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Helical Tubuland Diols: A Synthetic and Crystal Engineering Quest

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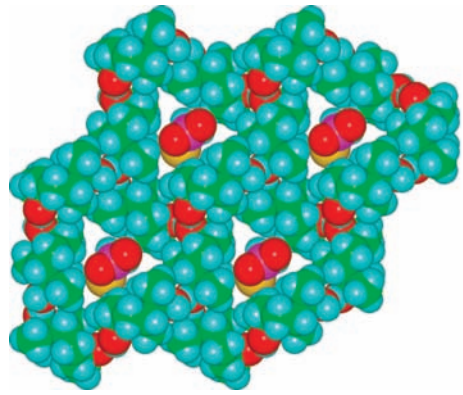
CONSPECTUS

Despite many advances in recent years, crystal engineering remains a risky venture. A successful outcome requires manipulation of the noncovalent bonding and properties such as size, shape, repulsion, attraction, polarity, and chirality. In this Account, we describe the interplay of crystal engineering and synthetic organic chemistry required to develop the family of helical tubuland diol hosts, the members of which exhibit a wide range of tube dimensions and inclusion properties.



Certain alicyclic dialcohols crystallize with a hydrogen-bonded network structure, termed the helical tubuland lattice, in space group $P3_121$ (or its enantiomorph $P3_221$). Double helices of diol molecules surround parallel tubes that contain guest molecules, which are included on the basis of size and shape rather than functional group. The crystal structure of $(diol)_3 \cdot (chloroacetic\ acid)_{1.2}$ is illustrative. These chiral helical tubulate lattice inclusion compounds are formed when the racemic host diol is allowed to crystallize from solution. Complete enantiomer separation occurs during this process, producing a 1:1 mixture of pure (+)- and pure (−)-crystals (a conglomerate).

The challenge of creating this family of compounds required the development of much synthetic chemistry, in particular new pathways to alicyclic ring systems with specific substitution patterns. It was also necessary to understand and control the supramolecular properties of the diol molecules. What makes the original compound tick, and why did it behave in this remarkable manner, when most of its structural neighbors crystallize totally differently? The synthesis of new helical tubuland diols requires not just preparation of a new molecular structure but also a transplant of the original unchanged hydrogen-bonding supramolecular synthon. Synthesis of the specific crystal space group is necessary.

This was achieved by defining structural characteristics, termed molecular determinants, which are essential for the helical tubuland structure to occur. If these requirements were met, then the target molecule had a high probability of success. This investigation has close conceptual parallels with the search for pharmacophore properties of bioactive molecules. In both situations, parts of a molecule with little or no chemical reactivity may actually play vital supramolecular roles. The review illustrates how crystal engineering is based on specific supramolecular properties that can be uncovered and then exploited by synthetic chemists.

Introduction

Crystal engineering is a subset of supramolecular chemistry aimed at achieving specific solid-state objectives. The synthetic target may be a particular type of structure, or it may be a designed functional property. Such outcomes require manipulation of not just the noncovalent bonding, but also combinations of properties such as size, shape, repulsion, attraction, polarity, and chirality. Success is therefore far from assured, despite

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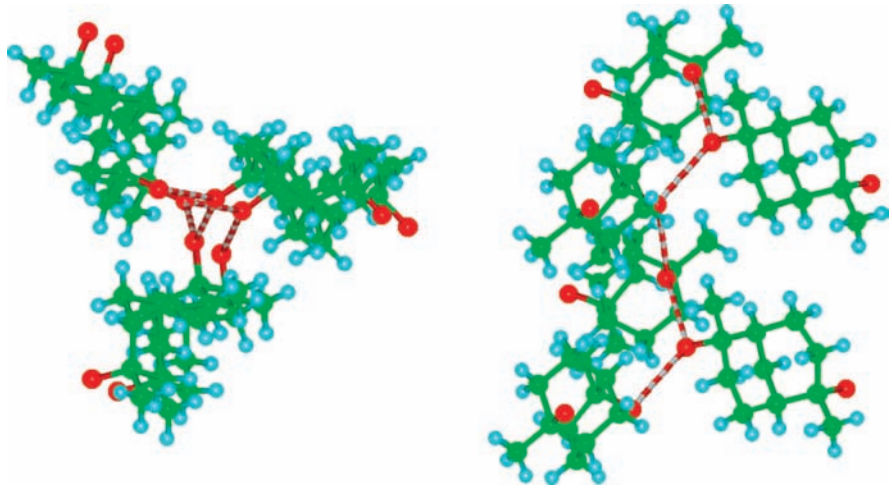


