578. *Cyclitols. Part XIII.*[1] *The Conformation of Cyclic Diketals: the Skew Conformation.*

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Measurement of intramolecular hydrogen bonding provides information about the conformation of cyclic diketals of inositols. When two *cis*-ketal rings are present, the compounds are predominantly in a skew conformation or possibly, with the two ketals in the 1,2:4,5-positions, in a conformation intermediate between skew and boat. A single ketal, or one *cis*- and one *trans*-ketal group, causes only a slight deformation of the chair form.

THE synthesis of cyclic ketals derived from inositols has been described in several papers of this Series.[1-3] Availability of these compounds gave us an opportunity to investigate the effect, on the conformation of the cyclohexane ring, of its fusion to two five-membered rings. The conformation of cyclic polyols can be studied by methods which determine the relative positions of the hydroxyl groups; we used the excellent method [4] of L. Kuhn, which consists in the study of intramolecular hydrogen bonding as disclosed by the hydroxyl stretching bands in the infrared spectra.

Before our results are discussed, two general comments are appropriate. First, it has often been claimed that attachment of a five-membered ketal ring forces the cyclohexane ring into a boat or half-chair conformation. Such conformational change is by no means necessary. The cyclopentane ring is not planar and, as Pitzer and Donath showed,[5] it can accommodate a dihedral angle * as large as 46°. The dioxolan ring of the ketals may be somewhat flatter—the oxygen atoms offering less eclipsed interaction than methylene groups—but even the attachment of this ring to cyclohexane would require only a slight distortion, say 20°, in the dihedral angle of one carbon–carbon bond. The chair can yield to such distortion without being forced into a less favourable conformation. Eliel and Pillar [6] have found, by the use of Kuhn's method and by studying the rates of glycol

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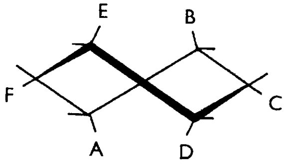
* The " dihedral angle " is the angle between two planes, one defined by the C–C bond and one of the C–X bonds on one carbon atom, the other similarly defined by the C–C bond and the C–Y bond on the other carbon atom. In the discussion of ring conformations, X and Y are carbon atoms forming the ring. In the later discussion of hydrogen bonding, X and Y are oxygen atoms.

[1] Part XII, Angyal and Hoskinson, preceding paper.
[2] Angyal and Macdonald, *J.*, 1952, 686.
[3] Angyal, Tate, and Gero, *J.*, 1961, 4116.
[4] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323.
[5] Pitzer and Donath, *J. Amer. Chem. Soc.*, 1959, **81**, 3213.
[6] Eliel and Pillar, *J. Amer. Chem. Soc.*, 1955, **77**, 3600.

fission, that the six-membered ring of perhydrobenzo[*c*]furan-5,6-diols is in the chair form, despite its fusion to a five-membered ring. The purpose of the present work was to determine whether the chair is still preserved when two five-membered rings are fused to it.

Secondly, it is still often assumed that, when the chair form is not possible or practicable, the boat form is the alternative. Yet it is known [7,8] that the boat conformation represents the state of *maximum* energy of the flexible form, and is taken up only under severe constraint, such as that caused by a 1,4-bridge. The skew conformation has the minimum energy of the flexible form; in our cases severe distortion of the chair form was found to have caused a change into skew forms.



The skew form (Figure) is characterised [7] by two pairs of carbon atoms, A,B and D,E, on opposite sides of the ring, which are nearly staggered, with a dihedral angle of 70·7°. The dihedral angle between all the other carbon atoms is 33·1°. The atoms B, C, D, and F are in one plane; C, E, F, and A are in another plane. Substituents at A, B, D, and E are in positions which are approximately equatorial and axial and will be described as " equatorial " and " axial "; at C and F the positions of the substituents relative to neighbouring substituents are more like those in cyclopentane. In order to benefit from the geometry of the skew form, *cis*-ketal rings must be formed by oxygen atoms with a dihedral angle of 33°; *trans*-ketal rings, on the other hand, will only be fused to the staggered atoms, where the dihedral angle between *trans*-hydroxyl groups is 49·3°.

