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Control of hydrogen bonding in the design of new diol lattice inclusion compounds

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In order to be able to predict and then synthesize new lattice inclusion compounds with the helical tubuland diol host structure, the hydrogen bonding modes of a range of bicyclic and tricyclic diols have been studied using X-ray crystallography. Several distinct types of lattice structure have been recognized. Steric factors play a major role in determining which of these is produced in a given case. Establishment of a series of structural rules provides a window of opportunity for duplication of the helical tubuland host lattice by deliberate design and synthesis. New inclusion compounds resulting from this approach are presented.

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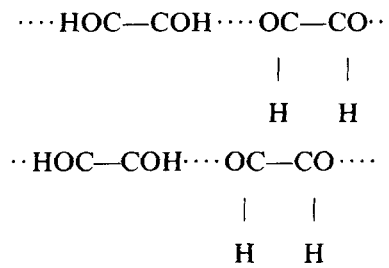
INTRODUCTION

Several years ago we synthesized the alicyclic diol **1** (see Fig 3) and discovered that it formed stable needle-like inclusion compounds when crystallized from most small common solvents.[1] Investigation of the structure of these compounds revealed that the guest molecules were contained in a series of parallel canals within the lattice.[2]

The structural core of this lattice type is a series of spiral spines of hydrogen bonds with trigonal symmetry (shown in Fig 1). Each of these spines is formed by three separate eclipsed columns of diol molecules each contributing one hydroxy group to give the hydrogen bonded sequence: ···OH···OH···OH···OH···. The diol molecules similarly form other spines through their second hydroxy group thereby propagating the lattice in three dimensions. As a result six spines and six diol molecules surround void spaces which have a roughly triangular shape (side *ca.* 6.3 Å) as shown in Figure 2. In the case of **1** the triangular unobstructed cross-sectional area is approximately 22.4 Å^2. The canal walls involve a double helical array of diol molecules hydrogen bonded in the sequence:



(where C—C represents the alicyclic skeleton in abbreviated form).

Projection views such as Figure 2 represent a slice through the needle axis of the crystal and consequently the helical characteristics are lost in these representations. These structures in space group $P3_121$ (or its enantiomorph $P3_231$) can only accommodate one diol enantiomer and are chiral materials. Thus crystallization

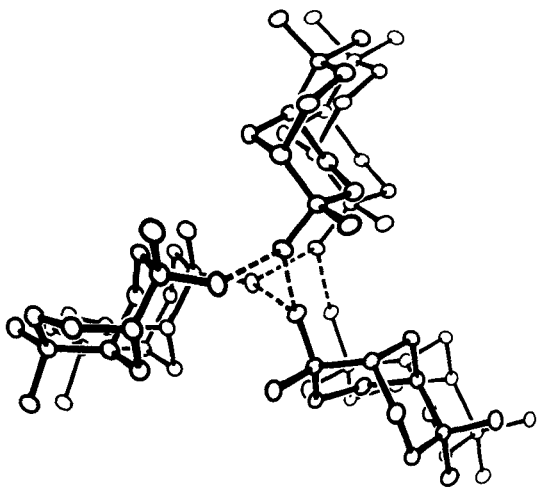


Figure 1 Part of a tight spiral spine of diol **1** molecules which constitutes the structural core of the helical tubuland lattice. The canal axis is vertical.

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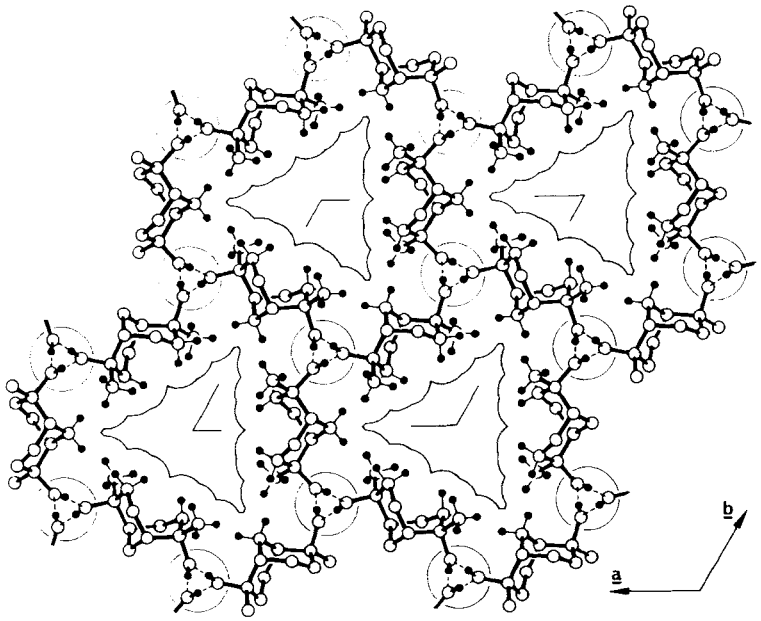

