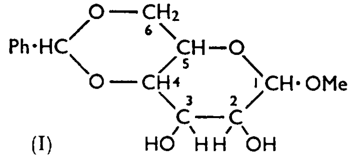
705. *Intramolecular Hydrogen Bonding in Methyl* 4,6-O-*Benzylidene*-D-*aldohexosides.*

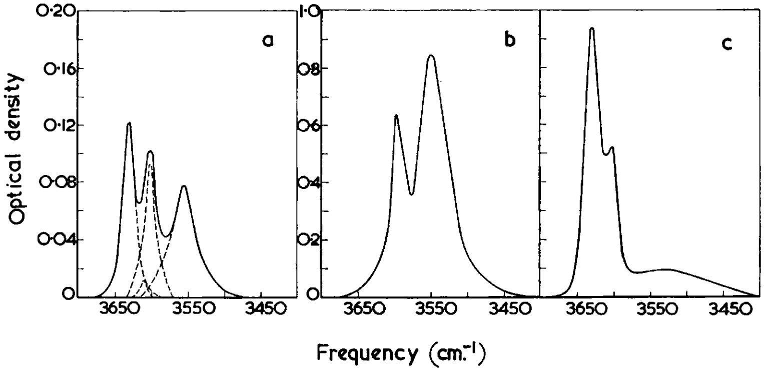
By H. Spedding.

Measurement of intramolecular hydrogen bonding provides information about the conformation of the pyranose ring in several methyl 4,6-*O*-benzylidene-D-aldohexosides. The C1 chair conformation is predominant, but its exact shape probably varies slightly. Hydrogen bonding in methyl 4,6-*O*-benzylidene-α-D-altroside and its two methyl derivatives is incomplete.

In methyl 4,6-*O*-benzylidenealdohexopyranosides (I), a hydroxyl-hydrogen atom can be bonded to the oxygen atom of the second hydroxyl group or to an acetal oxygen atom (either in a ring or on $C_{(1)}$) provided that the distance involved is not too great. Kuhn[1] found intramolecular hydrogen bonding in diols only if the calculated distance between the hydrogen atom of one hydroxyl group and the oxygen atom of the other was less than 3·3 Å. He also showed that intermolecular hydrogen bonding was avoided if the diols were examined as <0·005M-solutions in dry carbon tetrachloride: infrared absorption near 3630 cm.$^{-1}$ is then due to free secondary hydroxyl groups, and a decrease in frequency indicates hydrogen-bond formation, the size of the shift indicating the length of the hydrogen bond.[1]


(I)

Spectra, in hydroxyl stretching region, of 4,6-O-*benzylidene derivatives of* (a) *methyl* α-D-*altroside,* (b) *methyl* 2-O-*methyl*-α-D-*altroside, and* (c) *methyl* 3-O-*methyl*-α-D-*altroside in* CCl_4 (a, <0·005M; b, c, ~0·005M).



Peaks: a, 3630, 3601, 3556; b, 3596, 3548; c, 3629, 3602 cm.$^{-1}$.

If the molecule exists in one conformation only, then the maximum number of hydroxyl stretching bands is two: if the frequencies coincide then there is only one band. The spectrum of every diol, except one, measured in the present work under Kuhn's conditions showed either one pronounced band or two bands of the same order of intensity (as measured by maximum optical density).* The exception was the methyl α-D-altroside derivative whose spectrum (see Fig. a) showed three bands of the same order of intensity (plus a very weak shoulder at *ca.* 3610 cm.$^{-1}$). This anomaly is considered separately below and is excluded from the main discussion. Since, in general, only the upper limit

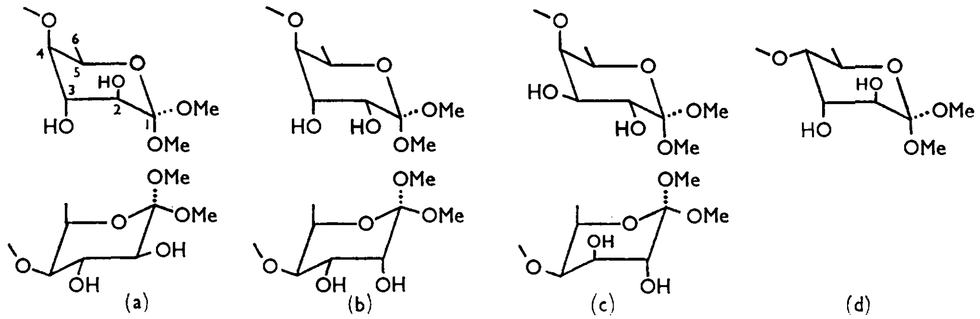
---

* The spectra of three of these diols showed an additional but very much weaker shoulder.

