599. *Hydrogen Transfer to Quinones. Part III.*[1] *Conformational Effects on the Kinetics of Hydrogen Transfer from Carbohydrates.*

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It has been shown previously that in aqueous solutions of alcohols the energy of photo-excited quinones is degraded by processes (*a*) and (*b*) (see below). Values of k_1/k_0 for various α- and β-D-aldopyranoses, methyl α- and β-D-aldopyranosides, and polypyranoses are now discussed in relation to variation in conformation. It is concluded that one side of the pyranose ring is more reactive than the other, owing to steric hindrance. In β-galactose, the most reactive of the free sugars studied here, three axial and one equatorial C–H bond on the unhindered side form a very reactive grouping, and replacement of any of these C–H by C–OH bonds reduces the reactivity. *O*-Methylation at position 1 of monosaccharides decreases the reactivity, again for steric reasons.

In the autoxidation of alcohols in aqueous solution photo-sensitized by sodium anthraquinone-2-sulphonate the energy of the photo-excited quinonoid sensitizer is degraded by two processes:[2]

(*a*) $$\mathrm{Q^*} + \mathrm{RH} \xrightarrow{k_1} \cdot\mathrm{QH} + \mathrm{R}\cdot$$

(*b*) $$\mathrm{Q^*} \xrightarrow{k_0} \mathrm{Q}$$

The radicals R· produced in the hydrogen transfer (*a*) subsequently react very rapidly to produce peroxy-radicals:[3]

$$\mathrm{R}\cdot + \mathrm{O_2} \xrightarrow{k_3} \mathrm{RO_2}\cdot$$

with $k_3 \gg k_1$, and the semiquinone reverts rapidly to the quinone form,

$$\cdot\mathrm{QH} + \mathrm{O_2} \xrightarrow{k_2} \mathrm{Q} + \mathrm{HO_2}\cdot$$

with $k_2 \gg k_1$. All subsequent reactions of $\mathrm{RO_2}\cdot$ and $\mathrm{HO_2}\cdot$ are very rapid compared with (*a*). Reaction (*b*) is a first-order, adiabatic, radiationless transfer from the photo-excited state to the ground state.[2] The rate of oxygen absorption obeys the equation [1,2]

$$\frac{1}{-\mathrm{d}[\mathrm{O_2}]/\mathrm{d}t} = \frac{1}{I} + \frac{1}{I} \cdot \frac{k_0}{k_1} \cdot \frac{1}{[\mathrm{RH}]},$$

where I is the rate of activation, proportional to the intensity of the incident light. Values of k_1/k_0 can be calculated from this equation; if one sensitizer is used, they constitute a measure of the relative reactivity to the sensitizer.[1,2] It has been shown that, with sodium anthraquinone-2-sulphonate as sensitizer, the oxidation is a direct hydrogen-atom transfer to the photo-excited quinone, with attack only at C–H bonds α to hydroxyl groups in alcohols.[2,4] Values of k_1/k_0 have been determined for a range of alcohols, polyalcohols, ethers, and ketones [1] and a suitable extrapolation of this towards cellulose is the measurement of k_1/k_0 values for simple sugars.

Reeves [5] has confirmed that the simple sugars described in this paper exist in the C1 chair form (I) in solution, McDonald and Beevers,[6] by *X*-ray crystallography, that

[1] Part II, *Trans. Faraday Soc.*, 1961, **57**, 1719.
[2] Wells, *Trans. Faraday Soc.*, 1961, **57**, 1703.
[3] Bolland and Cooper, *Proc. Roy. Soc.*, 1954, *A*, **225**, 405.
[4] Wells, *Nature*, 1956, **177**, 483.
[5] Reeves, *Adv. Carbohydrate Chem.*, 1951, **6**, 108.
[6] McDonald and Beevers, *Acta Cryst.*, 1952, **5**, 654.

solid α-D-glucose exists in the chair form with axial and equatorial C–OH bonds, and Ferrier [7] that β-D-glucose exists in the chair form with equatorial C–OH bonds.

