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On Reactivities of Hydrogen Atoms in Carbohydrates and the Assignment of Structures to α- and β-Anomers of Pyranoses. An Interpretation of Experiments by C. F. Wells

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In part I the temperature-independent reactivities of pyranoses determined by Wells are analyzed. It seems hardly possible to avoid the conclusion from the analysis that in sugars with C1 conformation (Reeves) the assignment of the configurations E and A of the HO-group at C_1 to the α- and β-anomers is α-E, β-A. The analysis shows that equatorial hydrogen atoms in the same ring are interchangeable. This has numerical consequences which are compatible with the facts if and only if the assignment mentioned above be adopted.

In part II it is shown that probably only equatorial hydrogen atoms are subject to the Wells-reaction, hydrogen atoms in methoxyl-groups seem to be non reactive, but the carbon bonded hydrogen in the $HOCH_2$-group does certainly react. A table showing the distribution of the reactivity on substituents at C_1, C_2, C_4 and C_5 is given.

PART I

Wells has embodied his results [1-4] concerning the photosensitized autoxidation of carbohydrates and other alcohols in a recent paper [1] in the Journal of the Chemical Society. He interprets his results in terms of differences in steric hindrance. This concept is certainly indispensable to structural chemistry but it has the drawback that its application can only lead to qualitative conclusions. One of the reasons for this is that velocities of chemical reactions are, in most accessible cases, determined mainly by heats of activation and less by spatial conditions. But Wells has succeeded in determining a temperature independent quantity, a ratio between two velocity constants which are both independent of temperature. Therefore his results must yield information on the steric factors determining this ratio. He has not, however, fully utilized this advantage in so far as he has not tried to use his results to get independent information on the structures of the carbohydrates investigated. On the contrary, Wells takes the configurations for granted and then draws qualitative conclusions concerning the reactivity of hydrogen atoms in the

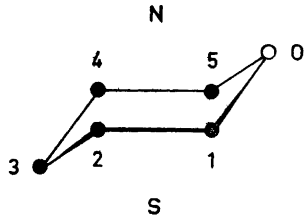

Fig. 1. The figure shows the conformation C1 (Reeves), supposed to be the C, O skeleton of D-pyranoses. Its mirror image 1C is supposed to be the skeleton of L-pyranoses. Heavy lines are above, or on the western side of, the plane of the paper. If 1,2,4,5 are on the equator, N is the north pole.

different positions from his measurements. However, his experimental method is so elegant and his measurements so accurate that it seems promising to use them for drawing more definite conclusions concerning the spatial arrangement of the atoms in the carbohydrate molecules, independently of information from other sources. The following is an attempt to do so.

A selection of substances investigated by Wells [1,3] is listed in Table 1. With three obvious exceptions all these compounds contain the pyranose ring. According to the investigations by Hassel and Ottar [5] and by Reeves [6] the conformation of this ring is for the D-series the one designated by Reeves as the C1 conformation. This has been confirmed by numerous X-ray investigations, and no serious criticism can be raised against it.

A nearly indispensable tool for visualizing the structures in question is a commercially available set of atomic models of the kind used by Wells.[1] The models should simulate the easy rotation of two single-bonded atoms relatively to each other.

If the carbon atoms are numbered according to the usual Fischer-Haworth convention, the carbon skeleton becomes the one shown in Fig. 1. Denoting the direction 1→2→3 as westward, the upper side of the ring becomes the north (N) side and the under side the south (S) side. According to Hassel and Ottar, and to Reeves the hydrogen atom at C_5 is axial on the south side (a_S). On the north side at most two and on the south side at most three hydrogen atoms can be axially located. We shall use the convention that the anomer having its hydroxyl group at C_1 in the equatorial (e) position is the E-form, the one having it in the axial (a_S) position being the A-form.

Wells has investigated the photochemical autoxidation (oxidation by oxygen) of different alcohols including those in Table 1. The reaction is sensitized by sodium anthraquinone-2-sulphonate, denoted in his equations by Q. He assumes and proves the validity of a sequence of reactions now to be described: In the first step Q is photo-activated by absorption of light:

$$\text{Light} + Q \rightarrow Q^*$$

Q * meaning the photo-activated form of Q.

