493. *Periodate Oxidation. Part IV.* The Effect of Conformation of Cyclic Glycols on the Rate of Periodate Oxidation.†*

By John Honeyman and C. J. G. Shaw.

The kinetics of oxidation by periodate of a number of cyclic α-glycols have been studied, mostly in aqueous solution at pH 4·06 and 25°. The relative rates of oxidation have been correlated with the strain associated with the formation of a cyclic complex in which the C–O bonds of the glycols are rotated to become more nearly coplanar. The effects of neighbouring groups and of the conformation of the glycols on the rate of oxidation are discussed. The two axial hydroxyl groups present in methyl 4 : 6-*O*-benzylidene-α-D-altroside fail to undergo oxidation. The results have further been correlated with formation of cuprammonium complex. Attention is drawn to the considerable lowering in the rate of periodate oxidations carried out in aqueous alcoholic media.

A number of the " dialdehydes " formed on periodate oxidation have been isolated and identified.

For a study of the effect of conformation of cyclic glycols on the rate of periodate oxidation, second-order rate constants in aqueous buffer solutions at pH 4·06 and 25° were determined for a number of compounds. In order to standardise conditions the same concentration of reactants was used in as many experiments as possible. Unfortunately, in three cases aqueous alcoholic solutions had to be used since the compounds were not sufficiently soluble in water. In order that there should be only one site of oxidation, all the compounds had one α-glycol group, which was usually in a pyranoside ring of known conformation.

* Part III, preceding paper.

† A summary of this paper was presented at the New York meeting of the American Chemical Society, September, 1957.

Second-order rate constants were determined for ten of the possible isomeric methyl 4 : 6-*O*-benzylidene-D-aldohexosides. The relative rates are demonstrated in Figs. 1 and 2. Because the benzylidene group in the anomeric altroside derivatives was unusually sensitive to acid hydrolysis, the second-order rate constants for these compounds were determined at pH 6·93 and 10·10.

The most stable conformation of the anomeric methyl 4 : 6-*O*-benzylidene-α-D-glycosides of allose, altrose, glucose, and mannose is the C1 chair form. Because there is a *trans*-junction between the two rings in each of these compounds this is the only possible chair conformation. Now, for periodate oxidation of the hydroxyl groups attached to $C_{(2)}$ and $C_{(3)}$ of the above compounds to occur, an intermediate cyclic complex must probably be formed in which the C–O bonds of the two hydroxyl groups are rotated to a greater degree of coplanarity. The ease with which this complex is formed, and

FIGS. 1 and 2. *Oxidation of methyl* 4 : 6-O-*benzylidene*-D-*glycosides at* pH 4·06 *and* 25°.

FIG. 1.

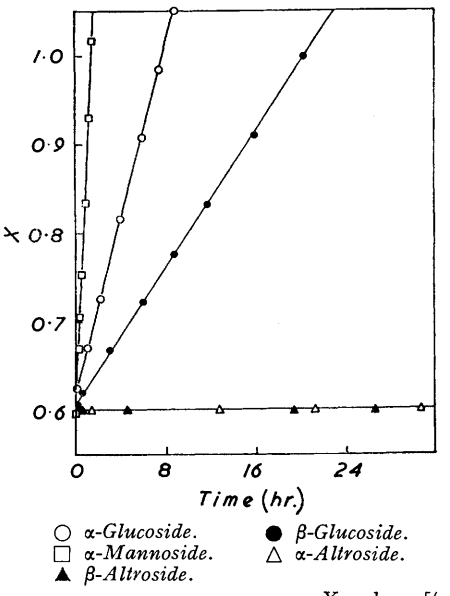
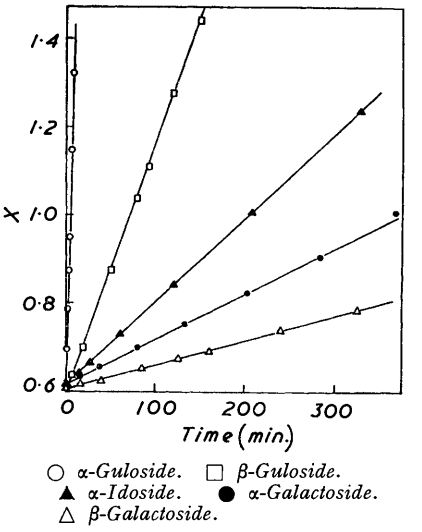


FIG. 2.



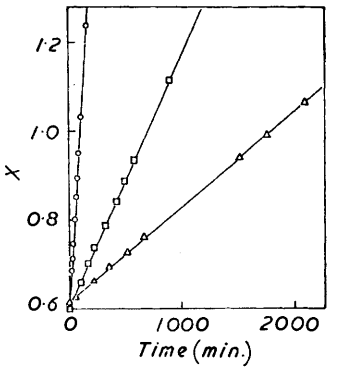
$$X = \log_{10}[(a - x)/(b - x)]$$

hence the relative rate of periodate oxidation (assuming that formation of the complex is rate-determining), will thus depend on the arrangement in space of the two hydroxyl groups. The chair pyranoside ring will respond in different ways [1] to the two different types of distortion imposed upon it by bringing the e,a- or the e,e-hydroxyl groups at $C_{(2)}$ and $C_{(3)}$ of the mannoside or glucoside derivatives into more nearly coplanar positions. The distortion induced by forcing adjacent equatorial and axial substituents more nearly into the same plane will lead to a flattening of the ring and an increase in the valency angles; all the axial atoms or groups will move further away from one another. This movement will require little energy. On the other hand, forcing two equatorial bonds more nearly into the same plane will entail a reduction in the separation of the axial atoms or groups, and therefore will require much more energy. Thus, cyclisation to form a complex involving the equatorial–axial substituents should take place more easily than that involving two equatorial groups. Forcing two axial bonds more nearly into the same plane would involve an even greater amount of energy, the energy barrier might even be too great to allow a complex to be formed at all, as in the case of the altroside

[1] Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929.