Barton [8] showed that, owing to close packing of axial groups, equatorial are more easily esterified than axial hydroxyl groups, that equatorial esters are the more easily hydrolyzed, and that in chromic acid oxidation of CH·OH groups, where only the α-C–H bond is attacked, the equatorial C–H bond is the more readily attacked. Bentley [9] observed that, in general, β-sugars (having an axial C–H bond at position 1) are more readily attacked than α-sugars by chlorine or bromine; he showed that in the few cases where the α-anomer is the more rapidly attacked, there is an axial C–H bond at position 1. Although Bentley's numerical values need qualification [10] his conclusions remain correct; in the absence of a knowledge of the exact mechanism of attack by chlorine and bromine on sugars, it is impossible to give a reason for the apparent reversal in this case.

The reactivities of cyclohexanediols to hydrogen transfer from α-C–H bonds to photo-excited sodium anthraquinone-2-sulphonate have been discussed in relation to Barton's postulate.[1] Cyclohexanediols obeyed the rule in a qualitative way, but other factors are evidently involved in causing the different reactivities of the *cis*-1,2- and the *cis*-1,4-diol. For methyl α- and β-D-glucoside the rule did not apply,[1] as the β-anomer (axial C–H bond at position 1) is more reactive than the α-anomer, as found for attack by chlorine or bromine.[9]

This oxidation by the photo-excited anthraquinone-2-sulphonate ion provides a means of examining the variation of reactivity in sugar rings with conformation, as the mechanism of the initial attack of the photo-excited quinone in aqueous solution is precisely known.

Experimental

Materials.—For the free sugars, the starting material for D-glucose and D-xylose was B.D.H. " AnalaR " stock; cellobiose and D-galactose were Kerfoot's Biochemical Reagents. α- and β-D-Glucose were prepared by Hudson and Dale's method; [11] the final sample of α-glucose, after considerable pumping in a vacuum, had $[\alpha]_D^2$ +110°; β-glucose had $[\alpha]_D^8$ +19°. α- and β-D-Galactose were prepared by Hudson and Yanovsky's method; [12] the final sample of α-galactose had $[\alpha]_D^{20}$ +144°; that of β-galactose had $[\alpha]_D^{20}$ +52°. α-D-Xylose was prepared by washing the D-xylose several times with 60% ethanol at 0°; the final sample had $[\alpha]_D^{20}$ +90°. β-D-Cellobiose was prepared by washing cellobiose with water at 0°, addition of acetone to the solution, washing the resultant precipitate with absolute ethanol and ether, and drying at 65°; it had $[\alpha]_D^{20}$ +16°. β-D-Mannose was a Gurr's Bacteriological Reagent and had $[\alpha]_D^{20}$ −16°. All rotations were determined for aqueous solutions by extrapolation to zero time.

β-Methyl cellobioside was supplied by Dr. D. I. MacGilvray and recrystallized from aqueous ethanol. Methyl α-D-mannoside, also supplied by Dr. D. I. MacGilvray, was recrystallized twice from water. Sucrose was B.D.H. " AnalaR " material, recrystallized from water.

All purified samples of sugars were finally thoroughly dried by pumping on a high-vacuum line, then stored in stoppered bottles in a desiccator.

Sodium anthraquinone-2-sulphonate was purified as described previously.[2]

Apparatus and Procedure.—These were as described earlier.[1,2] An oxygen pressure of 250 mm. was used throughout this work. Light from the ultraviolet lamp passed through a Chance O.X.1 filter fixed behind the quartz window of a small thermostat tank.

For sugars with a fixed configuration at position 1 the procedure was the same as for the other substrates.[1] For free sugars the rate of mutarotation was measured polarimetrically at 0°: application of the equation established by Kendrew and Moelwyn-Hughes [13] for opposing unimolecular reactions in the mutarotation of glucose and xylose showed that more than 95% of the sugars remained in the original anomeric form after 30 min. in aqueous solution at 0°.

[7] Ferrier, *Acta Cryst.*, 1960, **13**, 678.
[8] Barton, *Experientia*, 1950, **6**, 316; *Quart. Rev.*, 1956, **10**, 44.
[9] Bentley, *Nature*, 1955, **176**, 870; *J. Amer. Chem. Soc.*, 1957, **79**, 1720.
[10] Barker, Overend, and Rees, *Chem. and Ind.*, 1960, 1297, 1298.
[11] Hudson and Dale, *J. Amer. Chem. Soc.*, 1917, **39**, 320.
[12] Hudson and Yanovsky, *J. Amer. Chem. Soc.*, 1917, **39**, 1013.
[13] Kendrew and Moelwyn-Hughes, *Proc. Roy. Soc.*, 1940, *A*, **176**, 352.