The activated form may either become deactivated spontaneously, its excess energy becoming dissipated into the surrounding liquid, or it may remove a single hydrogen atom from the solute in question. The latter reaction results in the formation of two radicals, a semiquinone radical ·QH and the remainder R· of the alcohol RH. Only hydrogen atoms bound to a carbon atom which is itself bound to a hydroxyl group are attacked. Wells uses the expression that only hydrogen atoms which are "α" to a hydroxyl-group are

attacked. Both radicals are swiftly removed in further reaction steps, not requiring absorption of light. These steps need not concern us here as the velocity of autoxidation becomes determined by the velocity of the reaction

$$Q^* + RH \rightarrow \cdot QH + R\cdot \quad (1)$$

Writing the spontaneous deactivation process as

$$Q^* \rightarrow Q \quad (0)$$

we see that the fraction of the absorbed radiation utilized for causing the oxidation must be $k_1[RH]/(k_1[RH]+k_0)$, k_1 being a bimolecular and k_0 a unimolecular velocity constant. Wells states that both are independent of temperature. His further kinetic treatment shows that the reciprocal velocity of the autoxidation is a linear function of $k_0/k_1[RH]$. Inside small random deviations this agrees with his experiments. From the experiments he calculates the ratio k_1/k_0, in the following paragraphs denoted by r. Wells having measured concentrations in mole/litre, r has the dimension of a molar volume expressed in l/mole. As k_0 is independent of the nature of the reactant RH, r becomes a (relative) measure of the reactivity of different reactants with the activated molecule Q.* We may also say that r is a measure of the probability in unit time for Q * to react with the reactant in question. Finally, k_1 and k_0 being independent of temperature, r may be considered as a measure of the spatial accessibility of the reactant RH for Q,* because we may assume that every collision between Q * and the hydrogen atom in question leads to removal of the latter. These properties of the reactivity r indicate that it should be made up as a sum of partial reactivities, one for each mode of reaction. It is this additive property we are going to use in the sequel.

At first we try to calculate the difference in reactivity between an equatorial and an axial (a_N) hydrogen atom at C_4. To this end we may use the reactivities of α-D-galactose and α-D-glucose, the corresponding difference being 0.142 l/mole. Now, even if we ignore the assignment of α- and β-anomers to the E- and A-forms, we know that in the α-anomers of the two sugars the configurations at all the carbon atoms, including C_1 but excluding C_4, are equal. At C_4 we know the configurations from the classical works of E. Fischer, and

Table 1. Reactivities in l/mole according to C. F. Wells.

Substance	r	Substance	r
α-D-glucose	0.298	β-D-glucose	0.700
α-D-galactose	0.440	β-D-galactose	0.980
		β-D-mannose	0.910
Me α-D-glucoside	0.258	Me β-D-glucoside	0.440
Me α-D-mannoside	0.348		
		β-D-cellobioside	1.36
		Me β-D-cellobioside	1.36
Sucrose	0.424		
Ethanol	0.445		
Methanol	0.054		

of Haworth, combined with the Hassel-Ottar-Reeves model of the pyranose ring: In D-galactose the hydrogen at C_4 is equatorial, but in D-glucose it is axial (a_N). Therefore the difference between the reactivities of the hydrogen atom at C_4 in the equatorial and in the axial position respectively is 0.142 l/mole. Proceeding in the same manner with the β-pair: D-galactose, D-glucose we get the difference $r(H4e)-r(H4a_N) = 0.280$ l/mole. Thus the hydrogen in the 4e position is more reactive than the one in the $4a_N$ position. That the latter quantity is different from the former one will be discussed later.