Figure 2 Projection view of the helical tubuland diol host network (space group $P3_121$) in crystalline **1**. Hydrogen bonds are marked as broken lines, and the helical hydrogen bonded spines are circled. The triangular cross-sectional areas of the parallel canals are defined by including the van der Waals radii of selected hydrocarbon hydrogen atoms (marked as black circles).[1a]

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of the racemic diol yields a conglomerate.[3] The entire lattice provides the volume for occupation by guest molecules, hence the description of such combinations as lattice inclusion compounds.[4] Since the crystal comprises a tubuland structure[5] somewhat similar to those of urea and thiourea inclusion compounds[6] we have termed the host arrangement the helical tubuland lattice and the resulting inclusion compounds the helical tubulates.

RESULTS AND DISCUSSION

Synthetic philosophy

On discovery of this novel structure we were immediately interested to learn whether other helical tubuland diol hosts could be synthesized. If this could be achieved then we would obtain a family of materials whose canal sizes and shapes would differ, and which consequently would provide a series of compounds with a range of different inclusion properties.

Intuitively this seemed possible, but such an undertaking raised fundamental synthetic questions. Not only would new specific structures need to be prepared but these would also have to retain the exact crystal space group of the prototype diol. Modern computational chemistry is able to predict much valuable data for unknown compounds but accurate prediction of hydrogen bonding arrangements, crystal packing, and space groups is not yet possible.[7] Furthermore, if such predictions cannot be made for a pure chemical substance then what likelihood would there be of achieving this for a mixture of two components?

In initially deciding to investigate this problem we were encouraged by the pioneering work of MacNicol[8] on derivatives of Dianin's compound and the hexa-host compounds,[9] and also the striking results from the Toda[10] and Weber[11] research groups. Clearly, lattice inclusion compounds are subject to structural rules which could be manipulated in a logical manner.

First, perhaps the analogy can be drawn with that of biologically active compounds. Traditionally, organic chemists have followed up the discovery of a new active compound by attempting to synthesize analogues which retain this important property. Often success has been achieved by application of chemical intuition despite the supramolecular chemistry of the mode of action being unknown or not understood. Equally importantly, the synthesis of substances which disappointingly proved to be non-active provided key information about necessary structural arrangements and such data were fed back into the synthetic program.

Secondly, lattice inclusion compounds may be a particularly good type of compound to attempt isostructural synthesis. Traditional wisdom is that molecules will pack as closely as they conveniently can in the solid phase.[12] A host such as diol **1** obviously is prevented somehow from doing this and therefore is forced into alternative arrangements. Whatever the

exact causes of this behaviour it seemed likely that they might be capable of transplant into new diol hosts.

These synthetic attempts ultimately proved to be successful. There is indeed a family of helical tubuland hosts and these materials are proving to have a fascinating chemistry.

Diversity of multicyclic diol hydrogen bonding

In this paper we explore the differing modes of hydrogen bonding encountered in bi- and tri-cyclic diols and attempt to rationalize their structural behaviour. We have determined the crystal structures of some 30 multicyclic diols and have found distinct patterns in their hydrogen bonding.[1] Here we will restrict discussion just to diols which share the following structural criteria: (a) Rigid or semi-rigid multicyclic ring systems, (b) C_2 symmetry, or average C_2 symmetry in solution, (c) diols with methyl substituents.

So far, six distinct diol structural types have been identified: (1) Helical tubuland; (2) double-stranded, (3) layer, (4) pillar, (5) helical, and (6) hydrate structures. The first of these has already been described in detail for the case of diol **1**. Examples, diols **2**–**6** shown in Figure 3, of each of the other types follow.