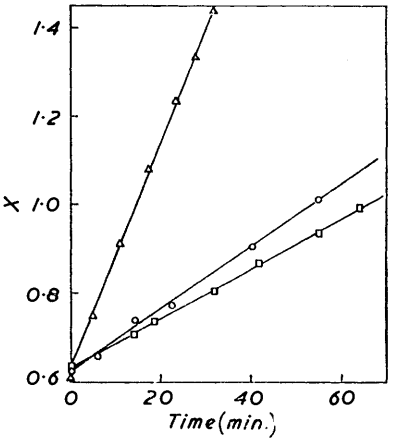
derivative. The mannose derivative, which has one hydroxyl group equatorial and the other axial, should form a periodate complex more easily than the diequatorial glucose system, whereas with the diaxial altrose, having an angle of 180° between the hydroxyl groups, formation of complex should be much more difficult, if not impossible. The experimentally determined second-order rate constants (Table 1) bear out this hypothesis, the relative rates for the derivatives of α-D-mannose and α-D-glucose being of the order 6 : 1, whilst the α-D-altrose derivative is not oxidised at all. The optical density of solutions of periodate showed no significant change on the addition of the altroside compounds; this is evidence in favour of the absence of any complex. Similarly the compounds do not form complexes in cuprammonium solution.[2] Cuprammonium complexes probably have a copper atom bridging the two oxygen atoms of the hydroxyl groups forming a five-membered ring, hence the geometrical requirement is similar to that for complex formation with periodate. However, we have found that altrose derivatives, such as methyl 4 : 6-di-*O*-methyl-α-D-altropyranoside, which can exist in the 1C conformation with equatorial hydroxyl groups at $C_{(2)}$ and $C_{(3)}$ are oxidised by periodate.

FIG. 3. *Oxidation of methyl* 4 : 6-O-*ethylidene*-D-*glycosides at* pH 4·06 *and* 25°.



□ α-*Glucoside.* △ β-*Glucoside.*
○ α-*Mannoside.*

FIG. 4. *Oxidation of methyl* 4-O-*methyl*-D-*glucopyranosides at* pH 4·06 *and* 25°.



○ α-*Glucoside.* □ β-*Glucoside.*
△ α-*Mannoside.*

With the anomeric methyl 4 : 6-*O*-benzylidene-D-glycosides of gulose, idose, galactose, and talose, the *cis*-junction of the two rings means that the pyranoside ring may be in the C1 or 1C conformation. The observed relative rates of periodate oxidation of the α-anomers of the gulose, idose, and galactose derivatives are approximately 100 : 2 : 1. The fact that methyl 4 : 6-*O*-benzylidene-α-D-idoside is oxidised suggests that it can exist in a conformation other than C1, which like the corresponding altroside has the diaxial system of hydroxyl groups on $C_{(2)}$ and $C_{(3)}$. The 1C conformation, where these hydroxyl groups are equatorial would be expected to be oxidised. This result accords with Reeves's observation [3] that the idoside forms a cuprammonium complex. Methyl 4 : 6-*O*-benzylidene-α-D-galactoside will exist in the C1 conformation with the diequatorial system of free hydroxyl groups. These results do not distinguish between the two possible chair conformations for the corresponding guloside compound, both of which have one equatorial and one axial hydroxyl group at $C_{(2)}$ and $C_{(3)}$. Evidence in favour of the C1 conformation will be produced later.

For the methyl 4 : 6-*O*-benzylidene-D-glucosides, -gulosides, and -galactosides the second-order rate constant for the α-anomer is greater than that for the β-anomer (Figs. 1

[2] Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 212.
[3] Reeves, *ibid.*, 1950, **72**, 1499.

and 2). A similar relation holds for the ethylidene analogues of glucose (Fig. 3), and for the anomeric methyl 4-*O*-methyl-D-glucopyranosides (Fig. 4). In the C1 conformations of all these compounds the $C_{(2)}$-hydroxyl group is equatorial. In the β series, the equatorial $C_{(1)}$-methoxyl group is so situated with respect to the equatorial $C_{(2)}$-hydroxyl group as to interfere sterically with the formation of a periodate complex. With the α-anomer, the $C_{(1)}$-methoxyl group is axial, and interferes less. When there is an axial,axial relation between the groups attached to $C_{(1)}$ and to $C_{(2)}$ of the pyranoside ring, then the situation is very different, and the rate constants for the α- and β-anomers might be expected to be similar, or even for that for the β-anomer to be the greater. However, no such pair of anomers is available. The fact that the rate constant for methyl 4 : 6-*O*-benzylidene-α-D-guloside is greater than that for the β-anomer, suggests that these compounds exist in the same conformation, C1, as the other glycosides showing the same relation between the rate constants for the α- and β-anomers. Another example of the equatorial glycosidic group of a β-anomer sterically interfering with the oxidation between $C_{(2)}$ and $C_{(3)}$ of a pyranose ring has recently been reported.[4]

The size of the glycosidic substituent at $C_{(1)}$ has a pronounced effect on the rate of periodate oxidation at $C_{(2)}$ and $C_{(3)}$. Thus, although methyl 4 : 6-*O*-benzylidene-β-D-glucoside is oxidised fairly slowly, 7-(4 : 6-*O*-benzylidene-β-D-glucopyranosyl)theophylline is unaffected by periodate, and phenyl 4 : 6-*O*-benzylidene-β-D-glucoside consumes periodate only extremely slowly. Unfortunately, owing to their insolubility in aqueous solutions, the last two compounds had to be studied in aqueous alcohol which we have found to give lower rate constants for periodate oxidation than do aqueous solutions. But by carrying out comparative reactions in aqueous alcohol, the influence of the glycosidic substituent has been clearly demonstrated. We have not established, however, whether this is a steric or electronic effect. 9-(4 : 6-*O*-Benzylidene-β-D-glucopyranosyl)adenine and 9-β-D-glucopyranosyladenine 4′ : 6′-(phenyl phosphate) have been reported [5] to be resistant to attack by periodate, but these compounds are insoluble in water, and the reactions were presumably carried out in non-aqueous media. Similarly, Harvey, Michalski, and Todd [6] found that 7-(4 : 6-*O*-benzylidene-β-D-glucopyranosyl)theophylline was unaffected by periodate either in aqueous suspension or dissolved in alcohol or dioxan. These results, determined in non-aqueous media, are of doubtful bearing on the effect on the reaction rate of the addition of alcohol to an aqueous oxidation solution, whilst the attempted heterogeneous reaction in an aqueous suspension of the glucoside is entirely irrelevant.