Similarly we get for the β-pair: D-mannose, D-glucose the difference $r(H2e)-r(H2a_N) = 0.210$ l/mole. Thus at C_4 and C_2 hydrogen atoms are no doubt more reactive in the equatorial than in the axial position. This agrees with a rule suggested by Barton [7,8] and quoted by Wells.[1] Inspection of the model shows, that owing to less shielding by neighbouring groups, equatorial hydrogen atoms are in fact exposed to attack from a greater fraction of the surrounding space than are axial ones. Wells quotes measurements showing the effect in oxidations by chromic acid, and Blom [11] quotes the experiments by Isbell and Pigman [9,10] on oxidation by bromine which point to the same. Incidentally, a fuller account of the literature concerning the preferred oxidation of equatorial hydrogen atoms is given by Blom.[11]

We now turn to the location of the hydrogen atom at C_1. From the reactivities in Table 1 we see, that β-D-glucose is more reactive than the α-anomer, the difference being 0.402 l/mole. Similarly we find from the pair β,α-D-galactose the corresponding difference to be 0.540 l/mole. This is evidently just the opposite effect of that to be expected if Barton's rule and the current assignment, α-A, β-E, were both valid: If Barton's rule is valid at C_1 the hydrogen in the β-anomer at this atom must be equatorial, but the current assignment requires it to be axial. Therefore one or the other of the two assumptions must be wrong. Concerning Barton's rule, inspection of the model shows that an equatorial hydrogen at C_1 is even more exposed to attack from the surrounding space than are the ones at C_2 and at C_4, its neighbour to the east being barely the ring oxygen. However, it might be argued that C_1 is unique in the pyranose ring by having two oxygen atoms as neighbours, while none of the other carbon atoms have more than one. This might certainly have an effect on the strength of the C_1-H bond. But again inspection of the model shows, that a hydrogen atom at C_1 is placed symmetrically with respect to the two heighbouring oxygen atoms whether it is equatorial or axial. Therefore, an effect on the difference in reactivity arising from the uniqueness of C_1 cannot reasonably be expected and we are left with the very strong suspicion that the assignment should be α-E, β-A and not the current one.

This has an important bearing on the somewhat surprising result concerning the difference in reactivity between equatorial and axial hydrogen atoms at C_4. From the α-pair: D-Galactose, D-glucose we calculated the difference 0.142 l/mole while the corresponding β-pair yielded 0.280 l/mole for a quantity which should be the same in the two cases. Now, tentatively accepting the assignment α-E, β-A, α-galactose has only one equatorial hydrogen, the one at C_4, while β-D-galactose has two, one at C_1 and one at C_4. Thus we have in the β-anomer two hydrogen atoms distributed on two equatorial sites. This distribution can be effected in two ways by interchange of the two atoms. For each

of these ways we get a difference between the reactivities of the equatorial (4e) and the axial ($4a_N$) hydrogen atom which should equal that calculated from the α-pair: D-galactose, D-glucose, 0.142 l/mole. Therefore the difference calculated from the β-pair must be divided by two to become comparable to the one from the α-pair. Thus we get from the β-pair 0.140 l/mole and from the α-pair 0.142 l/mole for the difference at C_4. In the sequal we shall adopt the mean value 0.141 and ascribe the deviations to the experimental uncertainty.

If, on the other hand, we had adopted the α-A, β-E assignment, the same argument would have required that the difference derived from the α-pair should be divided by two to be comparable to that derived from the β-pair that is, the quantities 0.071 l/mole and 0.280 l/mole should be comparable. Evidently therefore, the statistical consideration yields an additional and very strong support to the validity of the assignment α-E, β-A.

If we adopt the latter assignment and use the statistical argument we derive from the β-pair: D-mannose, D-glucose the difference at C_2 to be 0.105 l/mole.

The difference at C_1 we calculate from the values for the two D-glucoses at 0.402 l/mole. That it is so much larger than those at C_2 and C_4 may have two causes. In the first place an equatorial hydrogen atom at C_1 is evidently less shielded by its surroundings than are the other two equatorial atoms. In the second place the uniqueness of C_1 may have something to do with the extraordinary high reactivity of the hydrogen at this carbon atom.

PART II

In part I we have only discussed differences in reactivity between hydrogen atoms in the two possible positions. We may now ask whether it might be possible to arrive at absolute values. Actually the answer seems to be yes.