Double-stranded structures. Here the diol molecules are hydrogen bonded into chains but two adjacent chains also hydrogen bond to each other. The net result is a series of parallel double-stranded columns of diols with only van der Waals forces between the columns. This arrangement is typified by diol **2** whose crystal lattice is, in fact, comprised of two different doubly-stranded arrangements (Fig 4). As shown in the unit cell diagram, Figure 5, hydrogen bonding propagates the lattice in one dimension only.[13]

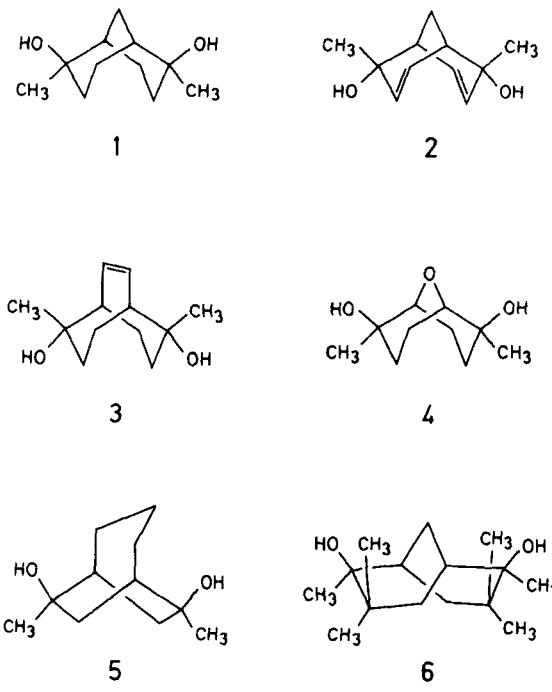

Figure 3 Structures of diols **1**–**6**.

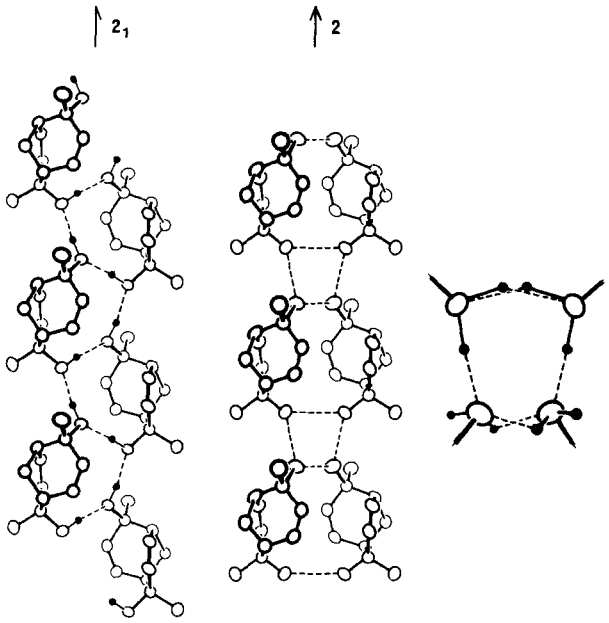

Figure 4 The double-stranded independent molecules A (left) and B (centre) of diol **2**. For the A molecules there is a 2_1 axis running between the two strands, whereas strands of B molecules lie around a two-fold axis. The disordered hydroxy hydrogen atoms of one cycle of the B-type are shown on the right.[13]

Layer structures. A very common lattice type is for four diol molecules each to contribute one hydroxy group to a hydrogen-bonded cycle.[14] Each of the other four hydroxy groups is contributed to a separate, new four-membered cycle and thus the hydrogen bonding network is propagated in two dimensions. Only van der Waals attractions are present between the separate layers. This type of structure is typified by diol **3** whose arrangement is shown in Figure 6.[15]

Pillar structures. If a heteroatom is present which can intercept the hydrogen bonding network then a complex arrangement can result such as with diol **4**. This is an example of a structurally simple molecule which encounters considerable difficulty in its crystal packing.[16] The unit cell contains 20 molecules of **4** involving six independent diols. Here the polar faces of many diol molecules hydrogen bond strongly to produce a series of pillars with polar interiors and hydrocarbon exteriors. These pillars have an octagonal coffin-shaped cross-section and are packed orthogonally (Fig 7). However these octagons can only