Increasing the chain-length of the alkyl group in the methyl 4 : 6-*O*-alkylidene-α-D-glucosides has little effect on the rate of oxidation (Fig. 5), but the benzylidene derivative is oxidised much faster. This is presumably due to an electronic effect. Similarly, methyl 4 : 6-*O*-benzylidene-α-D-mannoside is oxidised faster than the ethylidene derivative. The presence of a 4 : 6-phosphate ring greatly reduces the rate of oxidation. The rate constant for methyl α-D-glucoside 4 : 6-(hydrogen phosphate) is about twice that for the corresponding phenyl phosphate, so that the phenyl group exerts a steric or electronic effect which reduces the rate of oxidation. Nevertheless, contrary to a previous report,[7] methyl α-D-glucoside 4 : 6-(phenyl phosphate) is oxidised.

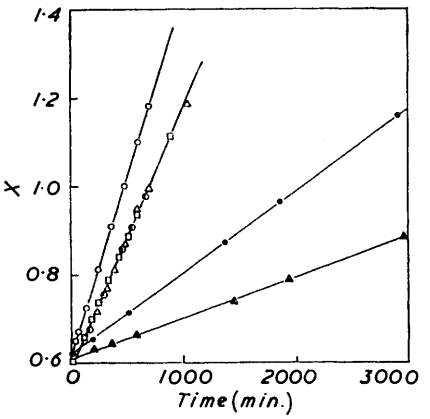
The marked differences in the observed rates of periodate oxidation of various cyclic glucosides have been discussed by Baddiley, Buchanan, and Szabó.[7] They considered that these differences arose through the steric factors which have been discussed above: the presence of (i) a $C_{(1)}$-substituent, (ii) a 4 : 6-ring, and (iii) a substituent on this ring. These authors' argument, with regard to the first of these factors, that since methyl α-D-glucoside 4 : 6-(hydrogen phosphate) was oxidised more slowly than glucose 4 : 6-(hydrogen phosphate) and since methyl 4 : 6-*O*-benzylidene-α-D-glucoside had a smaller

[4] Garner, Goldstein, Montgomery, and Smith, *J. Amer. Cnem. Soc.*, 1958, **80**, 1206.
[5] Barker and Foll, *J.*, 1957, 3794.
[6] Harvey, Michalski, and Todd, *J.*, 1951, 2271.
[7] Baddiley, Buchanan, and Szabó, *J.*, 1954, 3826.

rate of reaction than 4 : 6-*O*-benzylidene-D-glucose, there was evidence in favour of steric hindrance produced by the $C_{(1)}$-substituent, is invalid. With the two free sugars there are now three adjacent hydroxyl groups, and it is incorrect to compare the rates of oxidation of compounds containing different numbers of α-glycol groupings.

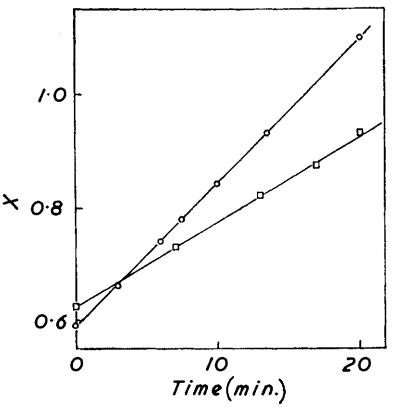
The anomeric methyl and phenyl D-glucopyranosides have been oxidised by periodate. The times taken for the reduction of one mole of periodate were about 45 minutes for the two methyl D-glucopyranosides, 65 minutes for phenyl α-D-glucopyranoside, and 69 minutes for phenyl β-D-glucopyranoside. Thus even though two α-glycol sites are being oxidised, and one is somewhat remote from the glycosidic group, the steric effect on the reaction rate is clearly shown. The effect of the glycosidic substituent on the oxidation of a remote α-glycol grouping is demonstrated in Fig. 6, where the oxidations of methyl and *p*-nitrophenyl 2-*O*-methyl-β-D-glucopyranoside are shown. The rate of oxidation at $C_{(3)}$ and $C_{(4)}$ is reduced by the *p*-nitrophenyl group at $C_{(1)}$; this may be a steric or electronic effect.

FIG. 5. *Oxidation of* 4 : 6-*substituted methyl* α-D-*glucosides at* pH 4·06 *and* 25°.



4 : 6-*Substituent*:
○ O-*Benzylidene*. □ O-*Ethylidene*.
◐ O-*Propylidene*. △ O-*Butylidene*.
● *Hydrogen phosphate*. ▲ *Phenyl phosphate*.

FIG. 6. *Oxidation of* ○ *methyl and* □ p-*nitrophenyl* 2-O-*methyl-β-D-glucopyranosides at* pH 4·06 *and* 25°.



The rates of oxidation of the 4-*O*-methyl, 4-chloro-4-deoxy, and 4-*O*-tosyl derivatives of methyl α-D-glucopyranoside are shown in Fig. 7. A considerable steric effect is apparent, although the large difference between the rate constants for the methyl and chloro-deoxy-derivatives suggests that steric factors are not the only ones operating. However, the chlorine atom also has a much greater effect than the methoxyl group in restricting the free rotation between the rings of *ortho*-substituted diphenyls.[8,9]

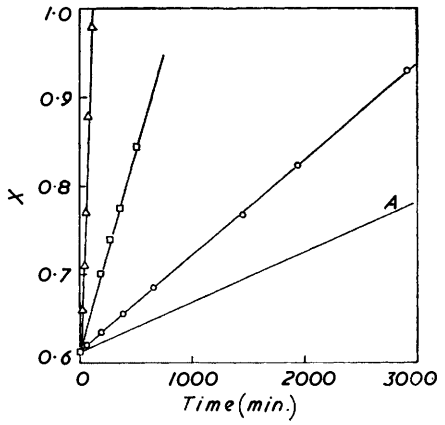
The relative rates of oxidation of the 2-deoxy, 2-*O*-methyl, and 2-*O*-tosyl derivatives of methyl α-D-glucopyranoside are shown graphically in Fig. 8. The steric effect of the $C_{(2)}$-substituent on the oxidation at $C_{(3)}$ and $C_{(4)}$ is very marked; the rate constant is reduced by a factor of 1000 on replacing a hydrogen atom by a tosyloxy-group. In the relative rates of oxidation of the 2-*O*-methyl, 2-chloro-2-deoxy, and 2-*O*-benzoyl derivatives of methyl β-D-glucopyranoside (Fig. 9), a considerable steric effect is apparent. There is again a large difference between the rate constants for the methyl and chlorodeoxy-compounds. The second-order rate constant for the periodate oxidation of methyl 2-*O*-methyl-α-D-altropyranoside is much greater than that for the corresponding glucoside derivative. This agrees with the tenet that the equatorial,axial pair of hydroxyl groups

[8] Stoughton and Adams, *J. Amer. Chem. Soc.*, 1932, **54**, 4426.
[9] Yuan and Adams, *ibid.*, p. 4434.

at $C_{(3)}$ and $C_{(4)}$ of the altroside compound in the chair conformations, will be oxidised more easily than the diequatorial system present in the glucoside.