Wells has determined the reactivity of ethanol at 0.445 l/mole. In this molecule there must be three orientations of the CH_3-group equally favourable for removal of the two hydrogen atoms in the $HOCH_2$-group. For each orientation the reactivity is therefore 0.148_3 l/mole. The same group appears in all the sugars so far discussed. According to the model there are two orientations relatively to the pyranose ring which are nearly (not exactly) equally favourable for reaction. From comparison of the models of ethanol and, *e.g.*, that of α-D-glucose it appears that the spatial accessibility of the pair of hydrogen atoms for each of the favourable positions in α-D-glucose must be about the same as it is in one of the favourable orientations in ethanol. Therefore we expect half of the reactivity of α-D-glucose minus the reactivity of the remaining axial hydrogen atoms to equal 0.148_3 l/mole. The half reactivity of the glucose being 0.149 we arrive at the conclusion, that axial hydrogen atoms do not react at all. This result, the all-or-none effect, is corroborated by the Wells reactivities of cyclohexanols, in particular that of *myo*-inositol, but a discussion of these reactivities must be postponed to a separate paper.

It is a question how we are to interpret the all-or-none effect. One possible interpretation may be that the anthraquinone sensitizer is so large and has such a form that it can only contact equatorial and not axial hydrogen atoms. But it may seem, that such an extreme case of steric hindrance be not very

Table 2. Distribution of Wells-reactivities on substituents at C_1, C_2, C_4 and C_5 in carbohydrates. Estimated by the author, totals to be compared with Table 1.

	CH_2OH,5e	H,1e	H,2e	H,4e	Total
α-D-glucose	0.298	0	0	0	0.298
β-D-glucose	0.298	0.402	0	0	0.700
α-D-galactose	0.298	0	0	0.141	0.439
β-D-galactose	0.298	0.402	0	2 × 0.141	0.982
β-D-mannose	0.298	0.402	2 × 0.105	0	0.910
Me α-D-glucoside	0.258	0	0	0	0.258
Me β-D-glucoside	0.258	0.182	0	0	0.440
Me α-D-mannoside	0.258	0	0.090	0	0.348

probable. Next, one might believe that the effect be due to an appreciable difference in strength of the two kinds of C—H bonds. Buth this is impossible because it is known [12] that the equilibrium constant for the mutarotation of D-glucose is to all intents and purposes independent of temperature. Perhaps the effect could be ascribed to differences in spin or spin orientation of the atoms implied in the reaction. Such differences would, at least, not cause a traceable influence of temperature on the equilibrium constant just mentioned, but it would certainly be premature to discuss this possibility in detail.

Table 2 shows the distributions of the reactivities on the groups at the four carbon atoms for compounds investigated by Wells. Besides previously discussed compounds the table includes his reactivities of three methylated sugars. They show that the reactivity of the $HOCH_2$-group is a little less in the methylated than it is in the non-methylated compounds. This may be understood as being due to the bulky CH_3O-group at C_1 which is not very distant from the $HOCH_2$-group at C_5. That the reactivity of the equatorial hydrogen at C_1 in Me β-D-glucopyranoside is less than half the corresponding quantity in the non methylated sugars may be due to a large shielding effect of the axial methoxyl-group at the same carbon atom, C_1.

At C_2, in D-mannose, the two reactivities are, respectively, 0.105 and 0.090 l/mole, showing a distinct but not very large shielding effect from the neighbouring methoxyl-group at C_1.

Furthermore Table 2 shows that the hydrogen in the methyl group in H_3CO- is most probably non reactive. This may seem odd because there are three hydrogen atoms being "α" to an oxygen atom in this group. Table 1, however, shows that the reactivity of methanol is very small, only 0.054 l/mole. Whatever that may mean, it shows, that its hydrogen atoms are very little if at all reactive. This evidently supports the statement above, that the hydrogen in the methyl group of the methylated sugars is non-reactive. One might be tempted to believe that in methanol and in this alcohol alone, the only reactive hydrogen atom is the oxygen-bonded one.

At present nothing much can be said of the reactivities of the di-saccharides. It seems quite natural that the reactivity of β-D-cellobiose is nearly twice that of β-D-glucose, but it is puzzling that the methylated compound has the same reactivity as that of the non-methylated one, while the reactivity of β-D-

glucose is certainly larger than that of the Me β-D-glucoside. It is also puzzling that sucrose, which contains three $HOCH_2$-groups has a reactivity which is less than three halves of that of one such group. Evidently the structures of the disaccharides are too complicated to permit at present a detailed discussion of these results.

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