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ACID HYDROLYSIS OF METHYL CHLORODEOXYGLYCOSIDES

TADASHI ISHII, ATSUSHI ISHIZU, AND JUNZO NAKANO
Faculty of Agriculture, Tokyo University, Tokyo (Japan)
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ABSTRACT

First-order rate coefficients, activation energies, and entropies of activation for the acid-catalysed hydrolysis of methyl β-D-glucopyranoside and seven methyl chlorodeoxyglycopyranosides have been determined on the basis of methanol yield. Increase in the number of chlorine substituents causes a decrease in the rate of hydrolysis. Replacement of the C-2 hydroxyl group by chlorine shows the greatest effect in decreasing the rate. Significant changes were found in the activation parameters; for instance, the entropies of activation were negative for three chlorodeoxyglycopyranosides. This is the first example of glycopyranosides having negative values for entropies of activation.

INTRODUCTION

In 1958, Boehm[1] reported that resistance of chlorodeoxycellulose to acid hydrolysis increases with increase in chlorine content. The authors discovered recently that a highly chlorinated cellulose[2] (d.s. of chlorine, 2.8) obtained by chlorination of cellulose linters with thionyl chloride in *N,N*-dimethylformamide and chloral is completely stable towards acid hydrolysis[3]. Substitution of the hydroxyl groups of methyl glycosides by chlorine is known to increase the acid-stability of the glycosidic bonds[4,5]. However, the effects of the position and number of chlorine substituents on the rate of hydrolysis have not been studied previously.

We now report on the acid hydrolysis of methyl β-D-glucopyranoside and seven methyl chlorodeoxyglycopyranosides, some of which represent units of chlorodeoxycellulose.

RESULTS AND DISCUSSION

Of the eight methyl glycosides used in this experiment, methyl β-D-glucopyranoside (**1**) and methyl 6-chloro-6-deoxy-β-D-glucopyranoside (**3**) represent, respectively, an unmodified D-glucose residue and a D-glucose residue chlorinated at C-6 in chlorinated cellulose. Although no chlorinated hexoses have been identified

amongst the hydrolysis products of cellulose chlorinated in the above-mentioned solvent, chlorination with thionyl chloride at secondary hydroxyl groups may be accompanied by Walden inversion, by analogy with chlorination of monosaccharides with sulphuryl chloride in pyridine[5] and of methyl maltoside with methanesulphonyl chloride in *N,N*-dimethylformamide[6]. Thus, methyl 3-chloro-3-deoxy-β-D-allopyranoside (5), methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (7), and methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (8) were synthesized as model compounds for sugar residues in chlorinated celluloses.

As glycosides are rather unstable to acids, their rate coefficients for acid hydrolysis are usually measured polarimetrically at temperatures lower than 100°. Methyl chlorodeoxyglycosides, on the other hand, are more stable towards acid than the usual glycosides. They were hydrolysed, therefore, in glass ampoules at 100, 110, and 120°, and the rate coefficients were calculated on the basis of the methanol released, as determined by g.l.c.

In order to check its validity, this method was used to follow the hydrolysis of glucoside **1** at 80, 90, and 100° in 0.5M sulphuric acid. The results are closely comparable with those[7] measured by the polarimetric method (Table I), although the mean deviation is higher for the g.l.c. method.

TABLE I

COMPARISON OF RATE COEFFICIENTS AND KINETIC PARAMETERS FOR THE HYDROLYSIS OF METHYL β-D-GLUCOPYRANOSIDE IN 0.5M SULPHURIC ACID

Method	$k \times 10^6$ (sec^{-1})			E ($kcal.mol^{-1}$)	$\Delta S^{\ddagger}$ *at 80°* ($cal.mol^{-1}.degree^{-1}$)
	80°	*90°*	*100°*		
Polarimetric[7]	24.1 (2.1)[a]	90.2 (1.8)	325 (2.5)	32.5	+10.7
G.l.c.	26.9 (6.5)	93.3 (7.4)	309 (4.4)	31.9	+11.2

[a]Data in parentheses: percent deviation from the mean.

The rate coefficients and kinetic parameters for hydrolysis of the chlorodeoxyglycosides are summarized in Table II. Clearly, introduction of chlorine substituents results in a decrease of the rate coefficients for acid hydrolysis. The rate coefficient decreases with increase in the number of chlorine substituents introduced and varies with the position of substitution.