FIGURE 1. Part of the infinite hydrogen-bonded chain of molecules surrounding a 3-fold screw axis that acts as the spine supporting the helical tubuland crystal structures. This example, diol **3**, is viewed (left) close to the *ab* plane and illustrates the eclipsed stacks of diols and (right) with the *c* axis vertical. Color code: O red; C green; H light blue. Hydrogen bonds are indicated by the dashed lines.

the considerable advances made in this field over recent years.[1−4] The development of the helical tubuland (HT) diol host family, first glimpsed in 1979,[5] is described here. Although the crystallographic and inclusion aspects of these substances have been reviewed previously,[6,7] this Account presents their first detailed analysis from a synthetic, supramolecular, and crystal engineering perspective.

The Helical Tubuland Structure

The HT diols are a group of alicyclic dialcohols that share a remarkable crystal structure and a number of distinctive physical characteristics. Their structural foundation is a series of infinite hydrogen bonded chains ···O−H···O−H···O−H··· O−H··· that surround crystallographic 3-fold screw axes, this supramolecular synthon[8] providing rigid rod-like spines that run along the *c* direction of the crystal (Figure 1). The molecules extending outward from each spine produce 3-fold stacks of eclipsed diols around the spine, and each molecule bears a second hydroxy group that contributes to another identical spine. This propagation generates a low-density hydrogen-bonded network lattice in which the diol molecules enclose tubes that may be filled by guest molecules to optimize the crystal density.[9]

The structure of the tube walls is especially interesting because they are constructed from two identical diol helices that are not directly linked through hydrogen bonding. Crystal symmetry places a 2-fold axis through each diol molecule. All hydroxy groups in a HT compound are identical and participate in one donor and one acceptor hydrogen bond, but along each tube wall helix the molecules act alternately as double donors (pointing inward) and double acceptors (pointing outward) as illustrated in Figure 2. All the molecules are

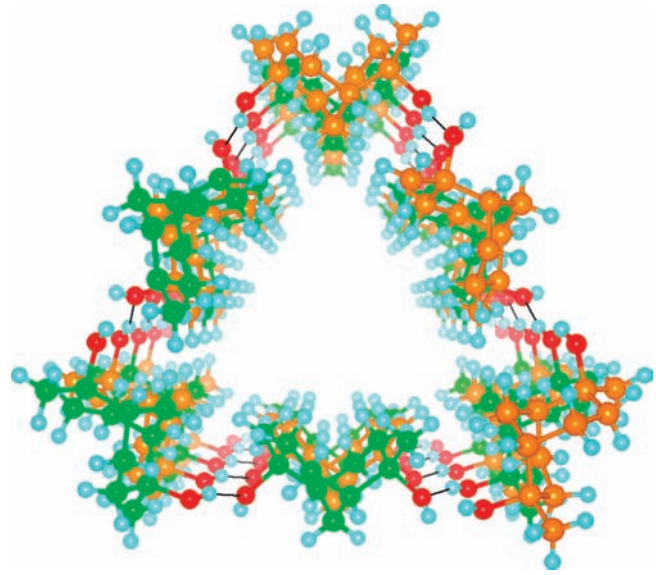


FIGURE 2. Perspective view down one tube of diol **3**, showing the packing of the inward (double H-donor) and outward (double H-acceptor) molecules and the double helical motif (orange or green C atoms).

crystallographically identical, however, since each is shared. Thus, a double hydrogen bond donor with respect to one tube is simultaneously a double acceptor to its neighboring tube, and *vice versa*.