[1] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.

of concentration was known, extinction coefficients could not be determined. Band frequencies and peak optical densities are shown in the Table.

Reeves predicted, and it has been confirmed, that most of the common D-sugars exist in the C1 conformation (Reeves's designation).[2] Formulæ (IIa—d) show the C1 and, where possible, the 1C conformations for the methyl 4,6-*O*-benzylidene-D-aldohexosides principally discussed below. Molecular models of the various C1 diols showed only one instance where a hydroxyl group would be hydrogen-bonded very weakly or not at all, namely, that on $C_{(3)}$ in the methyl β-D-idoside derivative (IIa) where the hydroxyl-hydrogen atom is *ca.* 3·2 Å from the nearest oxygen (that in the pyranose ring), and there was indeed a band at the " free " value of 3629 cm.$^{-1}$ in the spectrum of this compound. All other hydroxyl bands in the diols occurred at frequencies at least 14 cm.$^{-1}$ lower. For the methyl α-D-guloside derivative one band was shifted drastically, to 3517 cm.$^{-1}$; for the methyl α-D-idoside derivative there was only one band and that was also at a very low frequency (3533 cm.$^{-1}$). In the C1 conformation both these compounds have a pair of *cis*-axial C–O bonds at $C_{(1)}$ and $C_{(3)}$, and the latter compound also has a second such pair at $C_{(2)}$ and $C_{(4)}$. In these circumstances very close approach is possible between a hydroxyl group (*e.g.*, that on $C_{(3)}$) and an acetal oxygen atom (*e.g.*, that on $C_{(1)}$). (It is only in the same few cases that the hydrogen bond leads to a six-membered rather than a five-membered ring.) This arrangement causes a considerable decrease in the hydroxyl frequency, as shown by comparing the value for the bonded hydroxyl frequency [1] in *cis*-cyclohexane-1,3-diol (3544 cm.$^{-1}$) with those in the cyclohexane-1,2-diols (*cis*, 3587;



(II)

Methyl 4,6-O-benzylidene-α-D-aldohexosides: (*a*) idoside, (*b*) guloside, (*c*) galactoside, (*d*) altroside.
Top row: C1 conformations.
Bottom row: 1C conformations.
. . . . denotes orientation in the β-anomers.

Band frequencies (cm.$^{-1}$) *and peak optical densities* (*in parentheses*).

Compound	α-Anomer	β-Anomer
Methyl 4,6-*O*-benzylidene-		
-D-glucoside	3609 (0·34), 3578 (0·29)	3614 (0·20), 3603sh (0·18) *
-D-galactoside	3591 (0·40) **	3615sh (0·15), 3602 (0·16) †
-D-mannoside	3611 (0·47), 3597 (0·42)	—
-D-guloside	3593 (0·69), 3517 (0·74)	3610 (0·57), 3598sh (0·52)
-D-idoside	3533 (0·97)	3629 (0·24), 3564 (0·16)
-D-altroside	3630 (0·12), 3601 (0·10), 3556 (0·08) ‡	3600 (0·74)
-2-*O*-methyl-D-altroside	3596 (0·64), 3548 (0·85)	—
-3-*O*-methyl-D-altroside	3629 (0·93), 3602 (0·52) §	—

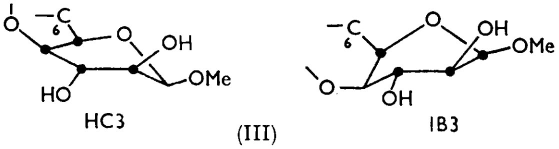
Very weak shoulders at * *ca.* 3559 cm.$^{-1}$; ** 3617 cm.$^{-1}$ and (doubtful) at *ca.* 3576 cm.$^{-1}$; † *ca.* 3546 cm.$^{-1}$; ‡ *ca.* 3610 cm.$^{-1}$. § Broad, weaker band at *ca.* 3525 cm.$^{-1}$.