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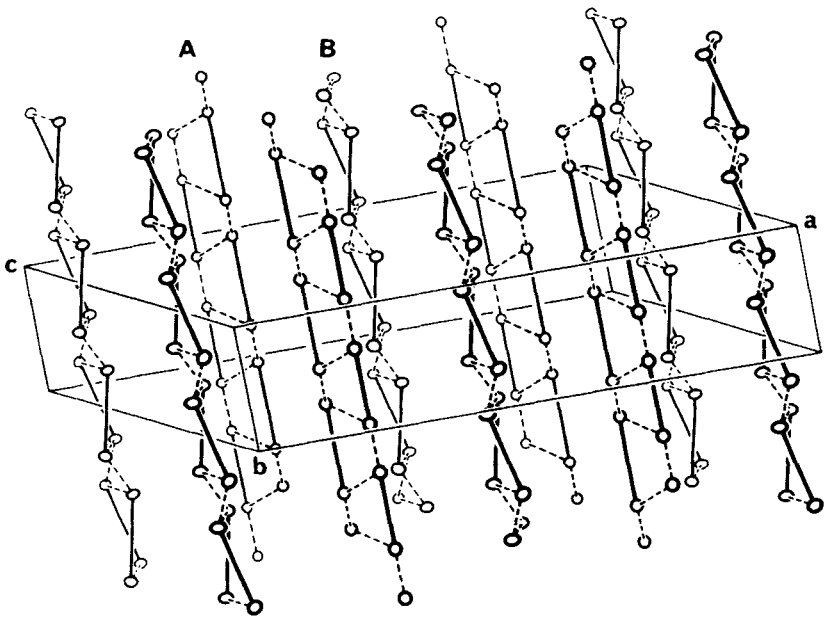

Figure 5 Arrangement of the hydrogen-bonded A- and B-type double strands of diol **2** in the unit cell, space group $C2/c$. For clarity, the diol molecules are represented as a single solid line connecting the two hydroxy groups of each diol. Hydrogen bonds are shown as broken lines.[13]

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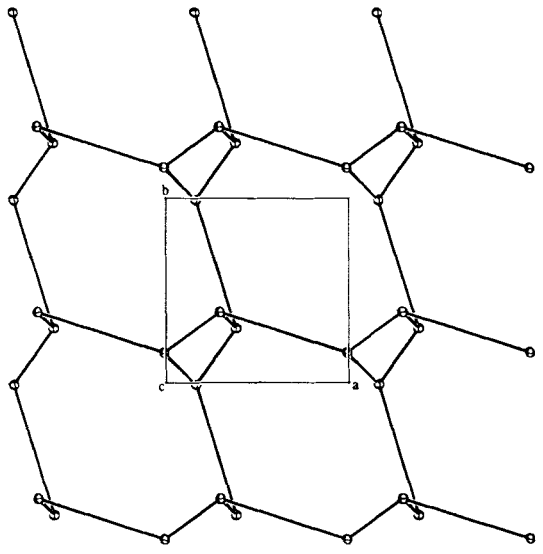

Figure 6 Diagrammatic representation of the layer structure (space group $P4_12_12$) of the diol **3**. Diol molecules are shown simply as solid rods connecting the two hydroxy groups. Oxygen atoms are drawn as open circles and hydrogen atoms are omitted. Four hydroxy groups each contribute to a hydrogen-bonded cycle. Extension of this arrangement through the other hydroxy groups produces a layer structure.[15]

pack by leaving square-shaped channels in a host-like manner along the pillar axis. These channels are occupied by further guest-like diol molecules which are only weakly hydrogen bonded to each other and to the pillars.

Helical structures. Other diols such as diol **5** crystallize with a helical arrangement.[15] Here hydrogen bonding is present as a continuous spiral in the c direction, with eight molecules constituting one turn of the helix. The other diol hydroxy groups form similar helices. Although the hydrogen bonding therefore is three-dimensional, the inter-helix volume is insufficient for inclusion properties to result (Fig 8).

Hydrate structures. Diol **6** is obtained as a monohydrate which retains its water of crystallization tenaciously.[17] In this structure the fully hydrogen-bonded water molecules function as links between four adjacent hydroxy groups to produce a layer structure (Fig 9).

Defining the molecular determinants

The diversity of hydrogen bonding arrangements encountered for diols **2**–**6** appears at first to be discouraging for the deliberate design of new helical tubuland diol hosts. For each of these five additional types of hydrogen-bonded structure a variety of different space groups has been encountered. Furthermore the five alternative types of structure usually do not result in conglomerates; both enantiomers are present in the crystals produced. Additional refinement of the synthetic protocol is clearly required.

