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Note

The unusually stable crystal structure of *neo*-inositol *

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neo-Inositol [2] (1,2,3/4,5,6-cyclohexanehexol) is one of the rarer inositol isomers with only two natural occurrences reported [3,4]. It is unusual in that, whereas low-molecular weight polyols are usually very soluble in water, *neo*-inositol has a very low solubility. This seems to indicate that the crystal structure is unusually stable, that is, the crystal lattice energy is exceptionally large, exceeding that of the solvated molecules in water and the difference in entropy between the solid and the dissolved states.

In 1982, Jeffrey and Wood [5] investigated the crystal structure of galactaric acid, which also has a low solubility in water, much lower than its diastereomers. These authors concluded that one of the factors responsible for the high crystal density of this structure was the presence of a cyclic ("homodromic") system of intermolecular hydrogen bonds.

neo-Inositol has a solubility even lower than galactaric acid; being about 1 part in 1000 of cold water. Even in boiling water its solubility is very low. Hence it appeared to be of interest to investigate its crystal structure.

1. Experimental

Crystal data.—Suitable crystals were grown from boiling water: $C_6H_{12}O_6$, M 180.2, triclinic, space group $P\bar{1}$, a 4.8005(3), b 6.5057(5), c 6.5066(5) Å, α 70.607(6), β 69.632(6), γ 73.669(5)°, V 176.51(2) Å^3, D_c 1.69 g cm^{-3}, $Z = 1$, μ_{Cu} 12.86 cm^{-1}. Crystal size 0.15 × 0.15 × 0.23 mm, $2\Theta_{max}$140°, minimum and maximum transmis-

* Cyclitols, Part XLI. For Part XL, see Ref. 1.

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sion factors 0.79 and 0.87. The number of reflections was 636 considered observed out of 663 unique data. Final residual R and R_w were 0.035 and 0.056, respectively.

Structure determination.—Reflection data were measured with an Enraf–Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using nickel-filtered copper radiation (λ 1.5418 Å). Data were corrected for absorption using the method of de Meulenaer and Tompa [6]. Reflections with $I > 3\sigma(I)$ were considered observed. The structure was determined by direct phasing and Fourier methods. Hydrogen atoms were located in a difference Fourier and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the nonhydrogen atoms were refined using full matrix least squares. Reflection weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o) = [\sigma^2(I_o) + (0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w = (\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography [7]. Structure solution was by MULTAN-80 [8] and refinement used BLOCKLS, a local version of ORFLS [9]. ORTEP-II [10] running on a Macintosh IIcx was used for the structural diagrams, and an IBM 3090 computer was used for the calculations.

2. Results and discussion

The structure and atom numbering scheme is shown in Fig. 1. Since *neo*-inositol is symmetrical, data are listed for only half of the molecule; C-4, C-5, and C-6 are designated as C-1^a, C-2^a, and C-3^a, respectively (a = symmetry transformation $1-x, 1-y, 1-z$). Atomic parameters are shown in Table 1, bond lengths, angles,

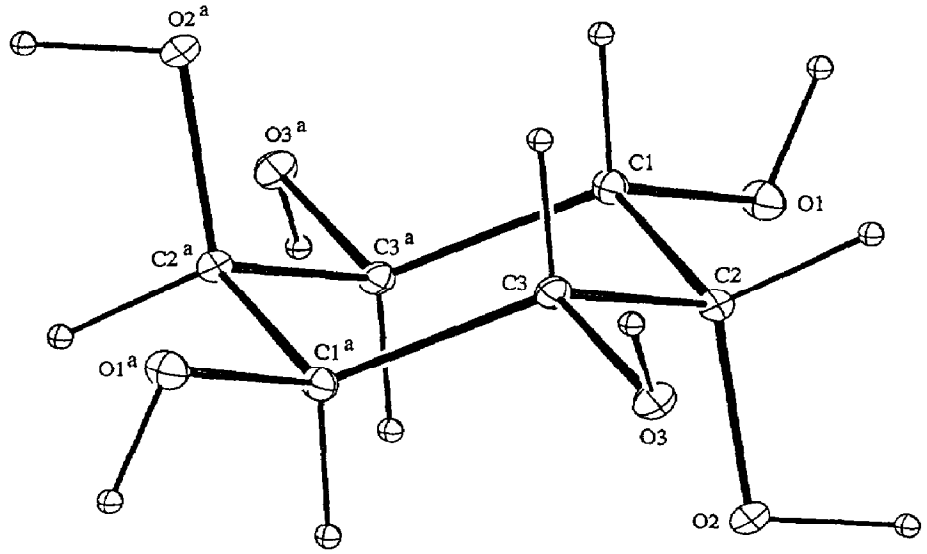


Fig. 1. ORTEP plot of *neo*-inositol, showing atomic notation and thermal ellipsoids.