This gives sufficient time to achieve an accurate initial rate of oxygen uptake with the following technique. A 3×10^{-4}M-aqueous solution (20 ml.) of sodium anthraquinone-2-sulphonate was cooled to 0°, the weighed sugar was quickly dissolved in this solution, and a portion (10 ml.) was pipetted into the chilled reaction vessel, which was then attached to the manometric apparatus and surrounded by the tank of water at 0°. The usual procedure [2] was followed for filling with oxygen, attaining gas–liquid equilibria, and determining the initial rate of oxygen uptake, except that the apparatus was filled with oxygen only once. Oxygen uptake was measured for long enough to assess an accurate initial rate, by which time the period between dissolving the sugar and ending the measurements was well outside the 30 min. allowed for retention of >95% anomeric form; but the actual initial rate period was within the 30 min. from dissolution of the sugar.

Results and Discussion

Plots of $1/(-\mathrm{d}[O_2]/\mathrm{d}t)$ against 1/[substrate] for all the monosaccharides and methyl glycosides are given in the Figure. They are all linear with a constant intercept on the ordinate, as found for the simple alcohols, ethers, and ketones.[1] The values of k_1/k_0 and

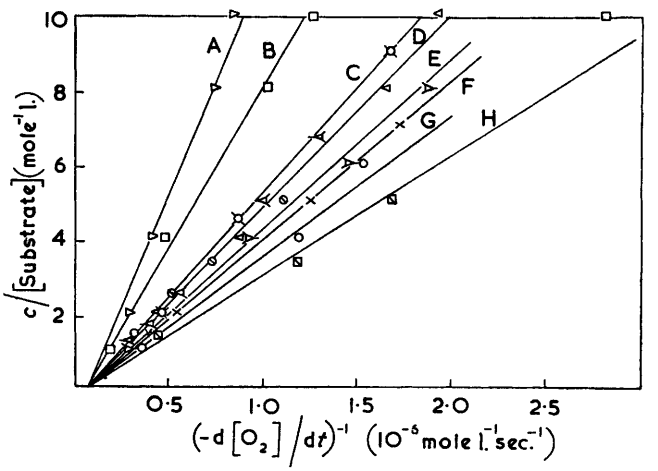


Photo-sensitized oxidation of monosaccharides and methyl glycosides at 0°. Concentration of sodium anthraquinone-2-sulphonate = 3×10^{-4}M.

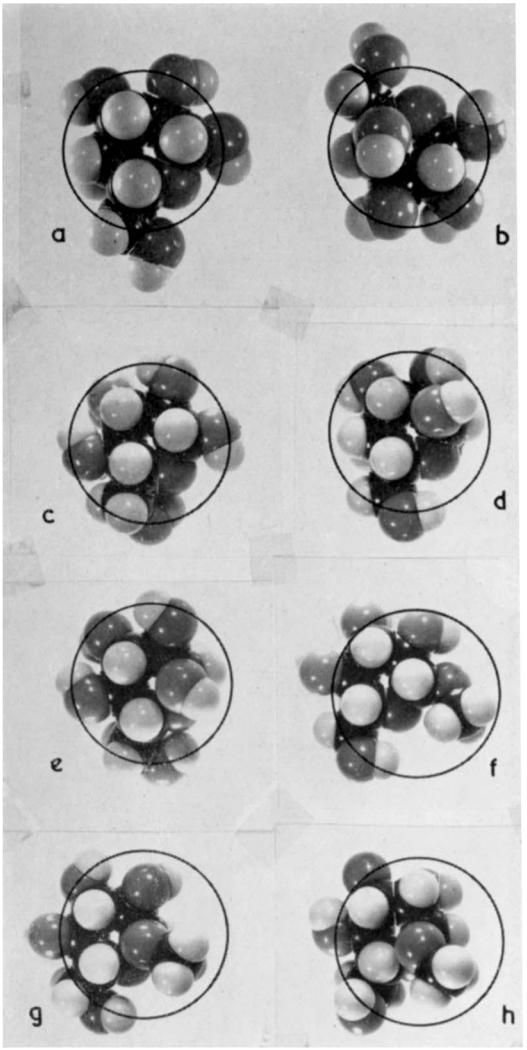
○ α-D-Glucose,; □ β-D-glucose; ▷ β-D-galactose; ◁ α-D-galactose; × methyl α-D-mannopyranoside; ➢ α-D-xylose; ≺ sucrose; ▨ methyl α-D-glucopyranoside; ⓘ methyl β-D-glucopyranoside; ♌ β-D-mannose.