First, it is necessary to avoid groups which can interfere with the hydroxy group hydrogen bonding. Thus the pillared structures, such as those formed by diol **4**, are ruled out.

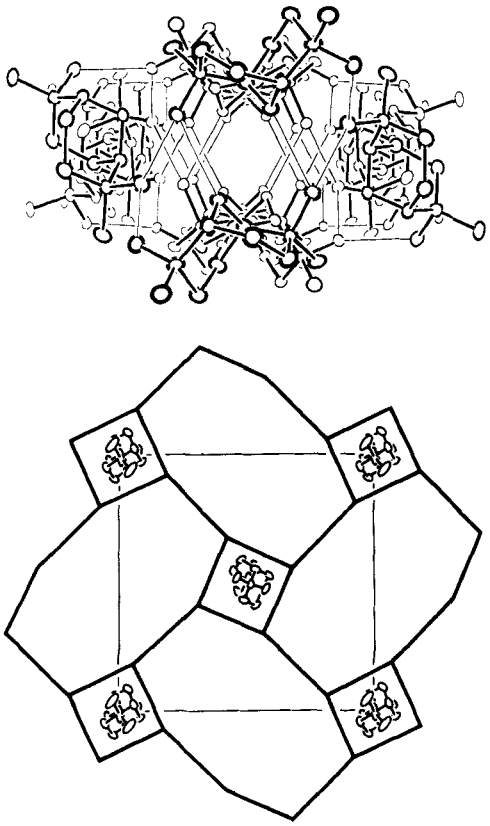

Figure 7 A detailed perspective view of one pillar formed by molecules of diol **4** is shown at the top. Hydrogen atoms are omitted for clarity. This arrangement produces a pillar with an octagonal coffin-shaped cross-section. The strong inward-facing hydrogen bonding (faint lines) results in a polar interior to the pillar and a hydrocarbon exterior. The lower Figure shows this arrangement projected onto the *ab* plane (space group $P2_12_12$) representing the pillars solely by their octagonal outline. These pack in a host-like manner leaving square-shaped canals occupied by guest-like molecules of diol **4** which are only weakly hydrogen bonded to themselves and the pillars.[16]

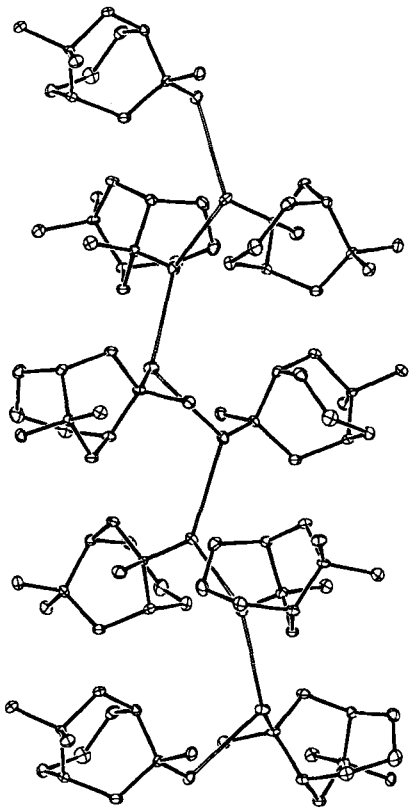

Figure 8 The hydrogen-bonded arrangement of diol **5** (space group $I4_1cd$) showing the continuous spiral spine along direction *c*. Eight diol molecules consitute one turn of the spiral surrounding the 4_1 axis of the unit cell.[15]

The double-stranded structures, such as those produced by diol **2**, can only form when there are no steric obstacles near the hydroxy groups. If steric crowding is only slightly increased then layer structures result. Thus diol **3** yields a layer structure simply by the presence of the addition of endo-hydrogen atoms compared with **2**.

Substituent groups close to the hydroxy groups increase the steric crowding too much for effective hydrogen bonding, as in the example of diol **6**. It is well known in other alcohol structures that this tends to result in hydrate formation, with the additional water molecules acting as spacer links between the organic molecules.[18]

If the diol skeleton has a very slight degree of twist incorporated in its carbocyclic skeleton, and a molecular bridge is inserted 'syn' to the hydroxy groups as a steric barrier to prevent formation of layer structures, then a helical structure is produced[15] as for diol **5**. If rather more twisting is possible, for example by conformational changes, then a helical tubuland structure can result.[1]

