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THE KINETICS OF THE ACID-CATALYSED HYDROLYSIS OF SOME METHYL 4,6-O-BENZYLIDENE-HEXOSIDES

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Abstract—Rates of hydrolysis at 40° of the benzylidene residue in methyl 4,6-O-benzylidene-D-hexosides by 96% aqueous ethanol which was 0·03 M in hydrochloric acid, have been measured. The hexosides were of the α- and *β-gluco-*, α- and *β-galacto-*, α-*manno*, α-*altro-* and α-*ido*-configurations. Similar hydrolyses were carried out with the 4,6-O-benzylidene derivatives of methyl 3-deoxy-α-D-glucoside and methyl 2,3-di-O-methyl-α-D-glucoside. It was shown that under the conditions specified no cleavage of the glycosidic bond occurred with any of the samples.

As the rate differences are small it is concluded that the geometry of the transition state corresponds closely to that of the initial state. Possible reasons for some of the rate differences observed are discussed in terms of steric and electronic features of the compounds.

IN 4,6-O-benzylidene derivatives of hexosides a 1,3-dioxan ring is fused to a pyranoid ring leading to a bicyclic system containing two six-membered rings. For hexosides of the D-*gluco-*, D-*manno-*, D-*altro-*, and D-*allo*-configurations the ring fusion is necessarily *trans*, whereas for those of the D-*galacto-*, D-*talo-*, D-*gulo-*, and D-*ido*-configurations the union is of the *cis* type. Very few quantitative measurements have been made of the rates of hydrolysis of sugar acetals and so the present work was undertaken in an attempt to determine the effect of different configurations on the hydrolysis of benzylidene acetals of various glycosides and in particular to compare the rates for *cis* and *trans* fused structures.

The compounds examined (see Table 1) were prepared as described in the Experimental section. The hydrolyses were carried out at 40° with 96 per cent aqueous ethanol which was 0·03*M* in hydrochloric acid. The course of the hydrolysis was followed spectrophotometrically, a method superior in this case to polarimetry because the changes in optical rotation in some of the hydrolyses are very small. Control experiments indicated that no cleavage of glycosidic linkage occurred with any of the samples during the hydrolyses. The measurements were treated in standard fashion and the results are shown in Table 1.

When the ring junction in 4,6-O-benzylidene-glycosides is *trans*, only one conformation in which both rings are in a chair form is possible, e.g. methyl 4,6-O-benzylidene-α-D-glucoside has conformation I. (For a review of the general stereochemical features of carbohydrates see Ferrier and Overend.[1]) (Although the carbon atom (*) attached to the phenyl group is asymmetric only one form of each of the 4,6-O-benzylidene derivatives of methyl altroside, methyl glucoside, and methyl mannoside (the *trans* fused compounds examined in this investigation) has been reported, and it is generally assumed that in these compounds the phenyl group occupies the equatorial position). With *cis* ring fusion two conformations, with both rings in a chair form, are possible. These have been denoted as "O-inside" and

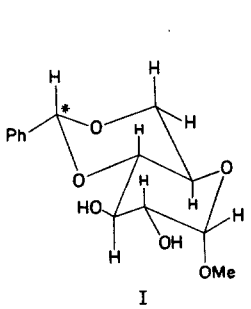
[1] R. J. Ferrier and W. G. Overend, *Quart. Rev. Chem. Soc.* **13**, 265 (1959).

"H-inside" forms.[2] Formulae II and III represent the "O-inside" and "H-inside" conformations of methyl 4,6-O-benzylidene-α-D-galactoside. It would be expected that structure II would be the more stable as it permits the hydroxyl groups attached at *C*(2) and *C*(3) of the pyranoside ring to occupy equatorial positions. Moreover the

TABLE 1. RATES OF HYDROLYSIS OF METHYL 4,6-O-BENZYLIDENE-HEXOSIDES AT 40·0 ± 0·1° IN 96% AQUEOUS ETHANOL 0·03 M IN HYDROGEN CHLORIDE