The double helix motif is iconic in structural chemistry and also has architectural applications such as the double staircase leading to the Vatican Museum and Le Grand Escalier of the Chateau Chambord in the Loire valley.[7] Especially noteworthy is the unique Marina Bay Bridge currently under construction in Singapore, where pedestrians will be able to walk through a double helical macro-scale version of DNA.[10] The HT version is different from these man-made structures, since its architecture comprises many double-helix-walled tubes running parallel along

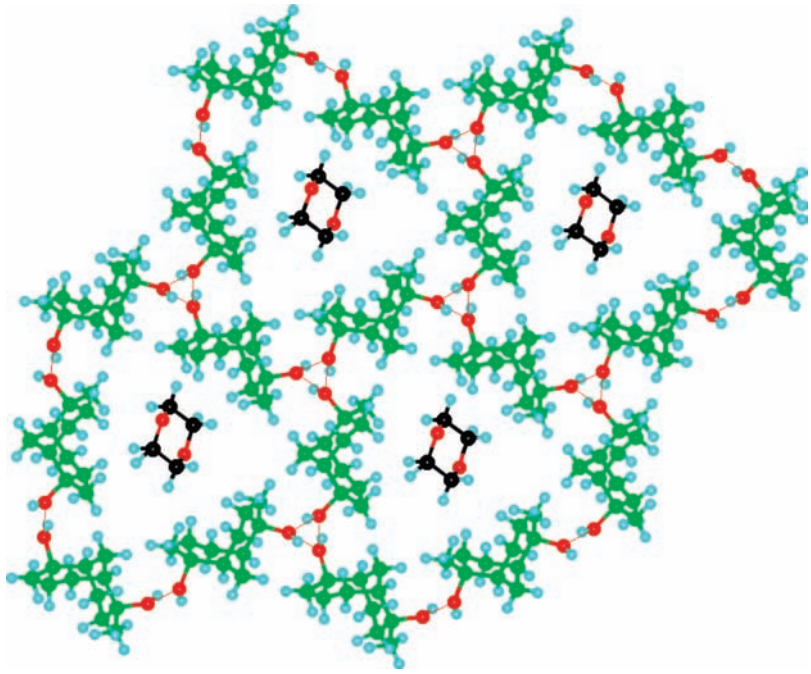


FIGURE 3. Section across the *ab* plane of four adjacent tubes in the crystal structure of $(\mathbf{3})_3 \cdot$(1,4-dioxane) with the guest carbons colored black. The helical spines appear as triangles in this projection, and the eclipsed stacks of diols surround each spine. For clarity, only one disorder component of the guest is shown.