Timell *et al.*[4] pointed out in their study on the stability of glucuronides that the effect of some substituents at C-5 can be rationally explained in terms of conformational, rather than electronic, effects. For example, the σ^* value increases in the order CH_2OH (+0.56), CH_2Cl (+1.05), and COOH (+2.94), but the rate of hydrolysis decreases in the order CH_2OH, COOH, and CH_2Cl. In their work, the relative rate of acid hydrolysis of methyl 6-chloro-6-deoxy-α-D-glucopyranoside (**2**) to that of methyl α-D-glucopyranoside was 0.15 in 0.5M sulphuric acid at 80°. In our work, the relative rate for the corresponding β anomers was 0.18 in the same acid at

TABLE II

RATE COEFFICIENTS AND KINETIC PARAMETERS FOR HYDROLYSIS OF METHYL CHLORODEOXY-D-GLYCOSIDES

Compounds	$k \times 10^5$ (sec^{-1})			E ($kcal.mol^{-1}$)	$\Delta S^{\ddagger}$ ($cal.mol^{-1}.degree^{-1}$) at 100°	$\Delta F^{\ddagger}$ ($kcal.mol^{-1}$)	*Relative rate at 100°*
	100°	*110°*	*120°*				
Methyl β-D-glucopyranoside (1)	30.90			31.9	+10.9	27.8	70.9
Methyl 6-chloro-6-deoxy-α-D-glucopyranoside (2)	2.400	7.943	25.70	34.7	+13.5	29.7	5.5
Methyl 6-chloro-6-deoxy-β-D-glucopyranoside (3)	5.401	17.78	56.24	34.4	+14.2	29.1	12.4
Methyl 2-chloro-2-deoxy-β-D-glucopyranoside (4)	1.288	3.548	9.730	28.8	−3.45	30.1	2.95
Methyl 3-chloro-3-deoxy-β-D-allopyranoside (5)	5.600	14.45	33.04	27.6	−3.95	29.0	12.8
Methyl 2,6-dichloro-2,6-dideoxy-β-D-glucopyranoside (6)	0.4360	1.087	3.051	28.8	−6.11	31.0	1
Methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (7)	2.138	8.944	30.67	39.1	+25.0	29.8	4.9
Methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (8)	2.455	7.348	18.24	30.0	+1.13	29.6	5.63

100°. Therefore, substitution of HO-6 by a bulky chlorine atom increases the stability towards acids of methyl α- and β-D-glucopyranosides almost equally. According to the most-widely accepted mechanism of acid hydrolysis of glycosides[8], the carbonium–oxonium ion having a half-chair conformation is assumed to be an intermediate, the formation of which from a chair conformation will be hindered by the bulky chloromethyl group at C-5 relative to C-4 (*cf.* Feather's explanation[9]).

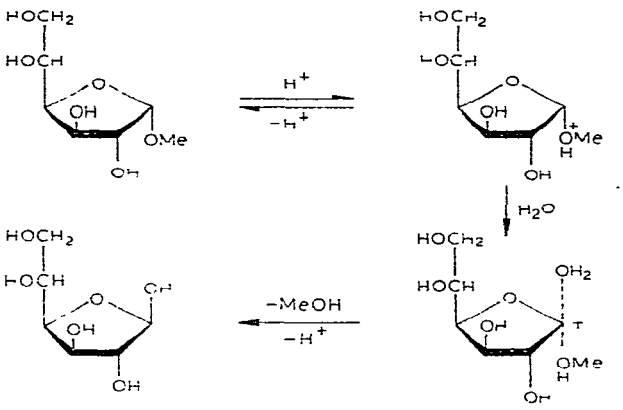
The glucoside **3** was hydrolysed about twice as fast as its α anomer. Generally[9], the rate ratio for anomers of methyl glycosides is approximately two. The result reported herein extends this generalization to methyl 6-chloro-6-deoxy-D-glucopyranosides.

Substitution of HO-2 by hydrogen greatly enhances the acid lability of methyl glucosides, because removal of the inductive effect of HO-2 enhances both the formation and decomposition of the conjugate acid in Edward's scheme[10]. For methyl 2-chloro-2-deoxy-β-D-glucopyranoside (**4**), on the contrary, HO-2 ($\sigma^*+1.55$)[11] is substituted by the stronger electron-withdrawing chlorine atom ($\sigma^*+2.94$), suggesting that this glucoside should be more stable than the parent glucoside **1**. This prediction is proved by the data in Table II. The conformational effect of the 2-chlorine atom can also be expected to contribute to this stabilization. It is not certain whether the hydrolysis of this compound proceeds according to Edward's scheme (this matter will be discussed later). However, the fact that the glucoside **4** is more stable than all of the other chlorodeoxyglycosides, with the exception of methyl 2,6-dichloro-2,6-dideoxy-D-glucopyranoside (**6**), may indicate that the 2-chlorine atom exerts the significant electronic effect.