The conformations were determined by studying the hydroxyl stretching bands in the infrared spectrum according to the method of Kuhn.[4] At a high dilution (<0·005M) in carbon tetrachloride, intermolecular hydrogen bonds are eliminated; an unbonded hydroxyl group shows as a peak at about 3630 cm.$^{-1}$, and intramolecular hydrogen bonds shift the peak to lower frequencies, the shift (Δν) being dependent on the O–O distance. When the two hydroxyl groups are on adjacent carbon atoms, complete eclipsing causes Δν values of about 100 cm.$^{-1}$ (camphanediols,[9] norcamphanediols [10]); a dihedral angle of 60° in *trans*-cyclohexane-1,2-diol gives rise to a shift of 32 cm.$^{-1}$, whereas the somewhat higher value of 39 cm.$^{-1}$ in *cis*-cyclohexane-1,2-diol indicates a slight reduction of the dihedral angle caused by hydrogen bonding. In *cis*-cyclopentane-1,2-diol,[4] where Δν is 61 cm.$^{-1}$, the dihedral angle is intermediate between staggered and eclipsed, probably similar to that in the skew form of cyclohexane. The position of the hydroxyl band thus indicates the approximate distance between hydrogen-bonded oxygen atoms.

Models for the different conformations of each inositol ketal were constructed from Dreiding and from Courtauld stereomodels and the distances between the various oxygen atoms were measured; this procedure was of considerable help in assigning the hydroxyl frequencies.

The hydroxyl stretching frequencies of a number of inositol ketals are shown in the Table. It will be noted that, the opportunities for hydrogen-bond formation being so manifold, in no cases was a free hydroxyl stretching frequency observed. Hence the Δν values were calculated by subtracting the observed frequencies from the standard frequency of 3629 cm.$^{-1}$ for free secondary hydroxyl groups; [11] an uncertainty of about ±5 cm.$^{-1}$ is thereby introduced, since there is some variation in the frequency of free hydroxyl groups between different diols.[4,12]

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[7] Hazebroek and Oosterhoff, *Discuss. Faraday Soc.*, 1951, **10**, 87; Bottomley and Jefferies, *Austral. J. Chem.*, 1961, **14**, 657.

[8] Reeves, *Ann. Rev. Biochem.*, 1958, **27**, 15; Johnson, Bauer, Margrave, Frisch, Dreger, and Hubbard, *J. Amer. Chem. Soc.*, 1961, **83**, 606.

[9] Angyal and Young, *J. Amer. Chem. Soc.*, 1959, **81**, 5467.

[10] Kwart and Vosburgh, *J. Amer. Chem. Soc.*, 1954, **76**, 5400.

[11] Cole and Jefferies, *J.*, 1956, 4391.

[12] Kuhn, *Spectrochim. Acta*, 1961, **17**, 650.

Infrared peaks in the hydroxyl stretching region.

Inositol	Ref.	Band frequencies (cm.$^{-1}$)	$\Delta\nu$ (cm.$^{-1}$)
1,2:4,5-Di-*O*-isopropylidenemuco- (I)	1	3602 (0·80) *	27
1,2:4,5-Di-*O*-isopropylidene-epi- (II)	2	3612 (0·69), 3569 (0·64)	17, 60
1,2:3,4-Di-*O*-isopropylidenecis- (III)	1	3565 (0·66), 3442 (0·21)	64, 187
1,2:3,4-Di-*O*-isopropylidene-epi- (IV)	2	3580 (0·39), 3550 (0·46)	49, 79
1,2:5,6-Di-*O*-isopropylidene-(−)- (V)	2	3610 (0·66), 3593sh (0·60) †	19, 36
1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-(+)- (VI)	2	3585 (0·45)	44
3,4,5,6-Tetra-*O*-methylmyo- (VII)	*a*	3585 (0·66)	44
1,2:5,6-Di-*O*-cyclohexylidenemyo- (VIII)	3	3612 (0·57), 3562 (0·41)	17, 67
2,3:4,5-Di-*O*-isopropylidene-1-*O*-methylmyo- (IX)	1	3605 (0·32)	24
1,2:3,4-Di-*O*-cyclohexylidenemyo- (X)	3	3612 (0·37)	17
2,3:5,6-Di-*O*-isopropylidene-1-*O*-methylmyo- (XI)	1	3612 (0·43)	17
3,4:5,6-Di-*O*-isopropylidene-2-*O*-methyl-(−)- (XII)	1	3573 (0·41)	56
3,4-*O*-Isopropylidene-2-*O*-methyl-5-*O*-tosyl-(−)- (XIII)	1	3602 (0·31), 3597sh (0·32)	27, 32

* The figures in parentheses refer to peak optical densities. † sh refers to shoulder. (*a*) Angyal and Bender, unpublished work.