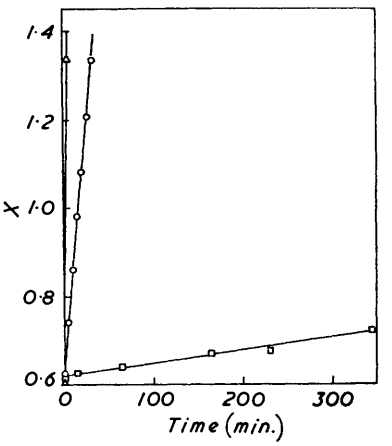
At pH 6·93 and 25°, each mole of methyl 3-amino-4 : 6-*O*-benzylidene-3-deoxy-α-D-altroside consumed one mole of periodate in about 20 hours. The " dialdehyde dihydrate " which crystallised was shown to be the compound obtained from methyl 4 : 6-*O*-benzylidene-α-D-glucoside. As methyl 4 : 6-*O*-benzylidene-α-D-altroside is unaffected by periodate, this result is surprising, and shows that the diaxial α-glycol and diaxial α-amino-hydroxyl systems are very different in their reaction with periodate. At pH 4·06 and 25°, less than one mole of periodate was reduced by the amino-altroside during 32 days; no compound crystallised from the oxidation solution. This very slow periodate reduction was probably due to the acid hydrolysis of the benzylidene group followed by oxidation (cf. methyl 4 : 6-*O*-benzylidene-α-D-altroside at this pH and temperature).

FIG. 7. *Oxidation of 4-substituted methyl α-D-glucopyranosides at* pH 4·06 *and* 25°.



4-Substituent:
△ O-*Methyl*. □ *Chloro-deoxy*. ○ O-*Tosyl*.
Curve A: *Methyl* 4-O-*tosyl*-6-O-*triphenylmethyl*-α-D-*glucopyranoside*.

FIG. 8. *Oxidation of 2-substituted methyl α-D-glucopyranosides at* pH 4·06 *and* 25°.



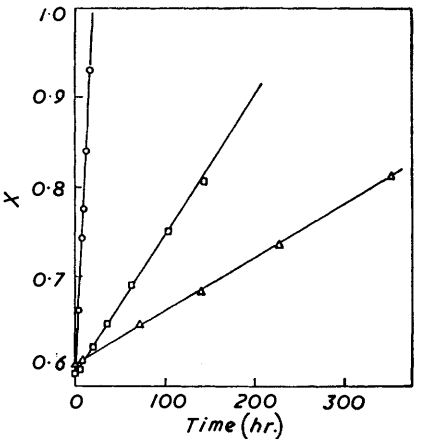
2-Substituent:
△ Deoxy. ○ O-*Methyl*. □ O-*Tosyl*.

The relative rates of oxidation of the *cis*- and *trans-cyclo*hexane-1 : 2- and -1 : 3-diols are shown in Fig. 10. As would be expected of the 1 : 2-diols the *cis*(e,a)-compound reacts more rapidly than the *trans*(e,e)-compound. The rate constants for both compounds are much greater than those for substituted glycopyranoside derivatives because of the absence of any steric hindrance due to neighbouring substituents, and because the *cyclo*hexane ring is not held in one particular conformation by a second ring. Neither *cis*- nor *trans-cyclo*hexane-1 : 3-diol was oxidised, and evidence from ultraviolet spectrophotometric studies suggested that no periodate–diol complex was formed. Similarly pentaerythritol, which possesses two very close but non-adjacent hydroxyl groups, might be expected to form a complex with periodate, but ultraviolet spectrophotometric data disproved this.

A number of the " dialdehydes resulting from the periodate oxidation of cyclic α-glycols have been isolated, some by direct crystallisation during reaction. Compounds differing only in the configuration of the oxidisable grouping give the same product. Thus, methyl 4 : 6-*O*-benzylidene-α-D-glucoside, methyl 4 : 6-*O*-benzylidene-α-D-mannoside, and methyl 3-amino-4 : 6-*O*-benzylidene-3-deoxy-α-D-altroside all gave the same hemialdal monohydrate.[10] A polarimetric study of the oxidation by periodate of methyl 4 : 6-*O*-benzylidene-α-D-guloside, -idoside, and -galactoside has shown that the specific rotation at the end of the oxidation is the same in each case (Fig. 11), suggesting that the same product

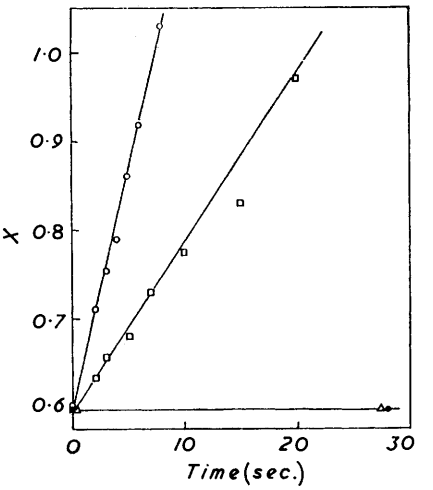
is formed. Methyl 4 : 6-*O*-benzylidene-β-D-galactoside and -β-D-guloside gave the same hemialdal monohydrate. Methyl 4 : 6-*O*-ethylidene-α-D-glucoside and -α-D-mannoside gave the same hemialdal, which crystallised from concentrated aqueous oxidation solutions. The formation of this product was also followed polarimetrically (Fig. 12). [In each case the infrared spectrum showed the presence of hydroxyl but not carbonyl groups.]

FIG. 9. *Oxidation of 2-substituted methyl β* D-*glucopyranosides at* pH 4·06 *and* 25°.



2-*Substituent*:
○ O-*Methyl*. □ *Chloro-deoxy*.
△ O-*Benzoyl*.

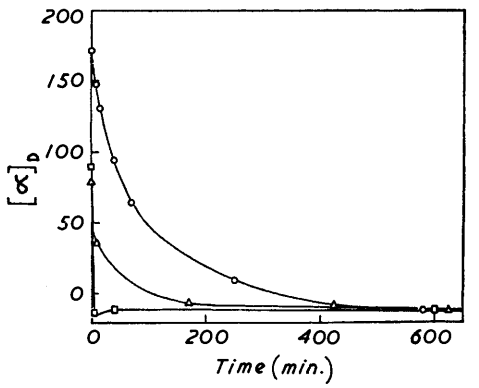
FIG. 10. *Oxidation of* cyclo*hexanediols at* pH 4·06 *and* 25°.