4,6-O-Benzylidene derivative of:	Ring fusion	10^5 k(sec^{-1})	Relative rate
Methyl α-D-glucoside	*trans*	15·7	2·7
Methyl β-D-glucoside	*trans*	8·97	1·5
Methyl α-D-mannoside	*trans*	20·6	3·5
Methyl α-D-altroside	*trans*	16·9	2·9
Methyl α-D-galactoside	*cis*	6·10	1·0
Methyl β-D-galactoside	*cis*	7·34	1·2
Methyl α-D-idoside	*cis*	5·92	1·0
Methyl 3-deoxy-α-D-glucoside	*trans*	17·4	2·9
Methyl 2,3-di-O-methyl-α-D-glucoside	*trans*	6·49	1·1

configuration at the acetal carbon atom is presumably that with the phenyl substituent in an equatorial disposition. Methyl α-D-idoside differs from methyl α-D-galactoside in the configuration at *C*(2) and *C*(3) only (e.g. see method of preparation in Experimental section). Consequently the "O-inside" and "H-inside" forms of methyl



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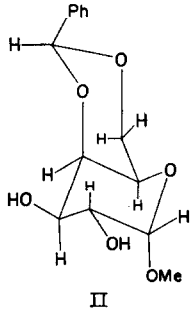

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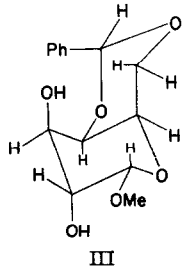

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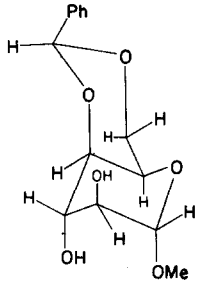

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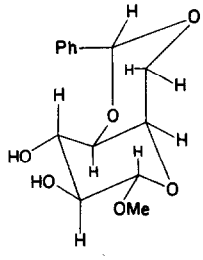
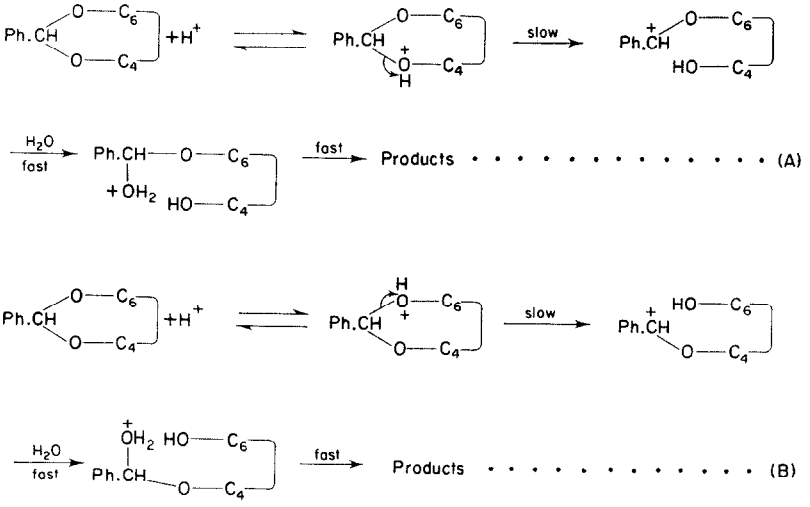


V

[2] J. A. Mills, *Adv. Carbohyd. Chem.* **10**, 44 (1955).

4,6-O-benzylidene-α-D-idoside might be represented by IV and V. Reeves[3] has claimed that his results with the cuprammonium complexing technique indicate that the sugar ring of methyl 4,6-O-benzylidene-α-D-idoside exists in the 1*C* conformation. This should not be taken however to imply that the molecule exists in the "H-inside" form (V) because the phenyl group would then occupy a most unfavourable steric position. It is probable that the molecule adopts a conformation involving half-chair or boat forms which allows the hydroxyl substituents at *C*(2) and *C*(3) to complex with the cuprammonium reagent, and which results in the phenyl group occupying a more favourable steric position. That two conformations are possible for the *cis* fused systems implies that the structure will be less rigid than that of the *trans* fused compounds, since minor displacements from one conformation towards the other may occur. Consequently it is not too difficult to envisage intermediate forms between the two extremes.

In discussing our results it is necessary to consider not only the stereochemistry of the benzylidene glycosides but also the mechanism of the acetal hydrolysis. Hydrolysis of benzylidene-acetals would be expected to follow the generally accepted mechanism for the hydrolysis of simple acyclic acetals.[4] As the acetals under consideration are unsymmetrical two mechanisms (A) and (B) are possible, dependent on which of the carbon-oxygen bonds undergoes heterolysis in the rate-determining step. It is not possible yet to distinguish between these pathways.