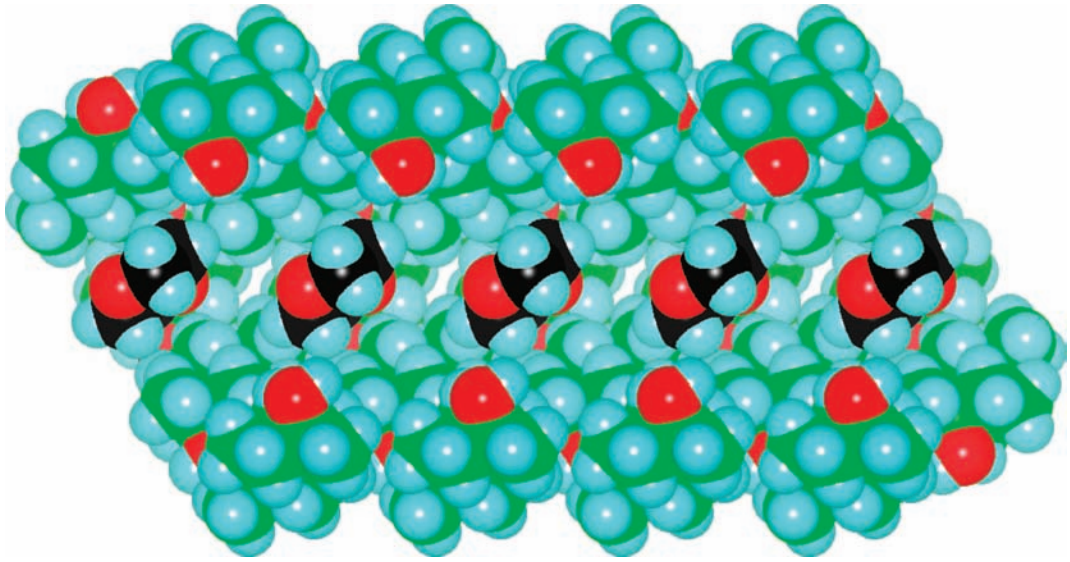


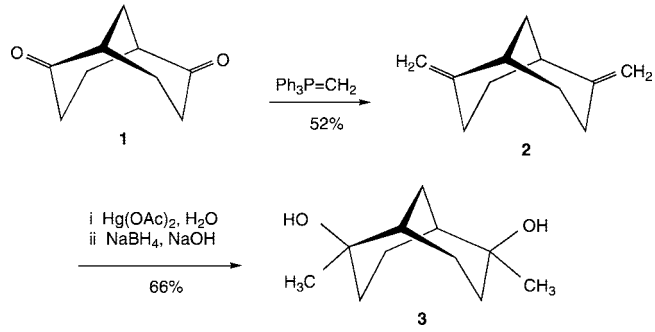
FIGURE 4. Cut-away view of just one tube in the crystal structure of $(\mathbf{3})_3 \cdot$(1,4-dioxane) with the three front stacks of diol molecules removed. The *c* axis is horizontal in this illustration.

the crystal *c* direction. Each double helix is independent if only one tube is considered but is, of course, linked to its neighbors by means of the hydrogen-bonded spines.

Many of the HT diols crystallize with tubes that are sufficiently large to enclose guest molecules, thereby yielding helical tubulate inclusion compounds. The interior lining of the tubes is normally hydrocarbon in nature. Thus the host–guest interactions are weak dispersion forces, making the HTs potent host molecules for a wide range of guest types. Inclusion is determined by the size and shape of the guest rather than its functional group composition. The example illustrated in Figures 3 and 4 has the composition $(\mathbf{3})_3 \cdot$(1,4-dioxane), but the host and guest arrangements are not necessarily commensurate in other cases.[9,11]

A family of HTs has been developed, and these provide a range of tube cross-sectional areas for guest inclusion. Those with the smallest tubes are capable of existing guest-free without collapse of the HT lattice.[6,9] This is a particularly rare property for small molecular building blocks that are only linked by weak intermolecular attractive forces.

SCHEME 1. Preparation of the First Bicyclic HT Diol **3**



Furthermore, the HT structure is handed and can contain only one diol enantiomer. Most molecules illustrated in the reaction schemes of this Account are chiral. In all such cases, racemic compounds were used, but only one enantiomer is shown for simplicity. Crystallization of a racemic HT diol results in spontaneous self-resolution to produce a conglomerate:[12] that is, a mixture of an equal number of chirally pure (+)- and (−)-crystals is formed, each in space group $P3_121$ or its enantiomorph $P3_221$. Arguably, the HT diols are the world record holders for a family of compounds that can be relied upon to self-resolve when they are crystallized.[13] Chirally pure HT diols can also be synthesized, if necessary, and the use of two of these will also be discussed.