○ cis-1 : 2-*Diol*. □ trans-1 : 2-*Diol*.
△ cis-1 : 3-*Diol*. ● trans-1 : 3-*Diol*.

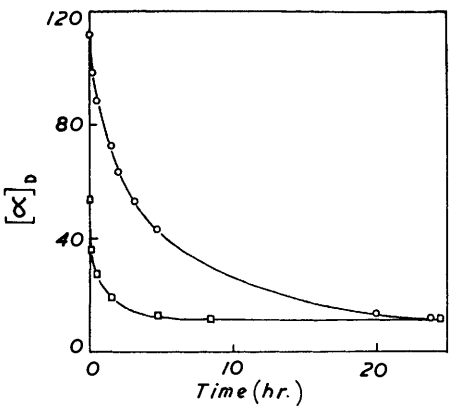
FIGS. 11 and 12. *Polarimetric analyses of* 4 : 6-*substituted methyl* α-D-*glycosides at* pH 4·06 *and room temperature* (ca. 20°).

FIG. 11.



4 : 6-*Substituent*: O-*Benzylidene*
○ *Galactoside*. □ *Guloside*. △ *Idoside*.

FIG. 12.



4 : 6-*Substituent*: *O*-Ethylidene.
○ Glucoside. □ Mannoside.

By comparing the second-order rates of periodate oxidation with the extent of reaction with cuprammonium solution,[2,3] measured by the decrease in conductivity on addition of the glycol, the close parallel between the two reactions has been further qualitatively demonstrated for the methyl 4 : 6-*O*-benzylidene-α-D-glycosides (Table 2). Cuprammonium solution has been shown to have a substantial conductivity decrement with

[10] Guthrie and Honeyman, *J.*, 1959, 2441.

both *cyclo*hexane-1 : 2-diols, the effect of the *cis*-compound being greater than that of the *trans*.[11] This agrees with the reaction of these compounds with periodate.

The similarity between the reactions of periodic acid and lead tetra-acetate has been discussed at length.[12] Although the rate of glycol cleavage with lead tetra-acetate has been considered in relation to the constitution of the glycol,[13,14] little attention has been paid to the effect of the conformation of the glycol.

Experimental

Optical rotations were measured in chloroform solution, unless otherwise stated.

Materials.—The periodate and buffer solutions were prepared as described in Part III.

Methyl 4 : 6-*O*-benzylidene-α-D-glucoside and the β-anomer,[15] prepared from methyl α- and β-D-glucopyranoside, respectively, had m. p. 164—165°, $[\alpha]_D^{18}$ +110·2° (*c* 1·2), and m. p. 198—200°, $[\alpha]_D^{18}$ −65·2° (*c* 0·96), $[\alpha]_D^{23}$ −77·8° (*c* 0·87 in water). The method of Irvine and Scott [16] was also used to prepare the α-anomer but the second isomer which they obtained was not isolated.

Methyl 4 : 6-*O*-benzylidene-α-D-altroside [17] and the β-anomer [18] were prepared from the corresponding glucosides, and had m. p. 170—171°, $[\alpha]_D^{18}$ +115° (*c* 1·4), and m. p. 188·5—189°, $[\alpha]_D^{20}$ −64° (*c* 1·0 in acetone), respectively. Methyl 4 : 6-*O*-benzylidene-α-D-mannoside [19] had m. p. 143—144°, $[\alpha]_D^{19}$ +63·2° (*c* 1·1). Methyl 4 : 6-*O*-benzylidene-α-D-guloside had m. p. 144—145°, $[\alpha]_D^{20}$ +80·3° (*c* 0·83), $[\alpha]_D^{22}$ + 88·9° (*c* 1·8 in water), and the β-anomer had m. p. 174—175°, $[\alpha]_D^{20}$ −88° (*c* 1·0). Methyl 4 : 6-*O*-benzylidene-α-D-idoside, prepared from the corresponding galactoside by Sorkin and Reichstein's method,[20] had m. p. 148—149°, $[\alpha]_D^{25}$ +48·8° (*c* 0·76). Methyl 4 : 6-*O*-benzylidene-α-D-galactoside [21] and the β-anomer,[20] prepared from methyl α- and β-D-galactopyranoside, respectively, had m. p. 166—167°, $[\alpha]_D^{21}$ +143·6° (*c* 1·6), and m. p. 199—200°, $[\alpha]_D^{22}$ −33·2° (*c* 1·3). Methyl 4 : 6-*O*-ethylidene-α-D-glucoside [22] and the β-anomer,[23] prepared from methyl α- and β-D-glucopyranoside and 1 : 1-dimethoxyethane, had m. p. 76—77°, $[\alpha]_D^{19}$ +111·3° (*c* 1·2 in water), and m. p. 188—189°, $[\alpha]_D^{20}$ −74° (*c* 1·9 in water). Methyl 4 : 6-*O*-ethylidene-α-D-mannoside, prepared from methyl α-D-mannopyranoside and paraldehyde,[24,25] had m. p. 116·5—117·5°, $[\alpha]_D^{19}$ +76·5° (*c* 1·4). Methyl 4 : 6-*O*-propylidene-α-D-glucoside [26] had m. p. 102°, $[\alpha]_D^{18}$ +122° (*c* 0·60). Methyl 4 : 6-*O*-butylidene-α-D-glucoside [27] had m. p. 108°, $[\alpha]_D^{20}$ +112·9° (*c* 2·4). Methyl 4 : 6-*O*-*iso*propylidene-α-D-guloside [28] had m. p. 132—134°, $[\alpha]_D^{20}$ +88·9° (*c* 1·8). Methyl α-D-glucoside 4 : 6-(hydrogen phosphate) [5] was prepared from the *cyclo*hexylamine salt by passage through Amberlite Ion-Exchange Resin IR-120 (H), in an aqueous solution which was used directly for oxidation by periodate. Methyl α-D-glucoside 4 : 6-(phenyl phosphate) [5] had m. p. 196—197°, $[\alpha]_D^{20}$ +100·8° (*c* 1·2 in ethanol). Methyl 4 : 6-di-*O*-methyl-α-D-altropyranoside [29] was obtained as a syrup, $[\alpha]_D^{20}$ +147° (*c* 0·50 in water), which has not been crystallised.