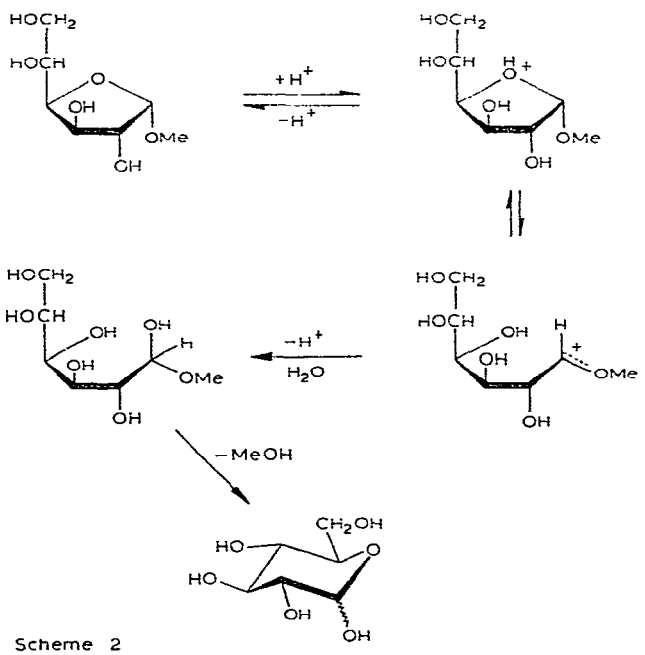
Introduction of a second chlorine atom results in further decrease of the rate coefficient by increasing the above-mentioned conformational and/or electronic effects, but the effects are much less than those expected from the effect of the first chlorine substituent. The chlorine atoms introduced at C-2 and C-6, for example, decrease the rate of the parent glucopyranoside by a factor of 24 and 5.7, respectively, whereas the introduction of chlorine atoms at both C-2 and C-6 decreases the rate by a factor of 71, which is less than the expected value (24×5.7).

Inspection of the kinetic parameters in Table II reveals that the values for the activation energy and the entropy of activation of methyl chlorodeoxyglycopyranosides vary over a wide range. Overend *et al.*[10] calculated the entropy of activation for the hydrolysis of 24 pyranosides at 60°; all values were positive, ranging from 4.1 to 23.0 $cal.deg^{-1}.mol^{-1}$, and all but two were greater than 10.0 $cal.deg^{-1}.mol^{-1}$. These data support the unimolecular mechanism. Timell *et al.*[4] reported later that nearly all values for the activation energy of the neutral glycosides fall within the range of 33 to 35 $kcal.mol^{-1}$, and that all glycuronides, with the single exception of the β-D-galactosiduronic acids, have energies of activation which are 3 to 5 $kcal.mol^{-1}$ lower than those of their neutral analogs. The entropies of activation were in the range of +0.5 to +8 $cal.deg^{-1}.mol^{-1}$. Based on these low values, it was suggested that glycuronides may be hydrolysed by a mechanism differing from that for neutral glycosides.

In the present work, three methyl chlorodeoxyglycosides (**4–6**) have negative values for the entropy of activation. Among glycosides studied previously, only glycofuranosides have negative values for the entropy of activation[10,12]. Two possible mechanisms for the hydrolysis of furanosides involve (*a*) a bimolecular replacement of the alcohol molecule from C-1 by water (Scheme 1) or (*b*) a ring-opening step[12] (Scheme 2) .The former mechanism would clearly be unfavorable for pyranosides, particularly with chlorodeoxyglycosides, owing to the considerable



Scheme 1



Scheme 2

non-bonded interaction in the transition state. The pathway (*b*) that involves a ring-opening step, therefore, may be more probable for methyl chlorodeoxyglycopyranosides having negative entropies of activation.

As with glycofuranosides, the chlorodeoxyglycosides **4–6** have low energies of activation, but this is not sufficient to offset the low entropy of activation. Thus, they are rather stable towards acid hydrolysis, in contrast to glycofuranosides. Glycoside **8** is similar to the above three glycosides in its low entropy and low energy of activation. In contrast, the alloside **7** has much higher values for the entropy of activation and energy of activation. For the two 6-chloro-6-deoxyglucosides these values are similar to those of neutral glycosides. Chlorodeoxyglycosides, therefore, can be classified into three groups based on their thermodynamic characteristics.