Beginnings

The excitement surrounding the discovery of the first HT diol structure by Bishop and Dance has been related previously.[14] Dione **1** yielded the diene **2** by Wittig reaction, and its subsequent hydration gave the diol **3**, which, completely unexpectedly, showed the unprecedented HT host properties (Scheme 1).[5,9,11]

These results raised immediate questions regarding the solid-state structure of these inclusion compounds and the scope of possible guest inclusion. More fundamentally, could other structural relatives of **3** be synthesized? The molecular packing arrangement was so elegant that we felt that it could not be unique. Its duplication would, however, require a combination of conventional organic synthesis and careful supramolecular design. In this case, the target required had a novel structure but was also one with the specific functional property of host behavior. Since the HT structure depends on formation of a specific crystal space group, a mandatory minimum requirement would be for new examples to contain an identical hydrogen-bonding motif. Careful organic synthesis and crystal engineering would be required to meet these needs.[15]

The Molecular Determinants

We approached this problem by trying to list a group of characteristics that might define HT behavior and that could be used as a guide for selecting appropriate synthetic targets. The resulting crystal structure data, both successes and noncompliant cases, could then be used to further refine these rules. We published our first iteration of the HT molecular determinants (MDs) in 1987,[16] but the version listed here represents our current level of understanding.

(a) The tertiary alcohol groups must have a methyl substituent. All attempts to use other substituents have given alternative hydrogen-bonding arrangements. The methyl group has the appropriate steric properties to induce the hydroxy groups to hydrogen bond around a 3-fold screw axis. It also has the correct size and rigidity to support the tube wall structure and prevent collapse to a denser structure.

(b) The alicyclic structure must have a small amount of twist. This may be built into a rigid alicyclic skeleton, or it may be attainable in the crystal by means of a small degree of conformational flexibility present in the ring system. This property assists the development of helicity during the assembly process.

(c) A bridge on the opposite side of the skeleton to the hydroxy groups is optional. Its size can therefore be modified, or it can be deleted entirely, to produce new HT diols with differing tube dimensions.

(d) A molecular bridge must separate the two hydroxy groups. This ensures that both hydroxy groups act independently of each other to form two separate helices. This bridge also buttresses the tube walls against internal collapse.

(e) Substituent groups around the periphery of the skeleton usually should be avoided. The only instances where substituents have led to success are where they are situated remote from the hydroxy groups and also occupy otherwise void space within the HT tubes. Such substituents must not interfere with the hydroxy group hydrogen bonding.

(f) The diol molecules must be capable of achieving average C_2 rotational symmetry in the solid state. The diol may have actual C_2 symmetry or may achieve this in solution (e.g., as indicated by ^{13}C NMR spectroscopy for **9**). For some diols with only a pseudo-C_2 axis due to their molecular substitution, average C_2 symmetry can be attained by means of disorder in the crystal. These compounds also produce HT diols.

Alicyclic diols that obey all six rules and are sterically capable of fitting this type of lattice lie within a window of oppor-

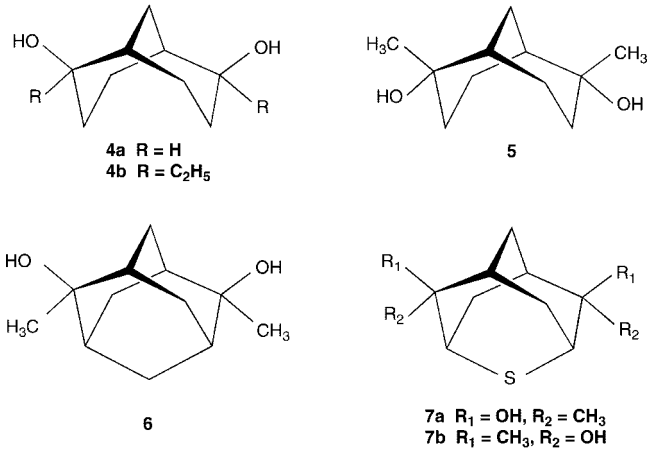


FIGURE 5. Closely related diol molecules **4**−**7** that do not crystallize with the HT structure.

tunity and will probably function as a HT diol. The experimental work leading to these conclusions will now be discussed.