The first six compounds appear to be in a skew conformation. 1,2:4,5-Di-*O*-isopropylidenemucoinositol (I) cannot be predominantly in the chair conformation (Ib) because the axial hydroxyl group in this form should give rise to a " free " hydroxyl stretching frequency; in fact, none was found. The observed $\Delta\nu$ value of 27 cm.$^{-1}$ corresponds to a hydrogen bond between *trans*-oxygen atoms. It is somewhat low for the dihedral angle of 49° provided by the skew form (Ia) for both hydroxyl groups (along AB and DE); but Spedding's values[13] for methyl 4,6-*O*-benzylidene-D-aldohexosides (some as low as 15—20 cm.$^{-1}$) show that the rigidity of the ring, owing to fusion to another ring and to numerous substituents, causes low $\Delta\nu$ values for bonding between *trans*-hydroxyl groups.*

It is to be noted that, of all the compounds investigated, the diketal of mucoinositol provides the most favourable arrangement for the boat conformation, with both ketal rings at the eclipsed " sides," and all oxygen atoms in " boat-equatorial " positions. Hence the most stable conformation of this compound may be intermediate between the skew and the boat.

1,2:4,5-Di-*O*-isopropylidene-epi-inositol (II) has the same geometry as the previous compound, except for one hydroxyl group; it is probably in the skew form (IIa) in which one hydroxyl group is now " axial." Bonding of this group to its *cis*-neighbour at a 33° dihedral angle explains satisfactorily the $\Delta\nu$ value of 60 cm.$^{-1}$. The other value, $\Delta\nu$ 17 cm.$^{-1}$, is again somewhat low for a *trans*-hydrogen bond. Here, again, there may be some deformation towards the boat form. The chair form (IIb), however, cannot be excluded; the distortion caused by the ketal rings may bring the *cis*-hydroxyl group sufficiently near to, and the *trans*-hydroxyl group sufficiently far from, its neighbouring oxygen atoms to explain the the values of 60 and 17 cm.$^{-1}$ for $\Delta\nu$.

1,2:3,4-Di-*O*-isopropylidenecisinositol is clearly in the skew conformation (III). The high $\Delta\nu$ value of 64 cm.$^{-1}$ indicates *cis*-interaction at 33° dihedral angle. The very low frequency band at 3442 cm.$^{-1}$ cannot be ascribed to hydrogen bonds between oxygen atoms on adjacent carbon atoms, or between axial oxygen atoms (Kuhn[4] reported 3544 cm.$^{-1}$ for *cis*-cyclohexane-1,3-diol and Spedding[13] found values between 3517 and 3556 cm.$^{-1}$). This band may be explained, however, by a transannular hydrogen bond between the two " axial " oxygen atoms in the skew conformation (III); Stolow[14] reported a band at 3480 cm.$^{-1}$ in the spectrum of a 2,5-di-t-butylcyclohexane-1,4-diol which was also assumed to have a skew conformation. Kuhn[12] found a hydroxyl band at 3478 cm.$^{-1}$ in the

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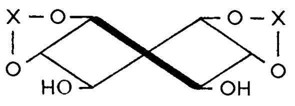
* Models also show that hydrogen bonding to a *trans*-oxygen atom in a dioxolan ring is less favoured than to a free hydroxyl group [as in (IV) and (V)], owing to the rigidity of the five-membered ring.

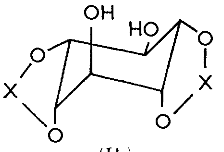
[13] Spedding, *J.*, 1961, 3617.

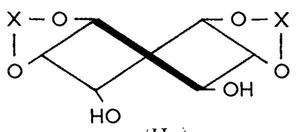
[14] Stolow, *J. Amer. Chem. Soc.*, 1961, **83**, 2592.

spectrum of butane-1,4-diol in which the hydrogen bond similarly closes a seven-membered ring.

The high Δν value of 79 cm.$^{-1}$ of 1,2:3,4-di-*O*-isopropylidene-epi-inositol (IV) also indicates a skew conformation, being due to a *cis*-interaction at the dihedral angle of 33°. The other Δν value of 49 cm.$^{-1}$ can be ascribed to the hydrogen bond between the two *trans*-hydroxyl groups at an angle of 49°.