Phenyl β-D-glucopyranoside (5 g.), powdered anhydrous zinc chloride (3 g.), and benzaldehyde (redistilled, 20 ml.) were shaken at room temperature for 24 hr. in a stoppered flask filled with nitrogen. After being left at 0° overnight, the resulting jelly was shaken with ice–water (250 ml.), a solid then separating. This was filtered off and washed successively with

[11] Kwart and Gatos, *J. Amer. Chem. Soc.*, 1958, **80**, 881.
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[27] Ansell, Ph.D. Thesis, University of London, 1951, p. 97.
[28] Buchanan, *J.*, 1958, 995.
[29] Robertson and Dunlop, *J.*, 1938, 472.

sodium hydrogen sulphite (10% aqueous solution, 200 ml.), saturated aqueous sodium hydrogen carbonate (100 ml.), water (100 ml.), and light petroleum (b. p. 60—80°; 1 l.) before being dried. Recrystallisation from aqueous ethanol gave feathery needles of phenyl 4 : 6-*O*-benzylidene-β-D-glucoside (1·8 g., 27%), m. p. 196—197°, $[\alpha]_D^{17}$ −66·5° (*c* 1·1 in pyridine). McCloskey and Coleman [30] give m. p. 194·5—195° (corr.), $[\alpha]_D^{25}$ −56·5° (*c* 2 in acetone).

Other compounds used were: methyl 4-*O*-methyl-α-D-glucopyranoside,[31] m. p. 94—95°, $[\alpha]_D^{25}$ +167° (*c* 1·2 in water); methyl 4-*O*-methyl-β-D-glucopyranoside,[32] m. p. 102—103°, $[\alpha]_D^{20}$ −18° (*c* 1·0 in water); methyl 4-*O*-methyl-α-D-mannopyranoside, m. p. 101—102°, $[\alpha]_D^{20}$ +83·9° (*c* 0·80 in water); methyl 4-chloro-4-deoxy-α-D-glucopyranoside,[28] m. p. 114—114·5°, $[\alpha]_D^{21}$ +130·9° (*c* 1·0 in water); methyl 4-*O*-tosyl-α-D-glucopyranoside,[33] m. p. 148—149°, $[\alpha]_D^{22}$ +107·6° (*c* 1·1 in ethanol); methyl 4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside,[33] m. p. 146—147°, $[\alpha]_D^{20}$ +74·9° (*c* 1·3); methyl 2-deoxy-α-D-glucopyranoside,[34] m. p. 90—91°, $[\alpha]_D^{20}$ +135° (*c* 0·67 in water); methyl 2-*O*-methyl-α-D-glucopyranoside, m. p. 147—148°; methyl 2-*O*-methyl-β-D-glucopyranoside, m. p. 97—98°; methyl 2-*O*-tosyl-α-D-glucopyranoside, m. p. 138—139°; methyl 2-chloro-2-deoxy-β-D-glucopyranoside, m. p. 163—164°; methyl 2-*O*-benzoyl-β-D-glucopyranoside,[35] m. p. 174—177°, $[\alpha]_D^{13}$ −1·8° (*c* 1·8 in acetone); methyl 2-*O*-methyl-α-D-altropyranoside,[36] m. p. 81—83°, $[\alpha]_D^{15}$ +111·6° (*c* 1·0); *p*-nitrophenyl 2-*O*-methyl-β-D-glucopyranoside,[37] m. p. 178—179°, $[\alpha]_D^{23}$ −90·2° (*c* 4·0 in aqueous ethanol); 7-(4 : 6-*O*-benzylidene-β-D-glucopyranosyl)theophylline,[7] m. p. 272—273°; methyl 3-amino-4 : 6-*O*-benzylidene-3-deoxy-α-D-altroside, m. p. 188—190°; *cis-cyclo*hexane-1 : 3-diol,[38] m. p. 85—85·5°; *trans-cyclo*hexane-1 : 3-diol,[38] m. p. 118—118·5°; *cis-cyclo*hexane-1 : 2-diol,[39] m. p. 98—99°; *trans-cyclo*hexane-1 : 2-diol,[40] m. p. 103·5—104°; pentaerythritol, m. p. 259—261°.

Kinetic Measurements.—All oxidations were performed at 25° in the dark. Aqueous buffer solutions were used for the majority of the oxidations, but in a few cases, where the reactant was insufficiently soluble in water, aqueous ethanolic solutions were used. For the titrimetric determination of second-order rate constants an approximately threefold excess of periodate was used. The solutions were $3·5 \times 10^{-3}$M with respect to the reactant and 14×10^{-3}M with respect to periodate. This usually involved about 0·1 g. of the reactant in 100 ml. of solution. With compounds not oxidised by periodate (*e.g.*, *cis-* and *trans-cyclo*hexane-1 : 3-diol, pentaerythritol, and the anomeric methyl 4 : 6-*O*-benzylidene-D-altrosides) a wider range of excess of periodate (three- to twenty-fold) was used, in order to try to achieve reaction.[41] Control experiments were always carried out. Analysis for periodate was carried out by Müller and Friedberger's,[42] Fleury and Lange's,[43] Malaprade's,[44] or Neumüller and Vasseur's [45] method. The four methods gave consistent results, but Malaprade's method was much less accurate than the others. Because Müller and Friedberger's method was quickest and easiest to carry out, it was employed in most of the oxidations. With a small excess of periodate (roughly threefold) all the reactions studied were of second-order with respect to glycol and periodate.

If a and b are the initial concentrations of periodate and glycol (in mole $l.^{-1}$), respectively, and x is the decrease in concentration of periodate (also in mole $l.^{-1}$) at time t, then, if k_2 is the second-order rate constant, measured in l. $mole^{-1}$ $sec.^{-1}$,

$$\log_{10}[(a - x)/(b - x)] = t[k_2(a - b)/2·303] + \text{constant}$$

From the slope of a graph of $\log_{10}[(a - x)/(b - x)]$ (for which the symbol X is used in all the Figures) against t, k_2 was calculated. All the experiments were carried out in at least duplicate, the second-order rate constant being reproducible to within 3 or 4%.

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[45] Neumüller and Vasseur, *Arkiv Kemi*, 1953, **5**, 235.