All $c = 1$ except β-D-mannose, $c = 0{\cdot}5$.

k_1/k_{EtOH} calculated from the slopes and intercepts of the plots are given in Table 1, which also includes earlier values for methyl α- and β-D-glucopyranoside.[1] The observation for the methyl glucosides that the β- is the more reactive anomer is seen to be true also for the free sugars glucose and galactose. There is little difference between the reactivities of

Table 1.

Carbohydrate	k_1/k_0	k_1/k_{EtOH}	Carbohydrate	k_1/k_0	k_1/k_{EtOH}
Me β-D-glucopyranoside ...	0·440	0·99	β-D-Glucose	0·700	1·57
Me α-D-glucopyranoside ...	0·258	0·58	α-D-Glucose	0·298	0·67
Me α-D-mannopyranoside...	0·348	0·78	α-D-Xylose	0·364	0·82
β-D-Mannose	0·910	2·04	β-D-Cellobiose	1·36	3·06
β-D-Galactose	0·980	2·20	Me β-D-cellobioside	1·36	3·06
α-D-Galactose	0·440	0·99	Sucrose	0·422	0·95



Molecular models of sugars.

(a) β-D-Galactose. (b) β-D-Galactose. (c) β-D-Glucose. (d) α-D-Galactose. (e) α-D-Glucose. (f) Methyl β-D-glucopyranoside. (g) Methyl α-D-glucopyranoside. (h) Methyl α-D-mannopyranoside.

(b) is viewed from above the pyranose ring; all the others from below.

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α-D-xylose and α-D-glucose, and therefore the primary alcohol group at position 6 cannot be the point where the major attack of the photo-excited quinone occurs. Moreover, reactivity changes when the orientation of the secondary CH·OH groups is changed, suggesting that attack of the photo-excited quinone is indiscriminate, in agreement with observations on the oxidation products of methyl glucosides.[14]

Table 1 shows that, of the monosaccharides tested, β-D-galactose (II) is the most reactive and so may contain a particularly reactive grouping. Plate (a) shows the approach to a model from below the ring and Plate (b) shows the approach from above the ring. Plate (b) shows that the "upper side" of the molecule has a big cluster of hydroxyl groups, with their attendant hydration in aqueous solution: presumably these will greatly hinder the approach of the larger quinone to the few C–H bonds lying on this side.[1] Plate (a) shows that the "under side" contains a cluster of three axial hydrogen atoms (at positions 1, 3, and 5), and one equatorial hydrogen atom (at position 4) (white atoms inside the circle), with a comparatively unhindered approach. Similarly, β-D-mannose (III), which has a high reactivity approaching that of β-D-glactose, has on the uninhibited "under side" three axial C–H bonds (at positions 1, 3, and 5) and an equatorial C–H bond (at position 2), and on the upper side only one axial C–H bond (at position 4) surrounded by hydroxyl groups.

Among the D-galactoses and D-glucoses, reactivity decreases in the order β-D-galactose > β-D-glucose > α-D-galactose > α-D-glucose. Plates (c), (d), and (e) show the approach from the under side of β-D-glucose, α-D-galactose, and α-D-glucose respectively. It is apparent from these models and from Table 2 that this decrease in reactivity can be

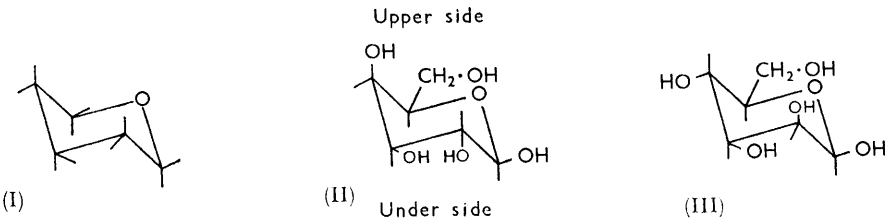


TABLE 2.

