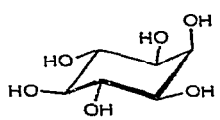
Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

Note

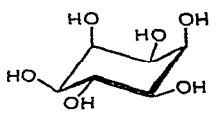
A comparison of the structures of *epi*- and *myo*-inositol

G. A. JEFFREY AND H. S. KIM
Department of Crystallography, University of Pittsburgh, Pittsburgh, Pa. 15213 (U. S. A.)
(Received April 13th, 1970)

Of the nine isomeric C_6 cyclitols, only *myo*-inositol (**1**), as the anhydrous compound[1] and the dihydrate[2], has been the subject of crystal-structure determination. We have now completed a determination of the crystal structure of the *epi* isomer (**2**). This isomer has an axially attached hydroxyl group on each of two alternate carbon atoms of the cyclohexane ring, which, because of the so-called 1,3-interaction[3], should cause strain in the molecule. The purpose of this study was to compare the geometry of this molecule (**2**) with that of (*a*) an ideal, strain-free model and (*b*) *myo*-inositol (**1**), which has only one axially attached hydroxyl group.



myo
1



epi
2

The crystal data for *epi*-inositol (**2**) are as follows: space group $P2_1/c$, $a = 4.841$, $b = 14.727$, $c = 11.236$ Å, $\beta = 115.85°$, with 4 molecules per unit cell. A Picker FACS I diffractometer was used with CuKα radiation to measure 1234 intensities, of which 309 had values less than two standard deviations (by counting statistics). The structure was solved by the centric direct method, and refined by anisotropic least squares to an $R = 0.031$ for all observed reflections, and $R = 0.049$ for all measured reflections.

The crystal-structure determination of **1** by Rabinowitz and Kraut[1] in 1964 had also been made from counter measurements, and was exceptionally accurate work for that time. An adequate number of intensities (1968) was observed, and the final *R*-value was 0.055. The unit cell of **1** contains two symmetry-independent molecules, thereby increasing the reliability of the averaged mean values for the intramolecular distances and angles. (The earlier determination of the structure of *myo*-inositol hydrate was based[2] on film methods. It is significantly less accurate and the results are not relevant to this comparison, apart from showing no evidence of any difference in conformation between the molecules in the anhydrous and hydrated crystals.)

The molecule of *epi*-inositol (**2**), like that of **1**, has a chair conformation (see Fig. 1). The mirror symmetry through C-1, O-1, C-4, and O-4, which should be exact for the free molecule, is closely maintained in the crystal structure; the deviations are less

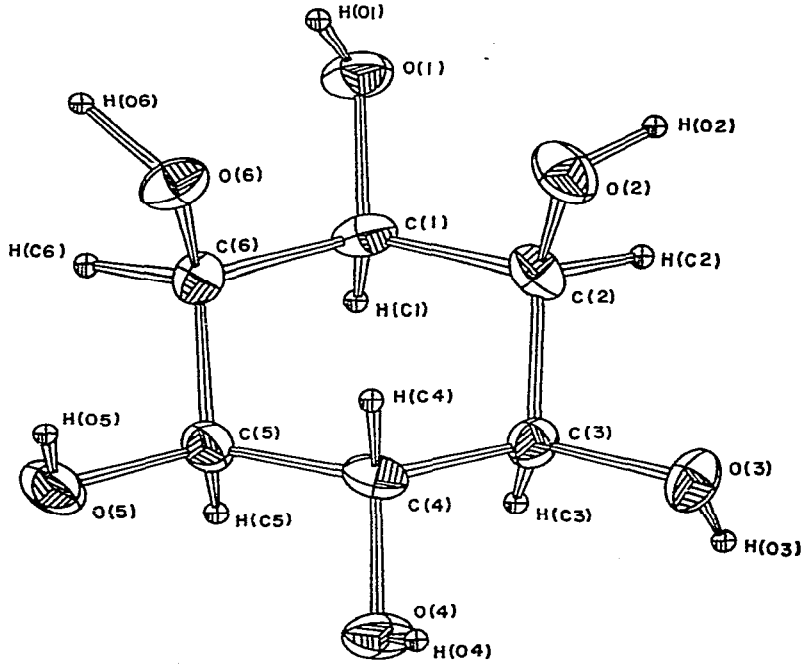


Fig. 1. The molecule of *epi*-inositol (**2**) in the crystal structure, viewed approximately normal to the central plane of the chair-shaped cyclohexane ring: C-1 and C-4 are below and above the plane, respectively. The ellipsoids define the atomic, thermal motion.