For all the methyl 4,6-O-benzylidene-glycosides studied the rates of acidic hydrolysis followed the first-order law. (Cf. the work of Newman and Harper[5] who obtained first-order rate constants for the acid-catalysed hydrolysis of cyclic ketals formed from simple acyclic diols and cyclic ketones. The results they obtained were those expected if the rate-determining step is the same as that established for the acid-catalysed hydrolysis of acyclic acetals.) From the results listed in Table 1 it can be seen that the effect of structure on the rate of hydrolysis is small, the fastest reaction

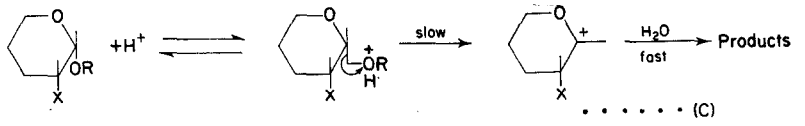
[3] R. E. Reeves, *J. Amer. Chem. Soc.* **72**, 1499 (1950).
[4] See C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 334. Cornell University Press (1953).
[5] M. S. Newman and R. J. Harper, *J. Amer. Chem. Soc.* **80**, 6350 (1958).

rate being only 3·5 times that of the slowest. In contrast to some acid-catalysed reactions in the sugar series, e.g. glycoside hydrolysis, configurational changes had only a small effect. This absence of steric influence on reactivity means that on going from the initial to the transition state there can be little increase or decrease in steric strain and hence little change in the geometry of the molecule. This is consistent with both mechanisms (A) and (B). In either case on going to the transition state there is a stretching of one of the acetal carbon-oxygen bonds and so the steric disposition of groups in the pyranoid portion of the molecule will not have changed greatly: hence their initial position will have little effect on the rate of reaction.

Rates of acetal hydrolysis of methyl benzylidene-glycosides are 2–3 times faster when the ring junction is *trans* than when it is *cis*. In so far as these rate differences are significant they may be taken to imply a slightly greater release of steric strain on going to the transition state for the *trans* fused compounds than for those *cis* fused.

There is a larger rate difference between the benzylidene derivatives of methyl α- and β-D-glucoside (*trans* fused) than between the corresponding galactosides (*cis* fused). This might be compared to Foster's[6] results on the stabilities of the borate complexes of the anomeric methyl D-glucopyranosides.

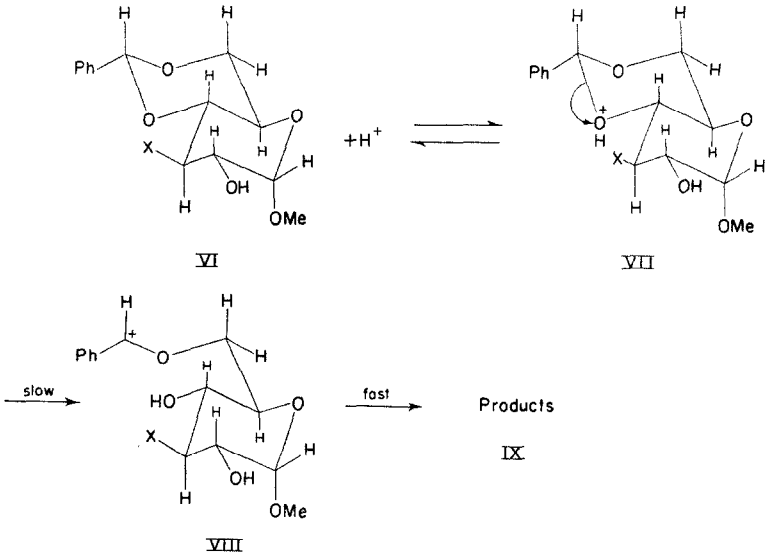
The only previous work on the rates of hydrolysis of the 4,6-O-benzylidene derivatives of methyl glycosides is that of Richards[7] who followed the changes in optical rotation on hydrolysis of methyl 4,6-O-benzylidene-α-D-glucoside and methyl 4,6-O-benzylidene-3-deoxy-α-D-glucoside with 0·004*N* ethanolic hydrochloric acid at 100°. He concluded that the benzylidene residue in the 3-deoxy-compound was hydrolysed at much the faster rate, and considered that this difference in rates was analogous to the much greater rate of hydrolysis of the methoxyl group of methyl 2-deoxy-glycopyranosides when compared with methyl glycopyranosides. The changes in optical rotation on going from methyl 4,6-O-benzylidene-3-deoxy-α-D-glucoside ($[M]_D$ +32,500) to methyl 3-deoxy-α-D-glucoside ($[M]_D$ +22,300) and from methyl 4,6-O-benzylidene-α-D-glucoside ($[M]_D$ +35,500) to methyl α-D-glucoside ($[M]_D$ +30,900), are small, and hence measurements of the rate of change of optical rotation cannot give a very accurate value for the rate of hydrolysis. Our results, based on the rate of formation of benzaldehyde, indicate that the rates of hydrolysis of these two compounds are almost identical. That the analogy drawn by Richards is a false one is shown by the following considerations. The mechanism of the hydrolysis of glycosides is not known with certainty but there are two possibilities[8] and we shall consider one of these, (C), but our arguments would apply equally well to the other. The pathway (C)