Disposition of C–H bonds at positions 1—5 of pyranose rings of carbohydrates.

	Under side		Upper side		
Carbohydrate	axial	equatorial	axial	equatorial	k_1/k_{EtOH}
β-D-Galactose	3	1	1		2·20
β-D-Mannose	3	1	1		2·04
β-D-Glucose	3		1	1	1·57
α-D-Galactose	2	1	2		0·99
α-D-Glucose	2		2	1	0·67

correlated with the total number of axial and equatorial C–H bonds on the uninhibited under side, *i.e.*, the C–H bonds within the circles, an axial being easier to remove than an equatorial hydrogen atom. In accord with this, methyl α-D-mannopyranoside [Plate (h)] is more reactive than methyl α-D-glucopyranoside [Plate (g)], as the former has the easily approachable equatorial C–H bond at position 2. Clearly, a C–H bond in the pyranose ring is more reactive on the under than on the upper side; on the under side an axial is more reactive than an equatorial C–H bond.

Any mechanism involving reaction with hydroxyl groups, such as was postulated [9] for other oxidants to make the results compatible with attack at equatorial groups only, is out of the question. The oxidation is specific to transference of hydrogen from α-C–H

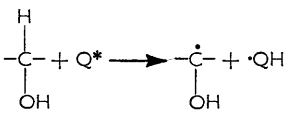
[14] Lock, unpublished work.

bonds:[2,4] any possibility of complex-formation between Q* and hydroxyl groups before this hydrogen transfer is eliminated because the plots in the Figure have the same intercept on the ordinate as was found for simple alcohols and ethers.[1,2]

Models show that the reactive assembly of C–H bonds at positions 1, 3, and 5 of β-D-glucose persists uninhibited in cellobiose. In agreement, the reactivity of cellobiose is twice that of β-D-glucose. In sucrose the fructofuranose unit is possibly less reactive than the glucopyranose unit.

Table 1 shows that there is a reduction in reactivity with *O*-methylation at position 1. This is contrary to the increased reactivity on methylation at the α-carbon atom in alcohols;[1] but it is comparable with the reduction in reactivity with methylation in ethers, which was suggested as due largely to steric hindrance of the reactive hydrogen atoms.[1] The smaller decrease in reactivity from α-D-glucose to methyl α-D-glucopyranoside than from β-D-glucose to methyl β-D-glucopyranoside is in agreement with steric hindrance as the cause of the reduced reactivity here: Plates (f) and (g) show that the β-methoxy-group is better able to inhibit the reactive grouping on the under side, especially the hydrogen at position 1, than is the α-methoxy-group where there is no hydrogen on the under side at position 1. However, methylation at position 1 appears to have no effect on the reactivity of cellobiose.

From the above it is apparent that a group of hydrogen atoms on the under side of the pyranose ring will be preferentially attacked by Q*, owing to inhibition of the reaction by the cluster of large hydroxyl groups, and possibly by the ring-oxygen atom, and their attendant water of hydration that are on the upper side. Most of the C–H bonds on the under side are axial, and an axial is attacked in preference to an equatorial C–H bond, which is contrary to Barton's postulate that equatorial groups *in general* are attacked in preference to axial groups. Presumably the equatorial hydrogen atoms in the cyclohexanediols are more reactive[1] than the axial hydrogen atoms owing to the absence of the large number of hydrated hydroxyl groups. However, there may be an additional reason why the axial C–H's on the under side are attacked in sugars. The closer packing of axial groups involves greater repulsion in axial than in equatorial positions. In a reaction involving abstraction of hydrogen to form a free radical, such as:



the repulsion energy of the hydrogen will assist the reaction. Nevertheless, the models (see the Plate) and Table 2 suggest that steric inhibition is the main factor responsible for the variation of reactivity with conformation in the sugars.

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