Table 1
Atomic coordinates for *neo*-inositol with standard deviations in parentheses

Atom	x/a	y/b	z/c	B_{eq} [a]
C-1	0.5090(3)	0.5972(2)	0.2612(2)	1.55(6)
C-2	0.4488(3)	0.7434(2)	0.4195(2)	1.53(6)
C-3	0.2935(3)	0.6247(2)	0.6616(2)	1.52(6)
O-1	0.6581(3)	0.7081(2)	0.0339(2)	2.06(5)
O-2	0.7264(2)	0.7872(2)	0.4152(2)	2.02(5)
O-3	0.2314(3)	0.7645(2)	0.8097(2)	1.87(5)
H(C-1)	0.3067	0.5802	0.2577	
H(C-2)	0.3077	0.8877	0.3647	
H(C-3)	0.0956	0.6034	0.6586	
H(O-1)	0.5211	0.7434	−0.0479	
H(C-2)	0.7145	0.9333	0.3383	
H(O-3)	0.0493	0.7565	0.9008	

[a] B_{eq} (Å^2) is the isotropic equivalent of the anisotropic temperature factor. The hydrogen atoms were assigned thermal parameters equal to those of the atoms to which they are bonded.

Table 2
Bond lengths (Å), bond angles (degrees), and torsion angles (degrees)

Bonds	Bond lengths	Bonds	Bond lengths
C–1–C–2	1.529(2)	C–1–O–1	1.437(2)
C–2–C–3	1.527(2)	C–2–O–2	1.429(2)
C–3–C–1 [a]	1.521(2)	C–3–O–3	1.441(2)
Bonds	**Bond angles**	**Bonds**	**Bond angles**
C–3 [a]–C–1–C–2	110.2(1)	C–3–C–2–O–2	109.1(1)
C–3 [a]–C–1–O–1	109.7(1)	C–2–C–3–C–1 [a]	110.2(1)
C–2–C–1–O–1	109.3(1)	C–2–C–3–O–3	109.3(1)
C–1–C–2–C–3	109.4(1)	C–1 [a]–C–3–O–3	111.2(1)
C–1–C–2–O–2	110.4(10		
Bonds	**Torsion angles**	**Bonds**	**Torsion angles**
C–3 [a]–C–1–C–2–C–3	−58.7(2)	C–3 [a]–C–1–C–2–O–2	61.3(1)
C–1–C–2–C–3–C–1 [a]	58.7(1)	O–1–C–1–C–2–C–3	−179.4(1)
C–2–C–3–C–1 [a]–C–2 [a]	−59.2(1)	O–1–C–1–C–2–O–2	−59.4(1)
C–3–C–1 [a]–C–2 [a]–C–3 [a]	58.7(2)	C–1–C–2–C–3–O–3	−178.8(1)
C–1 [a]–C–2 [a]–C–3 [a]–C–1	−58.7(1)	O–2–C–2–C–3–C–1 [a]	−62.1(1)
C–2 [a]–C–3 [a]–C–1–C–2	59.2(1)	O–2–C–2–C–3–O–3	60.4(1)

and torsion angles in Table 2 [1]. It might be worth noting that the lengths of the C–O bonds vary with the nature of the hydrogen bonding at the oxygen atom, as it also does in the structure of *epi*-inositol [11]. It is shortest at O-2 which only acts as

[1] Atomic coordinates, thermal parameters, and observed and calculated structure factors for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

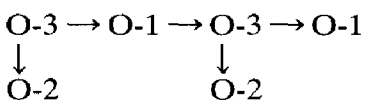
Table 3
Hydrogen bond distances and angles in the crystal structure of *neo*-inositol [a]

Hydrogen bond	Symmetry code	H · · · O (Å)	O · · · O (Å)	O–H · · · O (°)
O-1–H · · · O-3 [b]	*b* $x, y, z-1$	1.826	2.786(2)	169.73
O-2–H · · · O-3 [c]	*c* $1-x, 2-y, 1-z$	1.870	2.824(1)	167.36
O-3–H · · · O-1 [d]	*d* $x-1, y, 1+z$	1.750	2.693(2)	163.31

[a] The O–H bond lengths have been normalized to 0.97 Å to correct for the bonding electron density distortion [18].

donor, longer at O-1 which is donor and acceptor, and still longer at O-3 which donates one and accepts two hydrogen bonds.

There is a crystallographic centre of symmetry in the inositol molecule, which exists in an almost ideal chair conformation. Hydrogen bonding is extensive, with each molecule having twelve bonds with O–O distances ranging from 2.693 to 2.824 Å. Details are given in Table 3. The axial O-2 acts only as donor, as expected [12] owing to restricted space around it. To compensate for this, O-3 acts as donor and also as acceptor for two hydrogen bonds, and O-1 is involved in two bonds, one as donor and one as acceptor. The structure can be described as sheets, as shown in Fig. 2, and these sheets are linked by O-3–H · · · O-1 hydrogen bonds (not shown in Fig. 2) above and below the plane of the diagram to give a three-dimensional network. These intrasheet hydrogen bonds are the shortest ones (H · · · O 1.750 Å) in the crystal structure, though they are not unusually short [13]. The hydrogen bonds form branched infinite chains, shown diagramatically as follows:



There are no homodromic cycles of hydrogen atoms.

