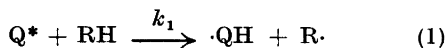


A Comment on J. A. Christiansen's Interpretation¹ of Experiments² by C. F. Wells on Reactivities of Hydrogen Atoms in Carbohydrates

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The present author² has determined the reactivities of various sugars and glycosides in the transfer of a hydrogen atom^{3,4} to photo-excited sodium anthraquinone-2-sulphonate Q* as a ratio of k_1/k_0 for,



He assumed that the sugars exist in the pyranose C1 conformation of Reeves,⁵ with the C—H and C—OH bonds disposed in equatorial and axial positions, as normally accepted: in particular, at carbon 1, the β -anomer has an axial C—H bond and the α -anomer an equatorial C—H bond. On this basis, he showed that the variation of reactivity among the sugars depended upon the number of C—H bonds projecting on the "underside" of the pyranose ring. This correlation is clearly shown in

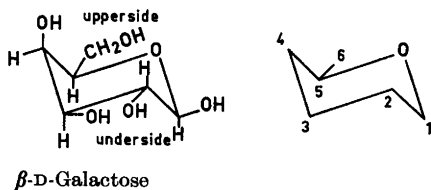


Table 1 for the free sugars (a misprint appeared in a similar table in Ref.²: the upperside dispositions for β -D-glucose and β -D-galactose were interchanged, but this did not affect the argument in the paper), with an axial more reactive than an equatorial C—H bond on the underside. It was suggested that the reactivity was greater on the underside due to the greater shielding of the upperside by the hydroxyl groups and their attendant hydration from the approach of the large Q*: molecular models were examined to show this effect (see the Plate in Ref.²). It had previously been shown⁶ that increasing hydration in poly-

alcohols reduces reactivity at individual >CHOH sites in the alcohol. Table 1 also indicates that a grouping of three axial hydrogen atoms on carbon atoms 1, 3, and 5, projecting on the underside, is particularly reactive, and it was suggested that the repulsion of these closely packed hydrogen atoms may also contribute to the high reactivity when the product of the hydrogen transfer is a free radical, as in this case (see eqn. 1).

However, Christiansen¹ has used these numerical reactivities determined by the present author in an attempt to show that the conformation at carbon 1 in the α - and β -anomers of glucose and galactose is the reverse of that normally accepted, *i.e.* he says that the β -anomer has an equatorial C—H bond and the α -anomer an axial C—H bond at carbon 1 (Part I of Ref.¹). In Part II of his paper he uses these results in an attempt to show that axial hydrogen atoms in the pyranose ring are completely unreactive, *i.e.* he says that all reactivity is due to the equatorial hydrogen atoms in the ring and the primary hydrogen atoms on carbon atom 6. These conclusions made by Christiansen are completely unacceptable to the present author, who regards the reasoning leading to them as fallacious owing to the following:

1. The disposition of all C—OH bonds, and therefore, with the tetrahedral arrangement found for the carbon atoms, of all C—H bonds, has been definitely established by X-ray crystallography for α -D-glucose by McDonald and Beevers⁷ and for β -D-glucose by Ferrier.⁸ These references were quoted in Ref.² by the present author: carbon 1 has an axial C—H bond for the β -anomer and an equatorial C—H bond for the α -anomer. Dissolving in neutral aqueous solution does not change these conformations at carbon 1 under the conditions of the oxidations experiments at 0°C:² such a change would merely involve mutarotation. The present author has shown² that, for the sugars used in Ref.², immediately after being dissolved in neutral aqueous solution at 0°C, the rate of oxidation is much faster than the rate of mutarotation. These conformations for D-glucose in the solid phase have been confirmed from a more detailed analysis of the crystallographic data for β -D-glucose by Ferrier,⁹ and have also been found by X-ray crystallography for α -D-glucose monohydrate by Killean, Ferrier and Young¹⁰ and for cellobiose by Jacobson, Wunderlich and Lipscomb.¹¹

Table 1. Disposition of C—H bonds at carbon atoms 1–5 in the free sugars.

Sugar	underside		upperside		k_1/k_0
	axial	equatorial	axial	equatorial	
β -D-Galactose	3	1	1	—	0.98
β -D-Mannose	3	1	1	—	0.91
β -D-Glucose	3	—	2	—	0.70
α -D-Galactose	2	1	1	1	0.44
α -D-Glucose	2	—	2	1	0.30

Table 2. Disposition of C—H bonds at carbon atoms 1–5 in the methylglycosides.