depicts an A-1 mechanism involving a pre-equilibrium proton transfer followed by the decomposition of the conjugate acid so formed in a unimolecular step. The overall rate of reaction will depend on the concentration of conjugate acid and on the rate of its unimolecular heterolysis. The effect of making a substituent (X) at *C*(2) more

[6] A. B. Foster, *Adv. Carbohyd. Chem.* **12**, 81 (1957).
[7] G. N. Richards, *Chem. & Ind.* 228 (1955).
[8] C. A. Bunton, T. A. Lewis, D. R. Llewellyn and C. A. Vernon, *J. Chem. Soc.* 4419 (1955).

electron-withdrawing would be to decrease the standing concentration of conjugate acid and to lower the rate of unimolecular heterolysis. Both factors will operate in such a way as to cause the overall rate to be reduced and methyl α-D-glucopyranoside (X = OH) would be expected to be hydrolysed more slowly than methyl 2-deoxy-α-D-glucopyranoside (X = H), as in fact is the case. With the 4,6-O-benzylidene derivatives, alteration of the hydroxyl residue at *C*(3) of the pyranoside ring for a more electron-withdrawing group would have little effect on the rate of 4,6-acetal hydrolysis if mechanism B was operative: the position of the change would be too remote from the site of bond fission to exert an effect of much magnitude. If mechanism A was operative (VI–IX) the same alteration would lower the standing concentration of conjugate acid but increase the rate of the unimolecular heterolysis. These two effects would tend to cancel out and the overall rate might be only slightly changed. It is reasonable therefore that the rates of hydrolysis of the benzylidene group in methyl 4,6-O-benzylidene-α-D-glucoside (VI, X = OH) and methyl 4,6-O-benzylidene-3-deoxy-α-D-glucoside (VI, X = H) should be closely similar. Obviously the effect of the methylene group at *C*(3) in compound VI, X = H) on the rate of hydrolysis of the acetal residue is not comparable with that in 2-deoxyglycosides on the rate of glycosidic cleavage.



VI VII VIII IX

EXPERIMENTAL

Materials. The 4,6-O-benzylidene derivatives were prepared by treatment of the methyl hexopyranosides with freshly distilled benzaldehyde in the presence of zinc chloride. Products were isolated in standard fashion and crystallized. The compounds listed in Table 2 were so prepared.

Methyl 4,6-O-*benzylidene*-2,3-di-O-*methyl*-α-D-*glucoside* was prepared in 67% yield by methylation (Ag_2O–MeI–Me_2CO) of methyl 4,6-O-benzylidene-α-D-glucoside and had m.p. 121–122°, $[\alpha]_D^{20}$ +97·9° (*c*, 1·5 in Me_2CO). (Irvine and Scott[15] report m.p. 122–123° and $[\alpha]_D^{20}$ +97·03° (in acetone) for this compound.)

Methyl 4,6-O-*benzylidene*-3-*deoxy*-α-D-*gluco*(*allo*)*side*, m.p. 177–180°, $[\alpha]_D^{27}$ +121·6° (*c*, 0·52 in $CHCl_3$) (Found: C, 62·7; H, 6·8. Calc. for $C_{14}H_{18}O_5$: C, 63·1; H, 6·8%), and methyl 4,6-O-benzylidene-α-D-altroside, m.p. 169–170°, $[\alpha]_D^{24}$ +127° (*c*, 0·50 in $CHCl_3$) were prepared from methyl

[15] J. C. Irvine and J. P. Scott, *J. Chem. Soc.* 575 (1913).

4,6-O-benzylidene-α-D-glucoside by the methods of Vis and Karrer,[16] and Richtmyer and Hudson[17] respectively. Methyl 4,6-O-benzylidene-3-deoxy-α-D-glucoside, m.p. 182°, was obtained also by benzylidenation of methyl 3-deoxy-α-D-glucopyranoside.

