34
	0.025	60	84
	0.025	70	216
	0.050	55	89
	0.050	60	134
	0.050	65	225
Ethyl (2)	0.025	50	97
	0.025	59	222
	0.025	70	571
	0.050	50	191
	0.050	55	291
	0.050	60	494
	0.050	65	705
1-Propyl[b] (3)	0.025	55	75
	0.025	60	120
	0.025	65	184
	0.050	55	169
	0.050	60	247
	0.050	65	411

[a] Acid used was hydrochloric acid. [b] Hydrolyses of 3 were effected in acidic 3:1 (v/v) water—1,4-dioxane.

carbonate diester has approximately the same acid stability as the unprotected glucofuranoside.

Because 3 is insoluble in water, its hydrolysis was studied in 3:1 (v/v) water–1,4-dioxane. To determine the effect of 1,4-dioxane on the hydrolysis reaction, hydrolysis of 2 and 3 was effected in various 1,4-dioxane–water solutions, 0.01 M in HCl, at 60°. The results of this investigation (not reported here) clearly showed that increasing the concentration of 1,4-dioxane in the aqueous solution used for hydrolysis rather rapidly decreased the rate constant for the hydrolysis reaction. This result may indicate a direct participation of water in the rate-determining step and, therefore, an A-2 reaction.

The products of hydrolysis were determined by t.l.c. The major product in each reaction co-chromatographed with D-glucofuranose 5,6-carbonate. Each product-solution also contained a minor component that co-chromatographed with D-glucose, indicating that the carbonate group had been removed from some molecules. However, in a separate study it was determined that, under the conditions employed, D-glucofuranose 5,6-carbonate is quite stable and that there was no significant change in optical rotation through removal of the carbonate diester group. Alkyl β-D-glucofuranoside was not detected in any of the reactions.

TABLE II

ACTIVATION PARAMETERS[a] FOR THE ACID-CATALYZED HYDROLYSIS OF ALKYL β-D-GLUCOFURANOSIDE 5,6-CARBONATES

Alkyl	*Acid normality*[b]	E_a *(kcal/mol)*	$\Delta H^{\ddagger}$ *(kcal/mol)*	$\Delta S^{\ddagger}$ *(cal/mol. deg)*	$\Delta G^{\ddagger}$ *(kcal/mol)*
Methyl (1)	0.025	20.3	19.6	−18.5	25.8
	0.050	20.5	19.8	−17.0	25.5
Ethyl (2)	0.025	19.5	18.8	−18.9	25.1
	0.050	19.3	18.6	−18.1	24.6
1-Propyl[c] (3)	0.025	19.8	19.2	−19.1	25.6
	0.050	19.6	19.0	−18.3	25.1

[a] Temperature used in calculations was 333 K. [b] Acid used was hydrochloric acid. [c] Hydrolyses of 3 were effected in acidic 3:1 (v/v) water–1,4-dioxane.

The mean energy of activation (E_a) for the acid-catalyzed hydrolysis of alkyl β-D-glucofuranoside 5,6-carbonates was 19.8 kcal/mol; the mean of previously reported values was[2,4] 21.3 kcal/mol. Entropies of activation ($\Delta S^{\ddagger}$) determined in this study ranged from −17.0 to −19.1 e.u., the mean being −18.3 e.u. They were approximately 10 e.u. more negative than the values reported previously[2,4] and, therefore, approximately 30 e.u. less than the entropies of activation reported for the acid-catalyzed hydrolysis of glycopyranosides, a reaction known to proceed by an A-1 mechanism[5].

Although there is a quantitative difference between the $\Delta S^{\ddagger}$ values determined in this investigation and those determined previously, the $\Delta S^{\ddagger}$ values are all negative in sign, which is indicative of a strained transition-state. However, a strained transition-state may be accounted for by either the A-1 mechanism suggested by BeMiller[5] or the A-2 mechanisms suggested by Overend *et al.*[2] and Capon and Thacker[4]. The E_a and $\Delta S^{\ddagger}$ values determined in this investigation can not, therefore, be used to rule out either proposed mechanism. The hydrolysis of glycofuranosides needs to be further studied. This preliminary study demonstrates that alkyl D-glycofuranoside 5,6-carbonates are appropriate compounds to use.

EXPERIMENTAL

Anomeric mixtures of methyl (1), ethyl (2), and 1-propyl (3) D-*glucofuranoside 5,6-carbonates.* — Compounds 1–3 were synthesized by the method of Haworth and Porter[6]. The reaction was monitored polarimetrically and was considered complete when the optical rotation of the solution became slightly negative. The reaction was stopped by neutralization with an anion-exchange resin pre-equilibrated with the corresponding alcohol. The anomeric mixtures were crystallized by the addition of ether.

Separation of the anomers of methyl and ethyl D-glucofuranoside 5,6-carbonate by fractional recrystallization was reported by Haworth *et al.*[6,7]. Hirst and Percival[8], using the same procedure, prepared ethyl β-D-glucofuranoside 5,6-carbonate. We found that the anomers could be obtained pure by column chromatography on silicic acid. However, only the β-D anomers were obtained in sufficient yield to use in this study.

A column (3 X 106 cm) containing 370 g of silicic acid was washed with 3 vols of abs. methanol, 1 vol of dry acetone, and at least 3 vols of 19:1 (v/v) chloroform–methanol. An anomeric mixture of an alkyl D-glucofuranoside 5,6-carbonate (0.3–0.4 g) was dissolved in 15–20 mL of 19:1 (v/v) chloroform–methanol, the eluting solvent; and the solution was added to the column. Fractions (5 mL) were collected and analyzed by t.l.c. Fractions containing the β-D anomer, the principal product, were pooled and evaporated. The collected β-D anomer was rechromatographed to ensure purity. Methyl β-D-glucofuranoside 5,6-carbonate (1) had m.p. 148.0–149.5°, $[\alpha]^{22}_{5461}$ –64° (*c* 1.7, water); reported[6] m.p. 143–145°, $[\alpha]^{22}_{5461}$ –75° (*c* 0.7, water). Ethyl β-D-glucofuranoside 5,6-carbonate (2) had m.p. 165.0–166.5°, $[\alpha]^{22}_{5461}$ –54° (*c* 1.7, water); reported[7,8] m.p. 164–165°, $[\alpha]^{19}_{5461}$ –55° (*c* 1.1, water). 1-Propyl β-D-glucofuranoside 5,6-carbonate (3) had m.p. 180.0–181.5°, $[\alpha]^{22}_{5461}$ –63° (*c* 2.0, acetone).

Hydrolytic-rate studies. — The acid-catalyzed hydrolysis of each of the three alkyl β-D-glucofuranoside 5,6-carbonates was effected at three or more temperatures and two or more acid concentrations. The hydrolyses were monitored by recording the change in optical rotation with time by means of a Bendix ETL-NPL automatic polarimeter equipped with a 546-nm interference filter and a water-jacketed cell (path length = 0.2 dm). Rate constants were determined by the method of Guggenheim[9] by using a least-squares fit of the data interpolated from smoothed recorder-curves.

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