Failures and First Successes

Our initial approaches led only to disappointment (Figure 5). Replacement of the methyl groups of **3** by either hydrogen or ethyl substituents gave compounds **4a** or **4b** with entirely different crystal structures.[17] The CD_3-substituent is appropriate, but CF_3 is not. Also unsuccessful was the doubly epimeric diol **5**. More unexpectedly, replacement of the bicyclo[3.3.1]nonane skeleton of **3** by the adamantane (**6**) or the thiaadamantane (**7a**,**b**) ring systems resulted in failure.[18]

Of course, the alcohol functional group can hydrogen bond in many alternative ways. Brock has analyzed monoalcohol crystal structures, finding a prevalence of high-symmetry space groups and that hydrogen-bonded rings and chains predominate.[19] Our noncompliant alicyclic diols tend to form cooperative hydrogen bonded $(O-H)_4$ or $(O-H)_6$ cycles, helical chains, and ladder assemblies (Figure 6). Although these supramolecular synthons contain closely related hydrogen-bonded arrangements, some crystal engineering prediction of these is possible.[15,18,20] However, the object of the present work was to avoid their formation entirely. Such control depends largely on the shape and bulk of the alicyclic diol and, especially, design of the steric environment surrounding the diol hydroxy groups. The six molecular determinants provide this degree of selectivity.

It was not until Stephen Hawkins prepared homoadamantane derivatives (Scheme 2) that success was achieved. He targeted the diols **9** and **11**, both of which do have a HT crystal structure. Diol **9** has a trilobed tube cross-section larger than the triangular cross-section of the original structure **3**. In contrast, the tubes of **11** are largely self-occupied by the diol molecules. Hence, compound **9** is another excellent host molecule, but **11** is only obtained guest-free.[21]

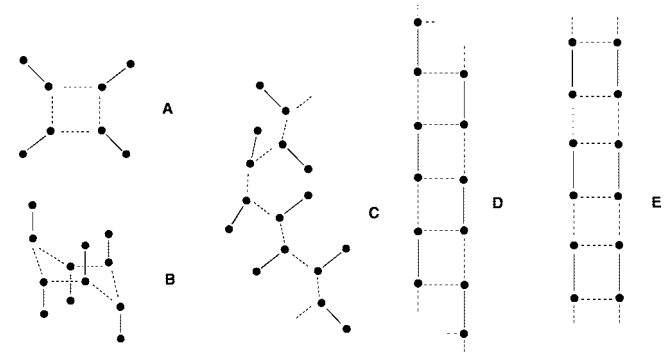
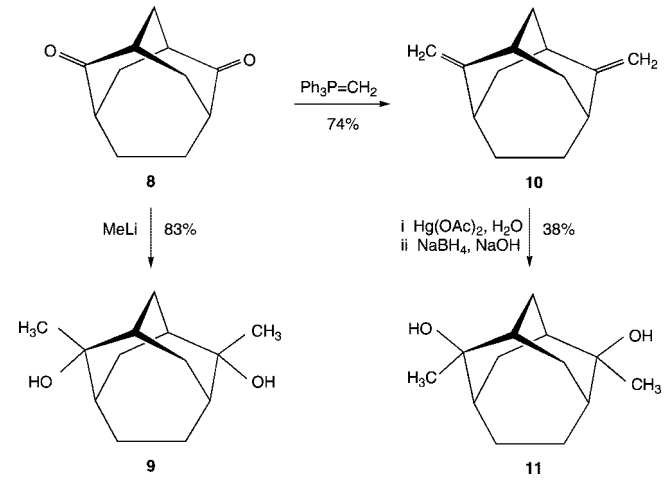


FIGURE 6. Typical hydrogen-bonded supramolecular synthons employed by non-HT forming dialcohols (represented here as dumbbell shapes with their hydrogen bonds shown as dashed lines): (A) $(O-H)_4$ cycle; (B) $(O-H)_6$ cycle; (C) helical chain; (D) staircase-ladder; (E) stepladder.