Methyl 4,6-O-*benzylidene*-α-D-*idoside*, m.p. 147–148°, $[\alpha]_D^{23}$ +52·1° (*c*, 1·0 in $CHCl_3$) was obtained from methyl 4,6-O-benzylidene-α-D-galactoside as initial material by Sorkin and Reichstein's[13] method. These authors quote m.p. 148–149° and $[\alpha]_D^{14}$ +49·2° ($CHCl_3$) for this compound.

TABLE 2. PHYSICAL CONSTANTS OF METHYL 4,6-O-BENZYLIDENE-HEXOSIDES

4,6-O-Benzylidene derivative of:	Solvent for crystallization	This work	Literature		Ref.
		m.p. $[\alpha]_D$ (*c*, on $CHCl_3$)	m.p.	$[\alpha]_D$ (in $CHCl_3$)	
Methyl α-D-glucoside	MeOH–H_2O; Pet. Ether–$CHCl_3$	161–162° + 120° (0·52)	164–165°	+117·5°	9
Methyl β-D-glucoside	EtOH–H_2O	198–199° − 67·4° (0·98)	199–200°	−62·3°	9
Methyl α-D-galactoside	EtOH–H_2O	168–170° + 160° (0·49)	170–172°	+166·5°[a]	10
Methyl β-D-galactoside	EtOAc–EtOH	198–200° − 35·7° (1·0)	200°	−35·1°	11
Methyl α-D-mannoside[b]	H_2O	140–144° + 69·7° (1·0)	146–147°	+71·7°	12

[a] Although our sample has a specific rotation close to that reported by Robertson and Lamb,[10] it differs from that quoted by Sorkin and Reichstein,[13] and by Bell and Greville.[14] Our sample however had a good elemental analysis (Found: C, 59·3; H, 6·5. Calc. for $C_{14}H_{18}O_6$: C, 59·55; H, 6·4%), and liberated the theoretical quantity of benzaldehyde (determined spectrophotometrically) on hydrolysis. Also it could be converted into authentic methyl 4,6-O-benzylidene-α-D-idoside.

[b] The main product of the reaction was methyl 2,3:4,6-di-O-benzylidene-α-D-mannoside, m.p. 173–178°. (A small amount of an isomeric dibenzylidene derivative, m.p. 97–98°, was also obtained.) Separation of the di- and mono-benzylidene compounds was facilitated by the greater solubility of the latter in water. Only one monobenzylidene derivative was obtained, which is in agreement with the work of Robertson,[12] who proved that it is a 4,6-derivative.

Procedure for rate measurements. A weighed amount of the benzylidene derivative (approximately equivalent to 50 ml of a 0·037 M solution) was dissolved in 40 ml 96% aqueous ethanol and the solution was placed in a thermostat maintained at 40° ± 0·1°. When the solution had attained thermostat temperature, 0·15 N ethanolic hydrochloric acid (10 ml) was added. At noted intervals of time portions (5 ml) were withdrawn, cooled to about +10°, and their optical densities at 320 mμ were measured with a Unicam S.P. 500 spectrophotometer. At this wavelength the only strongly absorbing species in the system is benzaldehyde. Eight portions from each solution were examined. The optical densities of the reaction solutions were all measured after 10 times the half-life of the reaction and the values were used, with the aid of a calibration curve, to calculate the concentrations of benzaldehyde at complete reaction. These all corresponded to between 99 and 101% of the amount of benzaldehyde calculated on the basis of the initial weight of benzylidene compound. In each case the initial optical density was taken as being that of a solution of the same concentration of the compound in 96% ethanol containing no hydrochloric acid.

Hydrolysis of the glycosidic linkages would not be expected under the conditions used since the rate constants for the hydrolyses of methyl hexopyranosides are 10^{-4}–10^{-5} sec^{-1} in 2 M hydrochloric acid at 60°. To confirm this the product from methyl 4,6-O-benzylidene -α-D-glucoside was isolated after 48 hr and was found to be methyl α-D-glucopyranoside, m.p. 166–167°, $[\alpha]_D^{20}$ +157° (*c*, 1·0 in water) (yield 85%). Also one of the more easily hydrolysed glycosides, namely methyl β-D-galactopyranoside was found to give a stable optical rotation $[\alpha]_D$ −22° (*c* = 1·0) for 46 hr under the reaction

[9] D. S. Mathers and G. J. Robertson, *J. Chem. Soc.* 696 (1933).
[10] G. J. Robertson and R. A. Lamb, *J. Chem. Soc.* 1321 (1934).
[11] J. W. H. Oldham and D. J. Bell, *J. Amer. Chem. Soc.* **60**, 323 (1938).
[12] G. J. Robertson, *J. Chem. Soc.* 330 (1934).
[13] E. Sorkin and T. Reichstein, *Helv. Chim. Acta* **28**, 1 (1945).
[14] D. J. Bell and G. D. Greville, *J. Chem. Soc.* 1136 (1955).
[16] E. Vis and P. Karrer, *Helv. Chim. Acta* **37**, 378 (1954).
[17] N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.* **63**, 1727 (1941).

conditions and to be recoverable in 90% yield. Glucose was shown to be absent at the end of each run by testing with Fehling's solution.