Addition of these molecular requirements to the three criteria used earlier provides a set of molecular determinants (or membership rules) which, if followed in the design of new diol molecules, is likely to afford new helical tubuland lattices.[19] In other words there is a window of opportunity which depends on molecular symmetry, the steric environment around the hydroxy groups, and the prevention of otherwise favourable hydrogen bonding patterns. Diol molecules outside this window have no likelihood, but those within this window have a high probability, of forming the helical tubuland lattice. Figure 10 shows the structures of four early examples of diols which obey all the above structural rules and which indeed do have this lattice.[1,20] For each of diols **7–10** the projected cross-sectional area of one canal only is shown. In two cases (**8** and **10**), parts of the diol molecules themselves occupy the canal locations. While being members of the helical tubuland family these compounds are unable to have inclusion properties. In contrast, the other two diols have large

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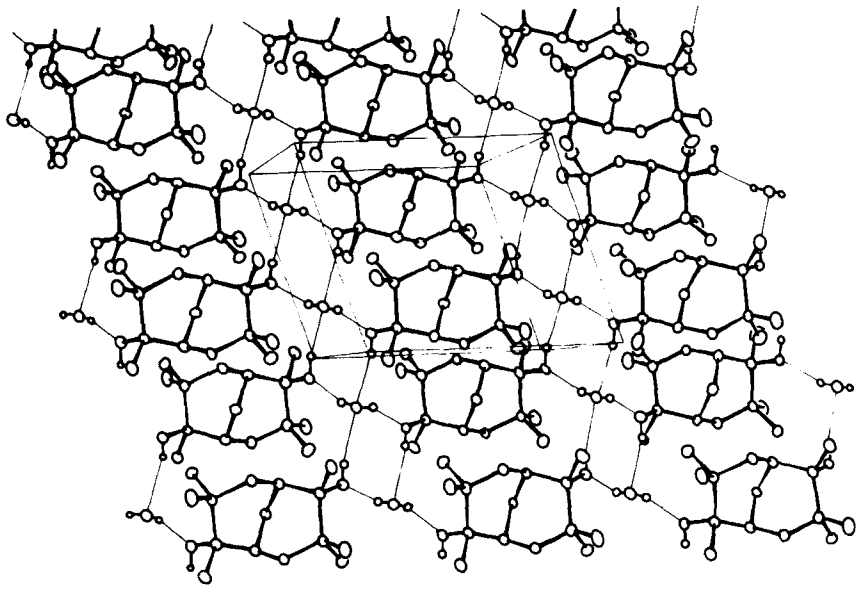

Figure 9 The packing arrangement of diol **6** and water molecules in the monohydrate structure (**6**)·(H_2O). Both enantiomers of **6** are positioned with their C-9 bridge up or down such that their ring subsituents are all orientated in the same direction. The fully hydrogen-bonded water molecules act as bridging links between four neighbouring diol molecules to produce the layer structure shown (space group $P\bar{1}$).[17]

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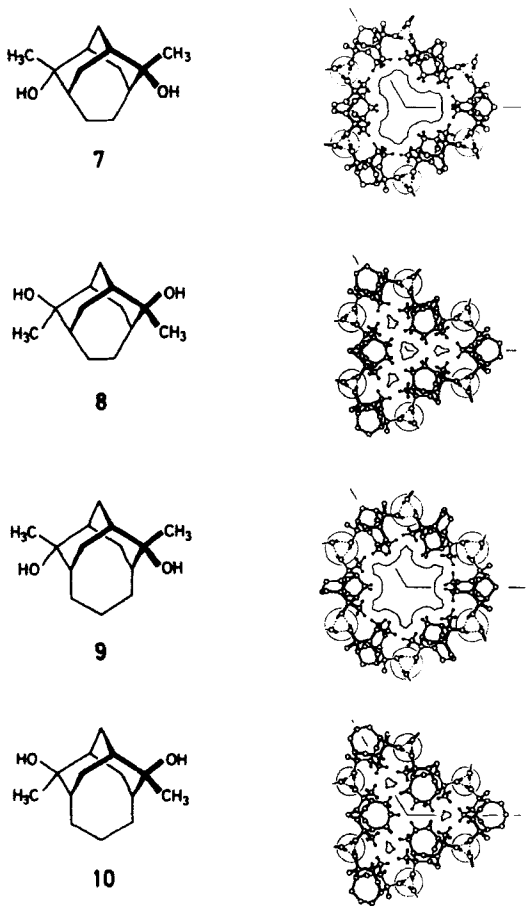