(Ia)


(Ib)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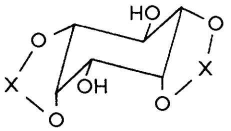
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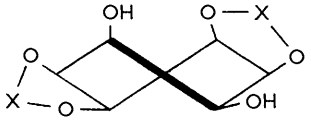
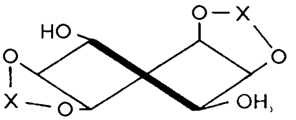
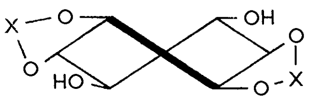

(III)


(IV)


(V)

(X = $>CMe_2$)

In 1,2:5,6-di-*O*-isopropylidene-(—)-inositol (V) the weak *trans*-interaction (Δν 19 cm.$^{-1}$) appears to indicate a skew form (dihedral angle about 90°); but a chair form, owing to the distortion caused by the ketal groups, might also explain this Δν value. The other *trans*-hydrogen bond (Δν 36 cm.$^{-1}$) is strong, in accordance with a dihedral angle of 49° between the two hydroxyl groups in the skew form. Only the second of these hydrogen bonds is present in 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-(+)-inositol (VI); its Δν value is now higher (44 cm.$^{-1}$) because a hydrogen bond to a methoxyl group causes a larger shift than one to a hydroxyl group.[12]

In only two of these compounds, (III) and (IV), does the evidence definitely prove the presence of a skew form, but it is compatible with its presence in the other compounds. It is probable that the constraint which favours the skew form in these two cases has the same effect in the others too.

The five derivatives of myoinositol (VII—XI) are all in the chair conformation. The first, 1,4,5,6-tetra-*O*-methylmyoinositol (VII), is not a ketal, and its Δν value of 44 cm.$^{-1}$ is in accordance with the presence of *cis*-hydrogen bonds, one of them to a methoxyl group. The other compounds have a ketal ring attached to *trans*-oxygen atoms: by forcing these atoms closer to each other, the *trans*-ketal ring increases puckering in that segment of the cyclohexane ring to which it is fused, and reduces it in the other segment. Hence the low value of 17 cm.$^{-1}$ for hydrogen bonding between *trans*-oxygen åtoms in compounds (VIII)—(X), increased to 24 cm.$^{-1}$ in compound (XI) because the bonding is to a methoxyl group. For the same reason the distance between *cis*-oxygen atoms is reduced, and in 1,2:5,6-di-*O*-cyclohexylidenemyoinositol (VIII) this effect is reinforced by the distortion due to the adjacent *cis*-ketal group. Hence the exceptionally high value of 67 cm.$^{-1}$ for a hydrogen bond between adjacent oxygen atoms in a chair conformation. Compounds (VIII), (IX), and (X) cannot be present in the skew form because then they would have an " axial " hydroxyl group which could not form a hydrogen bond and would give rise to a " free " hydroxyl band in the spectrum.

The last two compounds of the Table, (XII) and (XIII), are probably in the chair conformation too. The skew conformation would, in both cases, produce a dihedral angle of 33° between a hydroxyl and a methoxyl group which would require a higher $\Delta\nu$ value than observed (56 and 32 cm.$^{-1}$). Compound (XIII) has a hydrogen bond between a *cis*-hydroxyl and a tosyloxy-group; this appears to cause a shift of 27 cm.$^{-1}$, a figure which cannot be confirmed because data for comparison are lacking.

We conclude from this analysis of selected compounds that two *cis*-ketal rings fused to a cyclohexane skeleton will change it into a skew form, but one *cis*- and one *trans*-ketal, or a single ketal of any configuration, will leave it in the chair conformation, but somewhat distorted.

It must be emphasised that these conclusions are only valid for the conditions under which the spectra were taken, that is, in dilute solutions in carbon tetrachloride. The energy of the intramolecular hydrogen bond itself may have caused the preponderance of conformations which do not predominate in the solid state or in hydroxylic solvents. Such conformation-changing effects of the hydrogen bond have been observed in *cis*-cyclohexane-1,3-diol [4,15] and in methyl 4,6-*O*-benzylidene-α-D-idoside.[13,16]

Experimental.—The compounds studied were all prepared in these laboratories.

Carbon tetrachloride of " AnalaR " grade was stored over, and distilled from, phosphoric anhydride, as required. Solutions were prepared by heating the solute and solvent together on a hot plate, cooling, and filtering into the optical cell. Frequently the solute was not completely soluble, and the exact concentration was not determined.

The absence of intermolecular hydrogen bonding was confirmed by taking spectra at two concentrations, namely, 0·005M and 0·002M; peak frequencies and relative intensities remained unaltered.

Spectra were taken in 1 cm. quartz cells, on a Perkin–Elmer single-beam double-pass Monochromator, model 99, equipped with lithium fluoride optics. The instrument was calibrated against the spectra of ammonia and water vapour. *cis*-Cyclohexane-1,2-diol was measured in order to check the procedure: the two bands found at 3630 and 3590 cm.$^{-1}$, severally, agree with Kuhn's values.[4]

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[15] Furberg and Hassel, *Acta Chem. Scand.*, 1950, **4**, 597.
[16] Reeves, *J. Amer. Chem. Soc.*, 1950, **72**, 1499.