Ultraviolet Spectrophotometric Measurements.[46,47,48]—The optical densities of approximately 10^{-4}M-solutions of periodate were measured at 2260 and 2340 Å, in the presence of various glycols, a Unicam model SP.500 spectrophotometer being used with 1-cm. silica cells. The buffer solutions and the glycols (approximately 10^{-4}M-solutions) absorbed only very slightly in this region but owing to the effect of ultraviolet light on periodate solutions, this procedure can be unreliable, and was used only when periodate oxidation was known not to occur. In such compounds (methyl 4 : 6-*O*-benzylidene-α-D-altroside, *cis-* and *trans-cyclo*hexane-1 : 3-diols, and pentaerythritol), no change in absorption occurred on adding the glycol, suggesting that no glycol–periodate complex was formed.

Polarometric Measurements.—Enough glycol to give an initial rotation of at least ±1·0° was dissolved in buffer solution, excess of sodium periodate solution was added, and the solution was made up to a known volume with buffer. After mixing, the solution was rapidly transferred to a polarimeter tube (2 dm.), and the values of the optical rotation were noted against time until a constant value was obtained. A graph of the rotation, or the specific rotation, against time, was plotted.

Isolation of Products of Oxidations.—Analytical results were confirmed by isolation of products whenever possible. A slight excess of oxidant was allowed to react with the glycol in concentrated solution. When the reaction was judged, on evidence from rate studies or optical rotation, to be complete, the ions were removed either by precipitation by barium hydroxide solution,[49] or by passage through ion-exchange resins.[50] In a few cases the product crystallised directly from the reaction solution and was collected.

Summary of Results.—All the rate constants (collected in Table 1) are of second order unless otherwise mentioned. Second-order rate constants, k_2, are recorded in 10^3 l. mole^{-1} sec.$^{-1}$, and first-order rate constants in sec.$^{-1}$. Typical results are: Methyl 4 : 6-*O*-benzylidene-α-D-glucoside was oxidised at pH 4·06 and 25°; k_2 2·82, 2·82, 2·92, 2·93 (mean 2·88). At pH 6·93 and 25°; k_2 1·34, 1·36 (mean 1·35). The product, 7 : 9-dihydroxy-6α-methoxy-2-phenyl-*trans-m*-dioxano[5,4-*e*][1 : 4]-dioxepan hydrate,[10] which crystallised directly from the oxidation solution, was filtered off, washed with water, and dried. It had m. p. 143—144°, $[\alpha]_D^{20}$ +61·8° (*c* 4·0 in pyridine). Methyl 4 : 6-*O*-benzylidene-β-D-glucoside, pH 4·06; 25°; k_2 1·13, 1·04, 1·13 (mean 1·10). The product, 7 : 9-*dihydroxy*-6β-*methoxy*-2-*phenyl*-trans-m-*dioxano*[5,4-e]-[1 : 4]-*dioxepan hydrate*, did not crystallise from the solution, but was obtained by passing it through ion-exchange resins, evaporation of eluates, extraction of residues with chloroform, and recrystallisation from acetone–light petroleum (40—60°). The product crystallised as clusters of white needles, m. p. 118—119°, $[\alpha]_D^{20}$ −25·0° (*c* 0·80 in water) (Found: C, 53·8; H, 6·5. $C_{14}H_{16}O_6,2H_2O$ requires C, 53·2; H, 6·3%). The infrared spectrum showed the absence of carbonyl groups and the presence of hydroxyl groups.

With methyl 4 : 6-*O*-benzylidene-α-D-altroside at pH 4·06 and 25° periodate was consumed, but the benzylidene group was hydrolysed, liberating benzaldehyde. Similar results were obtained at 25° in aqueous unbuffered solutions. At pH 4·06 and 0°, at pH 6·93 and 25°, and at pH 10·10 and 25°, periodate was not consumed during 2 days. From these experiments, the altroside was recovered nearly quantitatively.

At pH 4·06 and 25° the benzylidene group of methyl 4 : 6-*O*-benzylidene-β-D-altroside was hydrolysed. At pH 6·93 and 25°, and at pH 10·10 and 25°, periodate was not consumed during 1 day. These oxidations were carried out in a mixture of buffer and alcohol (95 : 5) since the altroside was insufficiently soluble in buffer solution.

The product of oxidation of methyl 4 : 6-*O*-benzylidene-α-D-mannoside crystallised from the solution and had m. p. 143—146°, undepressed on admixture with the product from the glucoside; the infrared spectra of the two products were identical.

The product from methyl 4 : 6-*O*-benzylidene-β-D-galactoside, 7 : 9-*dihydroxy*-6β-*methoxy*-2-*phenyl*-cis-m-*dioxano*[5,4-e][1 : 4]-*dioxepan hydrate*, crystallised from the concentrated aqueous oxidation solution; it had m. p. 118—119° (from water) (Found: C, 53·2; H, 6·4. $C_{14}H_{16}O_6,2H_2O$ requires C, 53·2; H, 6·3%). The m. p. and analysis agree with unpublished values obtained by Hewitt G. Fletcher, jun.

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TABLE 1. *Second-order rate constants (k_2 in 10^3 l. mole^{-1} sec.$^{-1}$) for oxidations by periodate in aqueous buffer solutions of* pH 4·06 *at* 25° *(unless otherwise stated). (Numbers in parentheses refer to the number of individual values determined from which the mean k_2 was calculated.)*