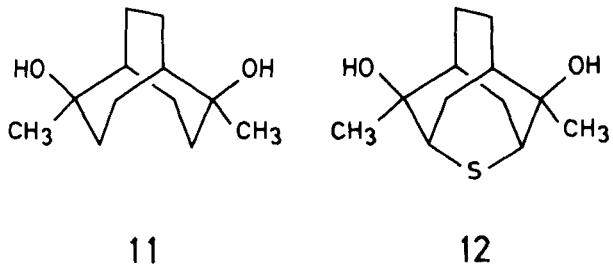
Figure 10 Structures of diols **7**–**10** showing one canal only of their helical tubuland lattice.[1,20]

canals and, like **1**, are potent host molecules for a wide variety of guests. Diol **7** can form two different, but related, host lattices.[21] Many guests result in helical tubulate inclusion compounds but with small guests an alternative lattice type is produced which we term the ellipsoidal clathrate type. Here both diol enantiomers are present and the guests are enclosed in ellipsoidal cavities resulting from constricted canals around four-fold axes.[22]

Design of new inclusion hosts: isostructural synthesis

Armed with the above knowledge it then became a practical proposition to design new diols which had a good chance of behaving in a similar fashion to **1** and **7**–**10**. A major aim here was to obtain a series of compounds with a variety of different canal sizes and shapes, so that a gradation of inclusion properties could be made available and exploited.

The new diols **11** and **12** (Figure 11) are examples of those which have been synthesized recently to confirm these ideas. Prior to its preparation we carried out molecular modelling studies on **11**, assuming that it would have the correct lattice type, in order to estimate its likely canal topology. This estimation (shown in Fig 12) led us to believe that the canal cross-section would be roughly circular in shape and would have an unobstructed area comparable with that of the previous diol **9** (which was the one with the largest canal cross-section).



11 12

Figure 11 Structures of diols **11** and **12** used in prediction of inclusion behaviour.

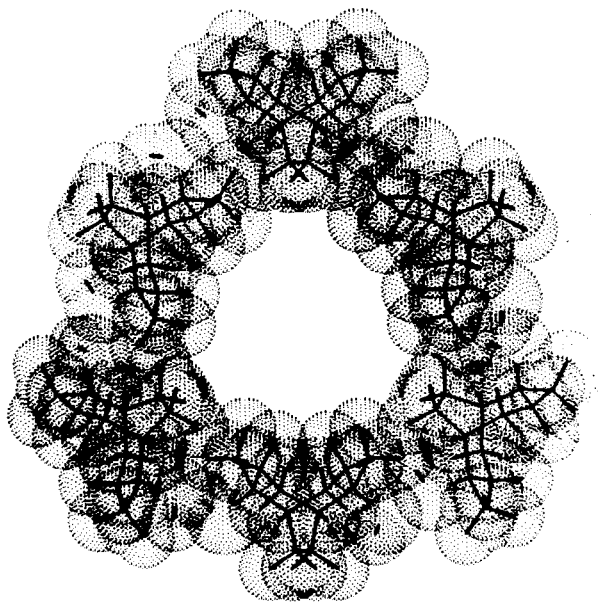


Figure 12 Predicted model of one canal of the helical tubuland crystal structure of diol **11**.[15]

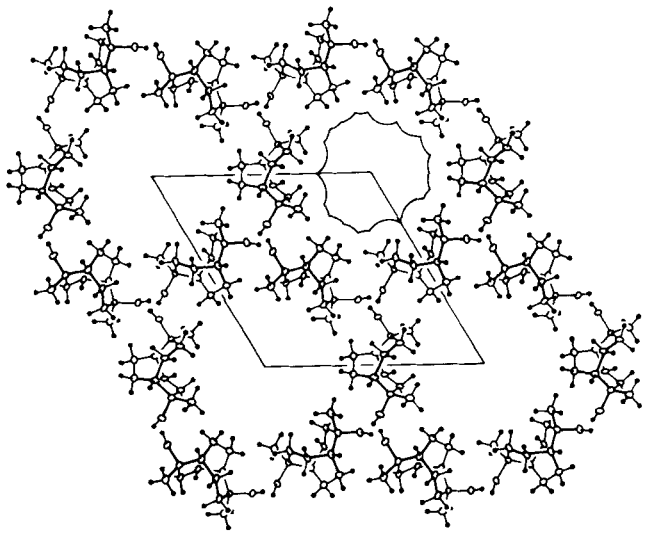


Figure 13 Projection view of the crystal structure of diol **11** determined by X-ray crystallography.[15]