---

[2] See Ferrier and Overend, *Quart. Rev.*, 1959, **13**, 265, and references therein.

trans, 3602). Of all the other diols in the C1 conformation—the methyl α-D-altroside still excluded—only the methyl β-D-idoside derivative has such a pair of axial C–O bonds. The lower-frequency band in this compound is at 3564 cm.$^{-1}$, which is 31 cm.$^{-1}$ higher than for the α-anomer. Since the frequencies of a free 2-hydroxyl group in both anomers should be within a few wave-numbers of each other, this difference when the group is hydrogen-bonded is interpreted as a small increase in the length of the hydrogen bond in the β-anomer. Such an increase in the $(C_{(2)}\cdot O-)H\cdots O(-C_{(4)})$ distance could be produced by a slight alteration in the shape of the pyranose ring, caused by the change in substitution at $C_{(1)}$; in any one conformation the ring is not rigidly fixed.^{2} This flexibility of the pyranose ring may similarly account for other differences in the frequencies of hydroxyl groups whose hydrogen atoms could lie at equal shortest distances from other oxygen atoms were the ring rigid, *e.g.*, the two hydroxyl groups in the α-D-glucoside and α-D-galactoside derivative [the orientation of groups on the pyranose ring in the former derivative is as shown in (II) for the galactoside, except that the $C_{(4)}$–O bond is equatorial in the glucoside in the C1 conformation]. Also the 3-hydroxyl group should be able to approach the oxygen on $C_{(1)}$ equally closely in the methyl α-D-guloside derivative and the methyl α-D-idoside derivative, yet there is a difference of 16 cm.$^{-1}$ in the frequencies of the corresponding bands. In this instance another factor can also arise: the 3-hydroxyl group in the methyl α-D-guloside derivative can be hydrogen-bonded at its oxygen atom (to the hydrogen of the 2-hydroxyl group) as well as at its hydrogen atom, but this is not possible in the methyl α-D-idoside derivative.

The results obtained are not only consistent with the existence of the pyranose ring in the C1 conformation in all the compounds, but also provide evidence against the 1C conformation in most of the instances where it has to be considered; throughout, these conformations refer to the D-series (4,6-*O*-benzylidene derivatives of glucosides, mannosides, and altrosides could not be formed if the ring were in the 1C conformation). Thus in the 1C conformation, the methyl α-D-idoside derivative and the methyl α-D-guloside derivative do not have a pair of *cis*-axial C–O bonds which the spectra indicate to be present in them, and the methyl β-D-idoside derivative would not have a free hydroxyl group, while the methyl β-D-galactoside derivative could have a very short hydrogen bond (between the 3-hydroxyl and the $C_{(1)}$-oxygen which would both be axial) that would give rise to a hydroxyl absorption band at a much lower frequency than actually found.



(III)

● Planar atoms.

The conformations of some methyl 4,6-*O*-benzylidene-D-aldohexosides have been studied previously in aqueous systems.^{3,4} The evidence from periodate oxidation ^{3} and cuprammonium complex formation ^{4} shows that the two hydroxyl groups in the methyl α-D-idoside derivative cannot be entirely in an axial-axial arrangement, as they would be in the C1 conformation. The experimental results would, in fact, be consistent with the 1C conformation. Evidence for the conformation of the methyl β-D-idoside derivative is not so definite. Thus complex formation with cuprammonium, which should occur readily if the pyranose ring were 1C, is poor.^{4} After reconsidering the evidence from complex formation Bentley recently concluded ^{5} that the conformation of the β-anomer under the experimental conditions employed is somewhere between a half-chair and a

---

[3] Honeyman and Shaw, *J.*, 1959, 2455.

[4] Reeves, *J. Amer. Chem. Soc.*, 1950, **72**, 1499.