	k_2
Methyl 4 : 6-*O*-benzylidene-	
α-D-glucoside	2·88(4) [a]
β-D-glucoside	1·13(3)
α-D-altroside	0·00 [b]
β-D-altroside	0·00 [c]
α-D-mannoside	15·9(3)
α-D-guloside	319(2)
β-D-guloside	35·5(2)
α-D-idoside	6·41(4)
α-D-galactoside	3·69(4)
β-D-galactoside	2·09(3)
Methyl 4 : 6-*O*-ethylidene-	
α-D-glucoside	2·06(3) [d]
β-D-glucoside	0·757(3)
α-D-mannoside	14·4(4) [e]
Methyl 4 : 6-	
O-benzylidene-α-D-glucoside	2·88(4) [a]
O-ethylidene-α-D-glucoside	2·06(3) [d]
O-propylidene-α-D-glucoside	2·02(2)
O-butylidene-α-D-glucoside	$2·01_5$(3)
Methyl α-D-glucoside	
4 : 6-(hydrogen phosphate)	0·647(2)
4 : 6-(phenyl phosphate)	0·331(2)
Methyl 4-*O*-methyl-	
α-D-glucopyranoside	23·3(2)
β-D-glucopyranoside	18·7(2)
α-D-mannopyranoside	90·8(2)
Methyl 4-	
O-methyl-α-D-glucopyranoside	23·3(2)
chloro-4-deoxy-α-D-glucopyranoside	1·56(3)
O-tosyl-α-D-glucopyranoside	0·377(3)
O-tosyl-6-*O*-triphenylmethyl-α-D-glucoside	~0·2 [f]
Methyl 2-	
deoxy-α-D-glucopyranoside	~500
O-methyl-α-D-glucopyranoside	76·7(2)
O-tosyl-α-D-glucopyranoside	0·646(2)
O-methyl-β-D-glucopyranoside	81·8(2)
chloro-2-deoxy-β-D-glucopyranoside	5·55(1)
O-benzoyl-β-D-glucopyranoside	2·12(2)
Methyl 2-*O*-methyl-β-D-glucopyranoside	81·8(2)
p-Nitrophenyl 2-*O*-methyl-β-D-glucopyranoside	51·3(2)
Methyl 2-*O*-methyl-α-D-glucopyranoside	76·7(2)
altropyranoside	~5,000
*cis-cyclo*Hexane-1 : 2-diol	11,700(2)
*trans-cyclo*Hexane-1 : 2-diol	4,100(2)
*cis-cyclo*Hexane-1 : 3-diol	0·00
*trans-cyclo*Hexane-1 : 3-diol	0·00
Methyl 4 : 6-*O*-*iso*propylidene-α-D-guloside	644(2)
Methyl 4 : 6-di-*O*-methyl α-D-altropyranoside	48·5(3)
7-(4 : 6-*O*-Benzylidene-β-D-glucopyranosyl)theophylline	0·00 [g]
Methyl 3-amino-4 : 6-*O*-benzylidene-3-deoxy-α-D-altroside	2·11(2) [h]
Pentaerythritol	0·00

[a] 1·35(2) at pH 6·93 and 25°. [b] At 0°; hydrolysis occurred at 25°. [c] In ethanol–buffer solution (5 : 95) at pH 6·93. [d] 0·211(2) at pH 4·06 and 0°; in ethanol–buffer solution (50 : 50). [e] 1·55(2) at pH 4·06 and 0°; 5·22(2) at pH 4·06 and 12·9°. [f] In ethanol–buffer solution (50 : 50). [g] In ethanol–ethyl acetate–buffer solution (70 : 25 : 5). [h] At pH 6·93.

TABLE 2. *Reaction of α-glycols with periodate and with cuprammonium solutions.*

α-Glycol group at $C_{(2)}$–$C_{(3)}$ of methyl 4 : 6-*O*-benzylidene-α-D-glycoside (Cl)	Rate of reaction with periodate	Extent of reaction with cuprammonium solution
e,a *e.g.* mannoside	rapid	medium
e,e *e.g.* glucoside	slow	small
a,a *e.g.* altroside	zero	none

The product of oxidation of methyl 4 : 6-*O*-benzylidene-β-D-guloside crystallised from a concentrated aqueous oxidation solution, and had m. p. and mixed m. p. with the corresponding galactoside product, 117—119°.

Methyl 4 : 6-*O*-ethylidene-α-D-glucoside on oxidation gave 7 : 9-*dihydroxy*-6α-*methoxy*-2-*methyl*-trans-m-*dioxano*[5,4-e][1 : 4]-*dioxepan*, which crystallised from a concentrated oxidation solution, and, after recrystallisation from water containing a few drops of dimethyl sulphoxide, had m. p. 143—144°, $[\alpha]_D^{20}$ +13·6° (*c* 0·90 in water) (Found: C, 45·3; H, 6·7. $C_9H_{14}O_6,H_2O$ requires C, 45·7; H, 6·8%). The infrared spectrum showed the absence of carbonyl groups, but the presence of hydroxyl groups.

Methyl 4 : 6-*O*-ethylidene-α-D-mannoside on oxidation gave the same product, m. p. 140—141°, $[\alpha]_D^{20}$ +13·5° (*c* 1·0 in water), as was given by methyl 4 : 6-*O*-ethylidene-α-D-glucoside (compared by m. p. and infrared spectrum).

With methyl 4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside in alcohol–buffer (50 : 50) there was considerable reduction in concentration of periodate in the blank during the long period required for completion of reaction, and this continually changing concentration made reproducible results hard to obtain.

At 25° 7-(4 : 6-*O*-benzylidene-β-D-glucopyranosyl)theophylline showed no uptake of periodate in 8 days in alcohol–ethyl acetate–buffer solution (pH 4·06) (70 : 25 : 5).

At pH 4·06 and 25° there was a very slow reduction of periodate by methyl 3-amino-4 : 6-*O*-benzylidene-3-deoxy-α-D-altroside: 0·2 mole after 147 hr. with a threefold excess of periodate, and 0·3 mole after 314 hr. with a seventeenfold excess of periodate. The product had m. p. 134—138°, undepressed when mixed with the oxidation product from methyl 4 : 6-*O*-benzylidene-α-D-glucoside; the infrared spectra of the two products were identical.

At 25° and pH values of 4·06, 6·93, and 10·10, with a two- to ten-fold excess of periodate, *cis-cyclo*hexane-1 : 3-diol was not oxidised during 7 days, and was quantitatively recovered after the removal of inorganic ions. At pH 4·06 and 25°, with a two- to ten-fold excess of periodate, the *trans*-1 : 3-diol was not oxidised during 6 days, and was quantitatively recovered.

At pH 4·06 and 25°, periodate was not reduced by pentaerythritol during 72 hr. with either a three- or a ten-fold excess of periodate. The pentaerythritol was isolated unchanged (95%) from the reaction solutions.

Phenyl 4 : 6-*O*-benzylidene-β-D-glucoside (*A*) was very slowly oxidised by periodate at 25° in alcohol–ethyl acetate–buffer solution (pH 4·06) (70 : 20 : 10). For comparison, methyl 4 : 6-*O*-benzylidene-α-D-glucoside (*B*) was also oxidised in this medium. Rate constants were not calculated, since in this medium there was a considerable fall off in the blank due to the reduction of periodate by solvents.

	Mol. of periodate reduced				
Time (hr.)	0	7	30	66	92
B in water	0·0	0·61	1·00	1·03	1·09
B in alcoholic medium	0·0	0·05	0·11	0·23	0·30
A in alcoholic medium	0·0	0·0	0·02	0·06	0·12

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