than 0.01 Å for the carbon and oxygen atoms. The methylene hydrogen atoms are also symmetrically situated (within the limits of their less precise location), but the hydrogen atoms of the hydroxyl groups show some significant deviations; this was to be expected, because their positions are determined by the asymmetric, intermolecular hydrogen-bonding between the molecules in the crystal, as shown in Fig. 2.

The C–C bond lengths in **2** vary from 1.523 to 1.530 Å, with a mean value of 1.527 Å. (In *myo*-inositol, the range is 1.508 to 1.533 Å, with a mean of 1.521 Å.) These differences are not regarded as significant. The C–O distances vary over a wider range, namely, 1.419 to 1.439 Å. It may be significant that the two greater distances, 1.435 and 1.439 Å, are associated with oxygen atoms that are involved in three hydrogen bonds. The four shorter distances, 1.419 to 1.429 Å, correspond to oxygens atoms having only one, or two, hydrogen bonds.

In *myo*-inositol (**1**), the C–O bond lengths vary over the same range (1.419 to 1.438 Å), with a mean of 1.429 Å. It is interesting that, in structure **1** also, there may be a similar, systematic relationship; the four oxygen atoms (in two molecules) that are involved in three hydrogen bonds or one hydrogen bond tend to have longer C–O

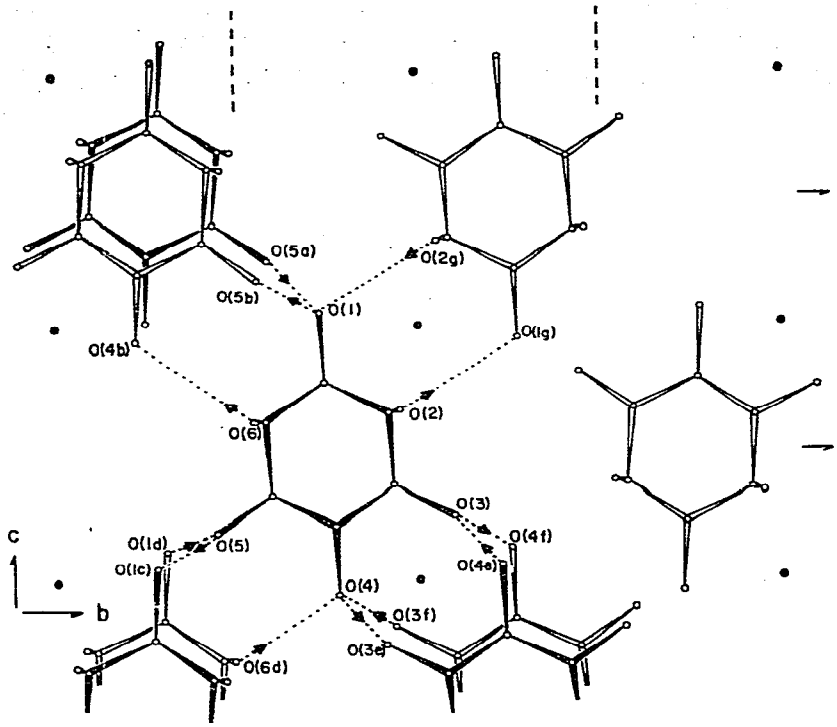


Fig. 2. The crystal structure of *epi*-inositol (2) viewed down the *a* axis, showing the asymmetric hydrogen-bonding environment of the central molecule. The dotted lines represent hydrogen bonds with arrows denoting the donor direction.

distances (namely, 1.435, 1.436, 1.436, and 1.428 Å) than the eight having the more common involvement in two hydrogen bonds. In the acyclic alditols, in which all oxygen atoms are associated with two hydrogen bonds, the mean C–O distance[4] is 1.429 Å. Apart from these small variations, which, if real, depend on the intermolecular environment, there is no evidence of other significant differences in bond lengths between the two isomers, **1** and **2**.