[5] Bentley, *J. Amer. Chem. Soc.*, 1960, **82**, 2811.

skew, forms which he designates HC3 and 1B3 respectively (see III). Examination of models shows that the slightest tendency for the C1 conformation to change towards HC3 considerably increases the $(C_{(2)}\cdot O-)H\cdots O(-C_{(4)})$ distance, and the deviation in ring shape would have to be very slight to be consistent with the hydroxyl band frequency of 3564 cm.$^{-1}$ found in the present work, if the 2-hydroxyl group were still hydrogen-bonded to the oxygen atom on $C_{(4)}$. In the HC3 conformation, however, it could be hydrogen-bonded to $O_{(1)}$ instead. In fact the distance $(C_{(2)}\cdot O-)H\cdots O_{(1)}$ is slightly less than in the C1 conformation, though not as small as the distance $(C_{(2)}\cdot O-)H\cdots O(-C_{(4)})$ when the $C_{(2)}-O$ and $C_{(4)}-O$ bonds are truly axial. It may be small enough to be consistent with a band frequency of 3564 cm.$^{-1}$, although this seems unlikely. The 3-hydroxyl group would still be free in the HC3 conformation. If the pyranose ring were in the 1B3 form, however, both hydroxyl groups could be hydrogen-bonded to the adjacent acetal oxygen atoms and there would not be a " free " hydroxyl absorption band at 3629 cm.$^{-1}$, as is the case. For these reasons we conclude that in dilute carbon tetrachloride solution the half-chair form HC3 may possibly exist, but not the skew form 1B3. It might be expected that the importance of intramolecular forces, such as hydrogen bonding, in determining conformation could depend greatly on the external medium, and this must be borne in mind when comparing the results of the different measurements on the methyl-D-idoside derivatives, and also the methyl α-D-altroside derivative (see below).

Methyl 4,6-*O*-benzylidene-α-D-altroside is now to be considered. Periodate oxidation [3] shows that this compound exists in the C1 conformation in aqueous solution, but the presence of more than two bands in the spectrum indicates that the compound exists in carbon tetrachloride solution as an equilibrium mixture of more than one form [it was checked that the extra absorption band(s) was not due to any hydroxyl-containing impurity, and moreover the spectrum of a dilute solution of the compound in carbon disulphide also showed three bands]. The spectra of the 2-*O*-methyl and the 3-*O*-methyl derivative of this compound, measured under the same conditions as for the diols, support this idea, for it appears that a similar equilibrium also exists in each of these. Thus each spectrum shows more than one band (Fig.). For the 2-*O*-methyl derivative there are bands at 3596 and 3548 cm.$^{-1}$ and for the other at 3629 and 3602 cm.$^{-1}$. These four bands almost coincide in frequency with those in the diol at 3630, 3601, and 3556 cm.$^{-1}$. (There is also a third, very broad, band at *ca.* 3525 cm.$^{-1}$ in the 3-*O*-methyl derivative, weaker than the other two bands in the spectrum of this compound.) If the diol exists in an equilibrium involving forms which differ in their pyranose ring conformation, one of these being the usual C1 form, the centre band at 3601 cm.$^{-1}$ would have to be a composite band arising from the 2-hydroxyl group in the C1 conformation and the 3-hydroxyl in the other, for the arrangement of *cis*-axial C–O bonds at $C_{(1)}$ and $C_{(3)}$ causing the band at 3556 cm.$^{-1}$ should belong uniquely to the C1 form while the free 2-hydroxyl group (3630 cm.$^{-1}$ band) should likewise be unique to the other form. It is difficult to find a conformation where one of the hydroxyl groups could not possibly be hydrogen-bonded, but two conformations that nearly fulfil this condition are the half-chair HC1 (Bentley's nomenclature [5]) and the strained form with $C_{(5)}$, O_{ring}, $C_{(1)}$, $C_{(2)}$, and $C_{(3)}$ planar. Irrespective of the position of the equilibrium the intensity of the composite band would therefore be greater than that of the highest-frequency band (and also greater than that of the lowest-frequency band if the integrated absorption intensities were equal), whereas in fact it has the lowest intensity of these three bands.