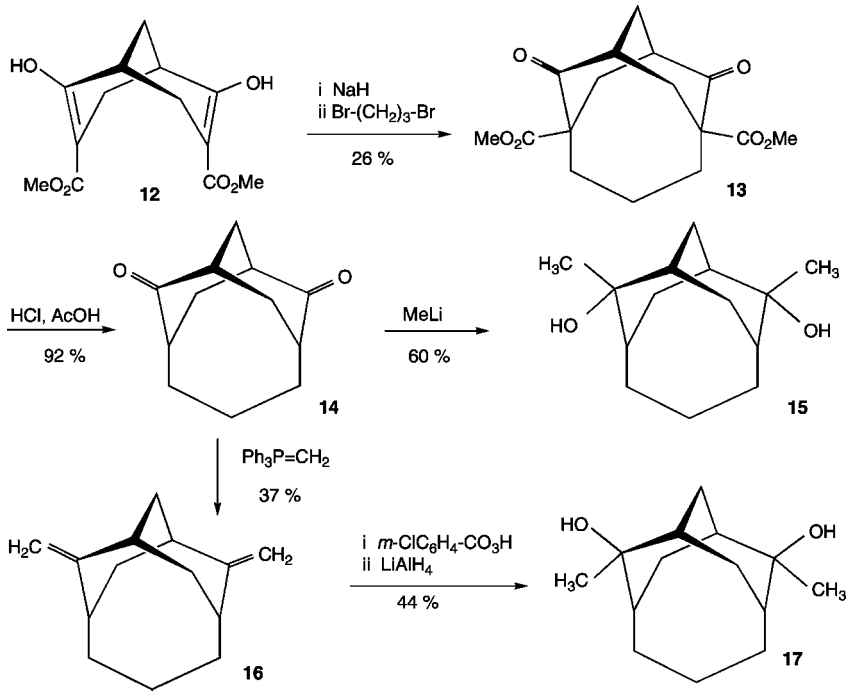
SCHEME 2. Synthesis of the Homoadamantyl HT Diols **9** and **11**



Analogous results were obtained using the bishomoadamantyl ring skeleton (Scheme 3). Diol **15** has an even larger, star-shaped tube cross-section and is another versatile host molecule,[21,22] whereas the tubes of **17** are now almost completely filled by itself.[21] In these syntheses, the use of the dione (**8** or **14**) and diene (**10** or **16**) intermediates allowed efficient access to both C_2-symmetric diols (**9** and **11** or **15** and **17**, respectively). The two faces of the carbonyl group, or its methylidene analogue, are dissimilar: that facing the methano bridge is more exposed and therefore provides good facial selectivity in the alkylation or hydration reactions illustrated.

These four successes confirmed our belief that a family of HT compounds did exist and could be synthesized in a logical manner. Observation of the inappropriate structures **4**−**7** also helped clarify the MDs and began to reveal how crystal engineering concepts could be used to our advantage. The tra-

SCHEME 3. Synthesis of the Bishomoadamantyl HT Diols **15** and **17**



ditional synthetic organic preparation of homologues by varying the alcohol substituents (H, Me, Et, etc.) was clearly inappropriate here, so MD (a) requires methyl groups exclusively. The most surprising finding was the failure of the adamantane **6** and thiaadamantane **7a**,**b** compounds to form the HT structure. Thus MD (b) requires a small degree of twist around the C_2 axis, or pseudo-C_2 axis, of the diol. This encourages development of the helical hydrogen-bonding chains. Such twisting is present in all five successful HT diols, where it can be assisted by conformational mobility, but it is absent in **6** and **7** due to their rigid frameworks.

It was also clear that the molecular bridges lying on the C_2 axis, far from being benign, played a significant role in the HT structure. Comparision of diol **3** with **11** and **17** revealed that the bridge *anti* to the hydroxy groups was optional. Thus MD (c) allows it to be varied in size, or even omitted. In contrast, for MD (d), the behavior of diol **5** demonstrated that the presence of a bridge *syn* to the hydroxy groups was critical in insulating these from each other. The tubes of the HT diols **11** and **17** are too small to accommodate guest molecules, but they do not collapse to yield a higher density structure. This demonstrates that the molecular bridges and methyl groups play important structural roles whereby these substructures lock the tube walls into place. This three-dimensional behavior has close analogies with the two-dimensional interaction of the voussoirs and keystone to produce a stone arch (Figure 7).[23] This characteristic applies across the whole HT family, but not all such tubes can survive when empty; for example, that of **3** can but not those of **9** or **15**.[6]