The hydrolysis of each compound was examined in duplicate and the differences in the mean values of the rate constants never differed by more than 3% for each of the compounds studied.

TABLE 3. HYDROLYSIS OF SOME METHYL 4,6-O-BENZYLIDENE-HEXOSIDES

(a) *Methyl* 4,6-O-*benzylidene*-α-D-*glucoside* (initial concentration 0·0375 M)

Time (min):	0	15	30	45	60	75	90	120	150	∞
D_t:	0·014	0·118	0·222	0·304	0·362	0·431	0·473	0·561	0·627	0·828
10^4k (sec^{-1}):	—	1·52	1·64	1·63	1·55	1·60	1·54	1·55	1·55	—

Mean $k = 1{\cdot}57 \pm 0{\cdot}04 \times 10^{-4}$ sec^{-1}: 50% hydrolysis in 74 min.

(b) *Methyl* 4,6-O-*benzylidene*-α-D-*altroside* (initial concentration 0·0375 M)

Time (min):	0	15	30	45	60	75	90	120	150	∞
D_t:	0·000	0·121	0·215	0·297	0·374	0·435	0·497	0·585	0·650	0·828
10^4k (sec^{-1}):	—	1·76	1·67	1·64	1·67	1·66	1·70	1·70	1·71	—

Mean $k = 1{\cdot}69 \pm 0{\cdot}03 \times 10^{-4}$ sec^{-1}: 50% hydrolysis in 68 min.

(c) *Methyl* 4,6-O-*benzylidene*-β-D-*galactoside* (initial concentration 0·0375 M)

Time (min):	0	30	60	90	120	150	180	240	300	∞
D_t:	0·018	0·114	0·204	0·285	0·349	0·407	0·462	0·550	0·612	0·825
10^5k (sec^{-1}):	—	7·04	7·28	7·44	7·33	7·31	7·40	7·48	7·40	—

Mean $k = 7{\cdot}34 \pm 0{\cdot}10 \times 10^{-5}$ sec^{-1}: 50% hydrolysis in 158 min.

(d) *Methyl* 4,6-O-*benzylidene*-α-D-*idoside* (initial concentration 0·0375 M)

Time (min):	0	30	60	90	120	180	240	300	360	∞
D_t:	0·028	0·108	0·185	0·243	0·306	0·407	0·485	0·557	0·609	0·830
10^5k (sec^{-1}):	—	5·85	6·05	5·78	5·91	5·92	5·86	5·99	5·97	—

Mean $k = 5{\cdot}92 \pm 0{\cdot}07 \times 10^{-5}$ sec^{-1}: 50% hydrolysis in 195 min.

(e) *Methyl* 4,6-O-*benzylidene*-3-*deoxy*-α-D-*glucoside* (initial concentration 0·0375 M)

Time (min):	0	15	30	45	60	75	90	105	120	∞
D_t:	0·016	0·136	0·238	0·316	0·388	0·449	0·513	0·555	0·602	0·827
10^4k (sec^{-1}):	—	1·78	1·78	1·71	1·70	1·70	1·76	1·73	1·78	—

Mean $k = 1{\cdot}74 \pm 0{\cdot}03 \times 10^{-4}$ sec^{-1}: 50% hydrolysis in 66 min.

(Errors after the ± sign are mean deviations from the mean.)

Results. All the results are summarized in Table 1 and detailed values for representative reactions are listed in Table 3 to give an indication of the extent and magnitude of the measurements. The first-order rate constants were calculated from the equation $k = \frac{2{\cdot}303}{t} \log \frac{D_\infty - D_0}{D_\infty - D_t}$, where D_0, D_t and D_∞ are respectively the optical densities of the reaction solution initially, after a time t, and at infinite time. This is the integrated first-order rate expression with the concentration terms replaced by the changes in optical density to which they are proportional. The experimentally observed times are recorded in minutes but the rate constants are given in sec^{-1}.

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