The important conformational angles and distances in *myo*-inositol (**1**), *epi*-inositol (**2**), and a strain-free model are shown in Fig. 3. It is seen that, in *myo*-inositol (**1**), there is a tendency for the cyclohexane ring to be flattened, as shown by the mean angle between the C–C bonds of 56.8°. The overall flattening is only very slightly increased in *epi*-inositol (**2**), with a mean ring C–C angle of 56.3°. The most obvious effect of the 1,3-interaction between O-2 and O-6 in *epi*-inositol (**2**) is to increase the nonbonding distance (from 2.50 Å in the ideal, strain-free model) to 2.96 Å. This increased separation corresponds to a rotation of 9° about each of the C-2–C-3 and C-5–C-6 bonds. Were it not for the constraint of the cyclohexane ring, this "outward" movement of O-2 or O-6 of 0.23 Å would correspond to a similar "upward" movement of C-1. In fact, C-1 moves only 0.10 Å, and the C-2–C-1–C-6 angle opens to 114.7°, as compared with the other C–C–C angles of the ring (108.7 to 110.8°,

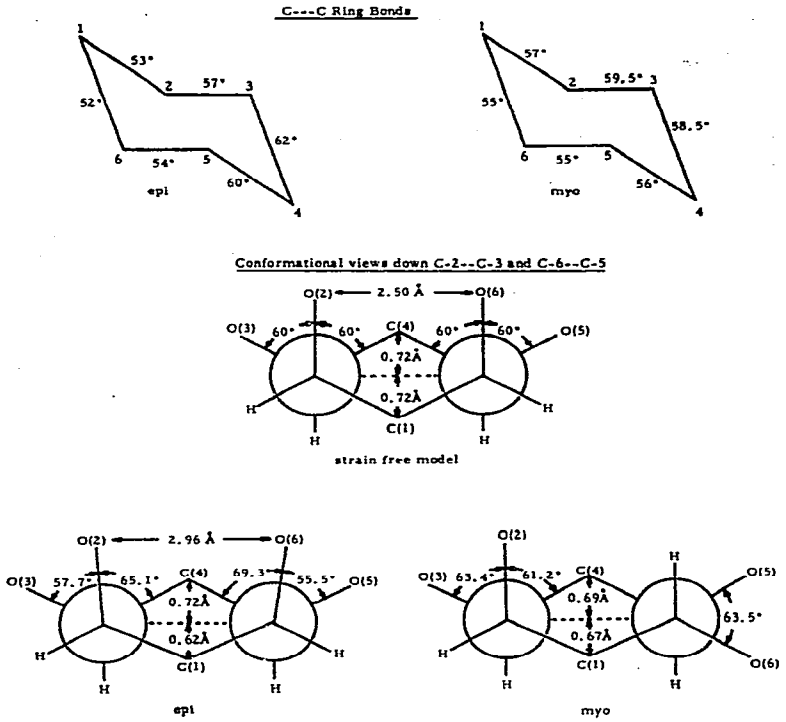


Fig. 3. Conformational angles in *epi*-inositol (2) and *myo*-inositol (1), with mean values from symmetry-independent molecules. The strain-free model is based on C–C = 1.527 Å, and tetrahedral angles. The mean value for the C–C–C (ring) angle is 109.7° in the two molecules of *myo*-inositol (1), and 110.0° in *epi*-inositol (2) (excluding that at C-1). Therefore, there is no justification for using the mean, acyclic C–C–C angle of 112.7° of the alditols[5].