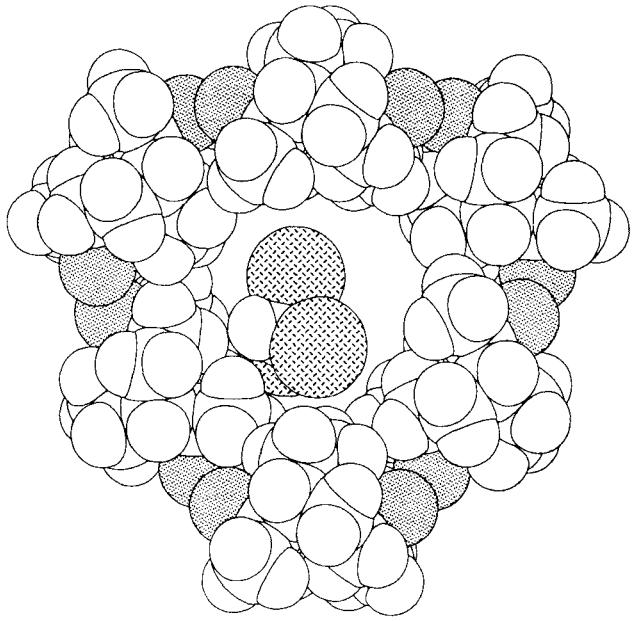


Figure 14 Projection view of one canal of the helical tubulate inclusion compound $(\mathbf{11})_3 \cdot (CHCl_3)_{1.5}$ showing a typical guest orientation in one canal of the crystal structure.[15]

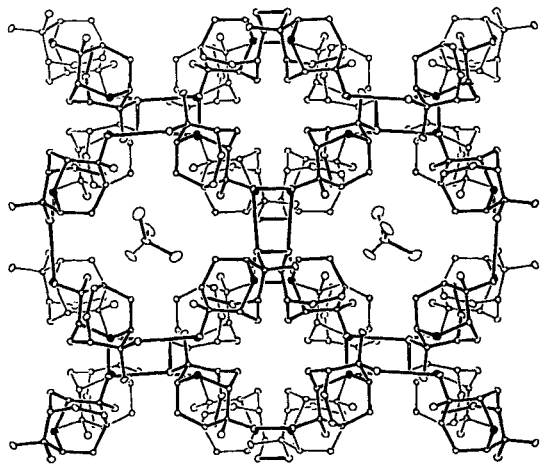


Figure 15 Crystal structure of the ellipsoidal clathrate structure of $(\mathbf{12})_4 \cdot (CHCl_3)$ projected along the canal axis. Hydrogen atoms are omitted for clarity. The positions and orientations of the chloroform guest molecules in the constricted canals are also shown.[15]

Crystallization of **11** from chloroform did indeed yield an inclusion compound. Figure 13 shows the actual X-ray single crystal structural determination proving that the compound does possess the helical tubuland host lattice. The canal cross-section shape is remarkably similar to the prediction. Furthermore the unobstructed area is the biggest so far encountered; 36.7 Å^2 compared with 34.7 Å^2 for diol **9**. A typical arrangement of the guest chloroform molecule in one canal of the structure is presented in Figure 14.[15]

Diol **12** contains a heteroatom as part of its structure but, unlike **4**, we did not expect it to interfere

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with the hydrogen bonding network. By analogy with diol **7** this compound was anticipated to produce an ellipsoidal clathrate inclusion structure when crystallized from chloroform. This was fully confirmed by experiment,[15] this inclusion compound being isostructural with the earlier compound (space group $I4_1/acd$). Figure 15 shows the crystal structure of **12** showing the arrangements of the chloroform guest molecules in their ellipsoidal cavities.

CONCLUSIONS

While the calculation of exact crystal structures of molecules from first principles remains unfulfilled at the present time we have demonstrated that, in at least some cases, prediction by analogy can be successful. A clear understanding of the factors influencing formation of the structure must be available so they can be applied to the synthesis of new hosts. Lattice inclusion compounds are a particularly suitable type of material for conducting such isostructural syntheses, and we predict that sets of molecular determinants will be discovered for other host systems. Application of these rules will then allow the logical development of new families of inclusion compounds.

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