Glycoside	underside		upperside		k_1/k_0
	axial	equatorial	axial	equatorial	
Methyl β -D-glucopyranoside	3	—	2	—	0.44
Methyl α -D-mannopyranoside	2	1	1	1	0.35
Methyl α -D-glucopyranoside	2	—	2	1	0.26

2. In discussing reactivity at equatorial and axial positions, Christiansen does not differentiate between C—H bonds disposed on the upperside and on the underside. Clearly, an equatorial C—H bond on the underside is more reactive than an axial C—H bond on the upperside (see Ref.² and Table 1 above). However, the real point in Ref.² is that *any* site is more reactive when its C—H bond is disposed on the underside than on the upperside, independent of axial or equatorial arrangement. It was therefore concluded that Barton's rule,¹² which states that equatorial positions are more reactive than axial positions, originally postulated from an examination of the reactivities of molecules where steric hindrance is absent such as disubstituted cyclohexanes, does not necessarily apply to more complex situations such as polyhydroxylated pyranose rings where special steric conditions exist, like the hydration of the hydroxyl groups. Consequently, this rule cannot be used to classify bonds as equatorial or axial in sugar rings, as suggested by Christiansen.¹ It should be noted, however, that data for hydrogen atom transfer to Q* from simple situations, the cyclohexanediols, obey Barton's rule, as expected.⁹

Table 2 shows that k_1/k_0 for the methylglycosides can also be correlated with the number of C—H bonds projecting on the underside, as done above for the free sugars in Table 1. k_1/k_0 cannot be correlated with the *total number* of equatorial C—H bonds in either Table 1 or Table 2. As mentioned above, it is clear from Table 1 that, on the underside, an axial C—H bond is more reactive than an equatorial C—H bond;² this is further supported by Table 2. An examination of models shows that the hydration on the upperside will be able to hinder the removal of an equatorial more than an axial hydrogen atom on the underside. No change is needed in this interpretation of the oxidative reactivities of C—H bonds in the pyranose ring originally made by the present author.²

The statistical treatment on pp. 2212 and 2213 of Christiansen's paper of the variation between the numerical differences of k_1/k_0 for α - and β -anomers has no justifiable basis.

3. The results cannot be used, as they have been by Christiansen in both Parts I and II, to draw conclusions depending on arithmetical agreement to *one* place in the third significant figure of values for k_1/k_0 . The accuracy of these ratios is probably

better represented by the values of k_1/k_{EtOH} given in Ref.² or the values of k_1/k_0 shown in Tables 1 and 2.

4. In Part II Christiansen bases his argument for the non-reactivity of axial hydrogen atoms on a comparison of reactivities for ethanol and α -D-glucose. The present author has clearly shown that such quantitative comparisons cannot be made:⁶ the reactivities of sugars, with many reactive sites, are less than the reactivities of alcohols and ethers with only one reactive site, due to the inhibiting hydration in the sugars and possibly the electron-attracting inductive effect of β -, γ -, and δ -hydroxyl groups. The only estimate that can be made about the primary hydrogen atoms on carbon atom 6 is by comparing α -D-xylose ($k_1/k_0 = 0.36$) with α -D-glucose ($k_1/k_0 = 0.30$), where the environments are the same: the conclusion here is that the steric inhibition by carbon atom 6 must outweigh the reactivity contributed by the two primary hydrogen atoms, which is the opposite of what Christiansen suggests from a comparison of ethanol and α -D-glucose. Moreover, the reactivity of a secondary C—H bond (such as present in the ring) is, in general, more reactive than that of a primary C—H bond.⁶ Thus, the conclusions of Table 2 in Christiansen's paper are invalid.

Christiansen also suggests that the reactivity of the C—H bonds α to the hydroxyl group in ethanol is dependent on the orientation of the methyl group in the β -position, with he suggests, three significant orientations. There is no sound basis for this suggestion, and the present author has clearly shown⁶ that the alkyl groups influence reactivity quantitatively through the electron-releasing inductive effect when allowance has been made for the number of C—H bonds α to the hydroxyl group.

5. The low reactivity of methanol is adequately explained by the attack of Q* on the methyl group only. The reactivity of methanol fits in quantitatively with the other monohydric alcohols when inter-

preted on the influence of the inductive effect.⁶ The effect of methylation in the sugars on carbon 1 is adequately explained by the screening by the methoxy group of the reactive C—H bonds in the ring:² reactivity at positions α to the glycoside link are analogous to ethers, not alcohols; and in ethers increasing alkylation reduces reactivity.⁶

Points 1, 2, and 3 above vitiate the conclusions reached by Christiansen in Part I, and points 3, 4, and 5 vitiate his conclusions in Part II. Moreover, the present author has shown⁶ that the interpretation of the reactivities in terms of molecular "collisions" is not as simple as stated by Christiansen on p. 2211 of his paper. No change is required in the interpretation of the reactivities of sugars in hydrogen atom transfer to Q* made by the present author,² and this interpretation is supported by the additional structural information and the analysis of reactivities for the methylglycosides given here.

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