with a mean of 110.0°). There is a corresponding, small widening of the cyclohexane ring across C-2–C-6 by 0.1 Å. The flattening of the ring at C-1 also tilts O-1 from the equatorial position into a quasi-axial position, such that it is 2.9 Å from O-2 and O-6, thereby invoking a repulsive interaction that also restrains further distortion of the ring. The remaining 0.13 Å (0.23 minus 0.10 Å) is accounted for by a distortion in the bond angles at C-2 and C-6, as shown by the angles of C-1–C-2–O-2 and of C-1–C-6–O-6 of 111.6 and 112.9°, respectively, as compared with a mean C–C–O angle of 110°. The angular distortions, arising from the 1,3-interaction, appear to be distributed approximately equally between distortion of the ring and of the C–C–O angles of the axial bonds.

In *myo*-inositol (1), there is no 1,3-interaction and the ring strain that occurs arises from the interaction of hydroxyl groups on *adjacent* carbon atoms at distances of the order of 2.8 Å. This effect is clearly shown in the increase of the dihedral angles involving the C–O bonds and the decrease in those of the ring bonds, as shown in Fig. 3. Its magnitude is approximately half that associated with the 1,3-interaction. Both C-1 and C-4 are 0.05 Å closer to the central plane than for the ideal model, and this displacement is evenly distributed at both ends. (This situation contrasts with

that for *epi*-inositol (**2**), for which the displacement, relative to the strain-free model, occurs only for C-1 and is twice as large, *viz.*, 0.10 Å.) An approximate calculation of the strain-energies was made by using the following formulas[3,5,6]. $E_\theta = 17.5\ (\Delta\theta)^2$ cal·mol^{-1} for bond-angle strain (in degrees), and $E_t = 1.40\ (1+\cos 3\omega)$ kcal·mol^{-1} for torsional strain (in degrees). E_θ was summed over the C–C–C and C–C–O bond angles, $\theta°$, by using the tetrahedral angle as the norm; E_t was summed over the dihedral ring-angles, $\omega°$. The values of the bending and torsional strain were 1.3 and 0.3 kcal·mol^{-1}, and 0.7 and 0.1 kcal·mol^{-1}, for *epi*-inositol (**2**) and *myo*-inositol (**1**), respectively. The numerical values are questionable, but the ratios of 5:1 in bond-bending to ring-torsion strain, and 2:1 between the two molecules constitute a reasonable result. The difference in relative, free-energy content of *epi*- and *myo*-inositol, estimated from the equilibrium constants of borate formation[3], is greater than these values, by a factor of >2.

This result, which emphasizes the relatively small effect of axial hydroxyl groups on conformation, is consistent with our observations[7] on the structure of 1,6-anhydro-β-D-glucopyranose, where the pyranose has the *1C* (D) conformation (with three axially oriented hydroxyl groups), not a boat conformation having all of the hydroxyl groups equatorially attached.

The internal consistency and rationale of these results, both for *epi*- and *myo*-inositol, support our initial assumption that intermolecular hydrogen-bonding plays only a secondary role in affecting conformational details in these compounds; the primary factors are the intramolecular, O–O nonbonding forces. However, these effects are quite small in the two cyclitols, which are rigid molecules; in marked contrast are the more flexible, alditol molecules, where significant conformational variety occurs because of restricted, but major, rotations about C–C bonds[4].

REFERENCES

1 I. N. Rabinowitz and J. Kraut, *Acta Crystallogr.*, 17 (1964) 159.
2 T. R. Lomer, A. Miller, and C. A. Beevers, *Acta Crystallogr.*, 16 (1963) 264.
3 *e.g.*, E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, John Wiley and Sons, New York, 1965, p. 356.
4 G. A. Jeffrey and H. S. Kim, *Carbohyd. Res.*, 14 (1970) 207.
5 F. H. Westheimer, in M. S. Newman (Ed.), *Steric Effects in Organic Chemistry*, John Wiley and Sons, New York, 1956, Chap. 12.
6 J. B. Hendrickson, *J. Amer. Chem. Soc.*, 83 (1961) 4537.
7 Y. J. Park, H. S. Kim, and G. A. Jeffrey, *Acta Crystallogr.*, in press.