The compactness of the molecule is characterized by its unusually high density (1.69 g cm^{-3}). A survey of 25 sugars and alditols [14] with five to seven carbon atoms disclosed densities in the range of 1.47–1.64. The crystal structures of four other inositols have been determined and their densities are as follows: *myo*- [15], 1.57; *chiro*- [16], 1.60; *muco*- [17], 1.64; and *epi*- [1], 1.66 g cm^{-3}. These inositols are readily soluble in water. Jeffrey and Wood [5] found that the insoluble galactaric acid had a higher density than other analogous compounds.

The compactness of the crystal structure is also indicated by the unusually low values of the temperature factors, both for carbon and for oxygen atoms.

It is instructive to compare the crystal structure of *neo*-inositol with that of its *epi* isomer [11]. In both structures there are two axial hydroxyl groups and both of these are only donors, not acceptors, of hydrogen bonds (in *chiro*- and *muco*-inositols the axial hydroxyl groups act as acceptors and donors but none of them is flanked by two equatorial hydroxyl groups). Each of the isomers has twelve intermolecular hydrogen bonds and in both cases they are arranged in infinite,

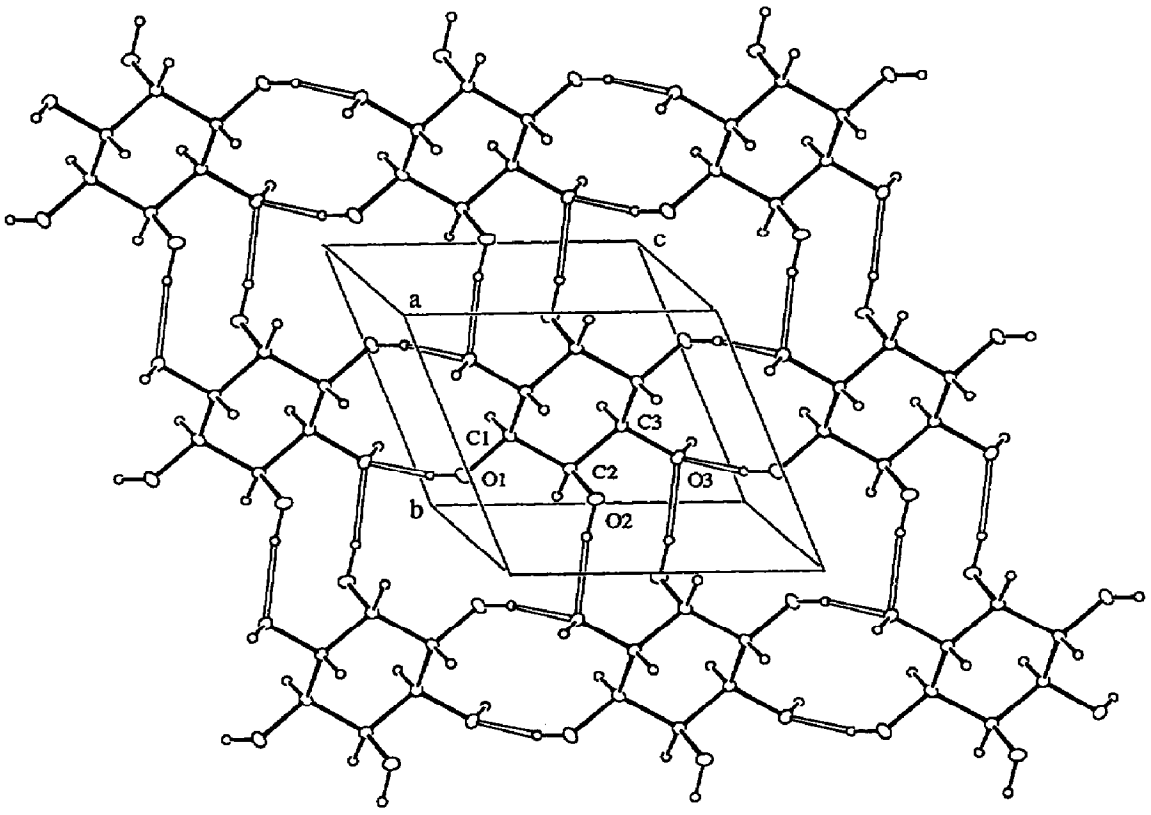


Fig. 2. The crystal structure and unit cell of *neo*-inositol. The double lines represent hydrogen bonds.

branched chains. There are no circular arrangements of hydrogen bonds in either structure. Yet, *epi*-inositol is readily soluble in water and *neo*-inositol is not.

Looking for possible reasons for this difference, there appear to be two. There is a regular, compact arrangement of molecules in the structure of *neo*-inositol, each molecule being attached by two hydrogen bonds to each of its four neighbours in the layer. In the structure of *epi*-inositol the bonding system is more scattered. In *neo*-inositol, the hydrogen bonds connecting the layers (two per molecule in each direction) are short (2.693 Å) and therefore strong, whereas in the structure of the *epi* isomer, the shortest hydrogen bond is 2.731 Å. These features may be responsible for the high density and low solubility of *neo*-inositol.

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