EXPERIMENTAL

Evaporations were carried out under diminished pressure below 45°. T.l.c. was performed on Kieselgel G (Type 60), using ethyl acetate–ethanol–water (45:5:3) and detection by charring with sulphuric acid. Column chromatography was performed on Kieselgel 60 (70–230 mesh, ASTM). Melting points are uncorrected.

Methyl β-D-glucopyranoside[13] (**1**), α and β anomers of methyl 6-chloro-6-deoxy-D-glucopyranoside[14] (**2** and **3**), and methyl 2-chloro-2-deoxy-β-D-glucopyranoside[15] (**4**) were synthesized by literature procedures. Methyl 3-chloro-3-deoxy-β-D-allopyranoside (**5**), methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**7**), and methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (**8**) were synthesized as described by Jones *et al.*[5,16].

Methyl 2,6-dichloro-2,6-dideoxy-β-D-glucopyranoside (**6**). — A solution of **4** (1.2 g) in *N*,*N*-dimethylformamide was treated with methanesulphonyl chloride (5.3 ml) for 16 h at 65°. After deformylation of the product with methanolic sodium methoxide at room temperature for 30 min, t.l.c. of the resulting syrup showed one major spot (R_F 0.65) together with a minor spot of the starting material (R_F 0.54). The syrup was eluted from Kieselgel 60 with ethyl acetate–ethanol–water (45:5:3) and recrystallized from ethyl acetate–chloroform (3:1) to give **6** (70%), m.p. 101.5–103.5°, $[\alpha]_D$ −12° (*c* 1.5, water).

Anal. Calc. for $C_7H_{12}Cl_2O_4$: C, 36.4; H, 5.23; Cl, 30.7. Found: C, 36.0; H, 5.08; Cl, 30.2.

Kinetic measurements. — Before acid hydrolysis, it was confirmed by g.l.c. that each compound contained neither methanol nor ethanol.

Sextuplicate aliquots (1 ml) of a 0.1M solution of each glycoside in 0.5M sulphuric acid were sealed in 5-ml ampoules under nitrogen to avoid oxidation of liberated methanol. Hydrolyses were conducted variously at 100, 110, and 120 ±0.1° to ~70% completion. After intervals, ampoules were cooled in ice–water, and the contents were neutralized with the calculated amount of aqueous sodium hydroxide. The liberated methanol was determined by g.l.c., using ethanol as an internal standard in a concentration similar to that of the methanol to be determined. A Model G-80

Yanagimoto gas chromatograph with a flame-ionization detector was used together with a steel column (225 × 0.4 cm) containing Chromosorb 101 (60–80 mesh). The column temperature was 120° and the inlet was maintained at 125°. The nitrogen flow-rate was 55 ml/min. The inlet was cleaned after each 30-μl injection of hydrolysate. Deviations from the mean were determined throughout and were usually in the range of 3–7.5%, with no value exceeding 10%.

In each hydrolysate, only two spots corresponding to the starting material and the corresponding reducing sugar were detected by t.l.c.

The kinetic data in Table III are typical.

TABLE III

HYDROLYSIS OF METHYL 3,6-DICHLORO-3,6-DIDEOXY-β-D-ALLOPYRANOSIDE IN 0.5M SULPHURIC ACID AT 100.5°

Time (*min*)	*Methanol* ($\times 10^6$ *mol*)	$k \times 10^5$ (sec^{-1})[a]
30	3.125	2.175
60	6.275	2.136
120	13.40	2.299
186	19.56	2.282
299	31.05	2.479
405	39.38	2.513

[a]Mean value of k, 2.314×10^{-5} sec^{-1}. Mean deviation, 6.2%.

Calculation of energies, entropies, and free energies of activation. — The energy of activation was obtained from a minimum of three rate constants, usually determined at 100, 110, and 120°. When log k was plotted against $1/T$, straight lines were obtained.

The entropy of activation was calculated for 100° from the following relationship: $T\Delta S^{\ddagger} = E - RT \ln (kT/h) + RT \ln (k'/h_0)$, where $R = 1.987$ cal.mol^{-1}.degree^{-1}, $T = 373$ K, $k = 1.381 \times 10^{-16}$ erg.mol^{-1}.degree^{-1}, $h = 6.625 \times 10^{-27}$ erg.sec, k' = first-order rate coefficient (sec^{-1}), and $h_0 = +0.741$ for 0.5M sulphuric acid.

The free energy of activation was calculated from relationship $\Delta F^{\ddagger} = E - T\Delta S^{\ddagger}$.

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