An alternative explanation is that each hydroxyl group in methyl 4,6-*O*-benzylidene-α-D-altroside and its two methyl derivatives is to be found in two orientations, but that the pyranose ring is always in the C1 conformation. The axial 3-hydroxyl group would, for the most part, be hydrogen-bonded strongly to the axial $C_{(1)}$-oxygen (absorption ~3550 cm.$^{-1}$), and to a small extent and more weakly to another oxygen atom, that on $C_{(4)}$, causing less intense absorption at ~3600 cm.$^{-1}$. The 2-hydroxyl group would in part be hydrogen-bonded to the oxygen atom of the pyranose ring (absorption at ~3600 cm.$^{-1}$), but would be free to a larger extent, causing a more intense band at ~3630 cm.$^{-1}$. (The band at *ca.* 3525 cm.$^{-1}$ in the 3-*O*-methyl derivative is not found in the diol and is therefore not considered here.) However, by comparison with the results from the other diols where *cis*-axial C–O bonds are encountered, the 3-hydroxyl would be expected to bond completely and not just in part. On the other hand, the suggestion of the largely free 2-hydroxyl group is not without precedent, for incomplete hydrogen bonding was considered as a possible explanation of absorption associated with free hydroxyl groups in the spectrum of 1,5-anhydro-2-deoxy-L-erythropentitol.[6]

Whatever the correct explanation, hydrogen bonding in methyl 4,6-*O*-benzylidene-α-D-altroside and its two methyl derivatives is not as complete as would be expected.

EXPERIMENTAL

The compounds were supplied as follows: the methyl 4,6-*O*-benzylidene-D-gulosides by Dr. Hewitt G. Fletcher, jun.; *trans*-cyclohexane-1,2-diol by Dr. F. S. H. Head; methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-altroside by Dr. J. W. W. Morgan; methyl 4,6-*O*-benzylidene-β-D-idoside and methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-altroside by Professor T. Reichstein; and the others by Dr. C. J. G. Shaw. All samples were analytically pure and were thoroughly dry. One further portion of methyl 4,6-*O*-benzylidene-α-D-altroside was heated *in vacuo* at 60° for 2 hr. and another was recrystallised from chloroform–light petroleum; the spectra of both were the same as that of the original.

Carbon tetrachloride was of "AnalaR" or Spectroscopy Grade, stored over phosphoric anhydride or, when necessary, distilled from and collected over this reagent. The solutions were prepared by shaking the required quantities of solute and solvent together and filtering the mixture through dry filter paper into the optical cell. Handling of solvent and solutions was done in a dry box. When, as was nearly always so, the solute did not dissolve completely, the concentration was not determined exactly. It was, however, always less than 0·005M. Methyl 4,6-*O*-benzylidene-α-D-altroside was particularly insoluble.

The absence of intermolecular hydrogen bonding was confirmed by making up solutions at two different concentrations of two typical compounds, the methyl α-D-glucoside and α-D-idoside derivative. The former was examined in *ca.* 0·002M- and *ca.* 0·0005M-solution, and the latter in *ca.* 0·0025M- and *ca.* 0·001M-solution. Dilution did not affect the peak frequencies or relative intensities.

The cells, 2 or 3 cm. thick, were of fused quartz (infrared quality). They absorbed very little in the region of 3650 cm.$^{-1}$. Spectra were measured on a Unicam SP. 100 spectrometer equipped with a 3000 lines per inch grating and kept at 30°, and frequencies were checked against water vapour and ammonia bands. *trans*-Cyclohexane-1,2-diol was measured in order to check experimental conditions. Two bands were found, at 3633 and 3600 cm.$^{-1}$, and this result agrees well with recorded values.[1,6,7]

I am particularly grateful to all those mentioned for kindly providing the compounds. In addition I am indebted to Drs. A. B. Foster and R. D. Guthrie for helpful discussion, and to Miss S. Burgess for measuring the spectra.

SHIRLEY INSTITUTE, DIDSBURY, MANCHESTER, 20. [*Received, February* 20*th*, 1961.]

---

[6] Brimacombe, Foster, Stacey, and Whiffen, *Tetrahedron*, 1958, **4**, 351.
[7] Cole and Jefferies, *J.*, 1956, 4391.