The Ring Expansion Approach

A significant early problem was the lack of literature methods for obtaining ring systems of interest or for making derivatives with the required substitution. Consequently, several new synthetic approaches have been devised, one of these

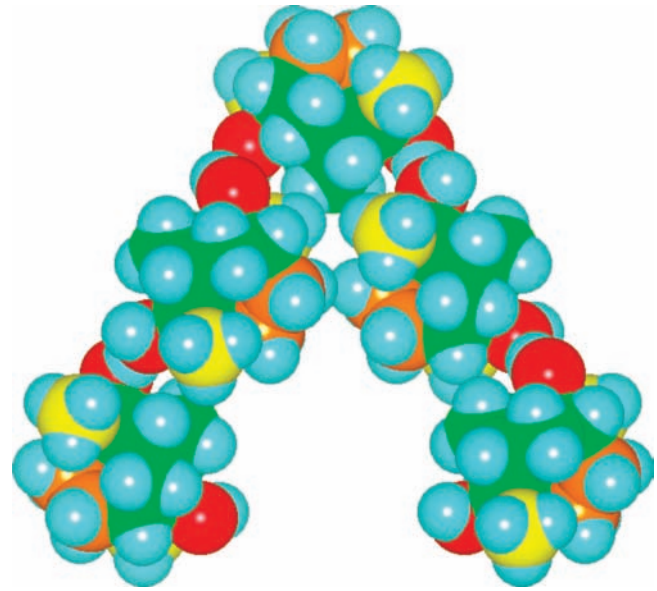
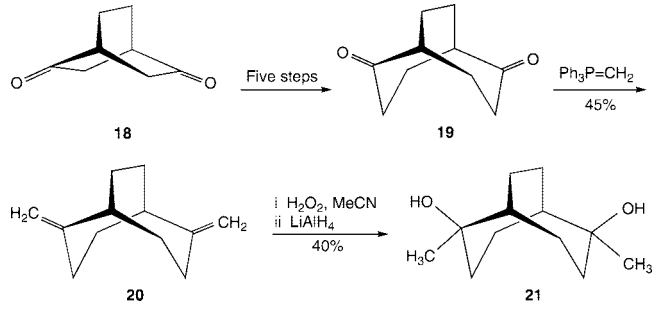
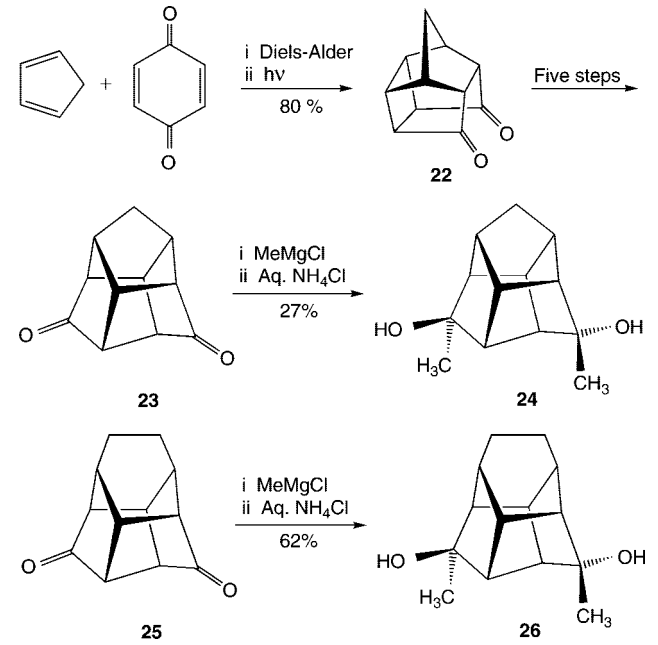


FIGURE 7. Part of the tube wall present in solid HT diol **11**, showing its relationship to a stone arch. Methyl C is yellow and ethano bridge C orange.

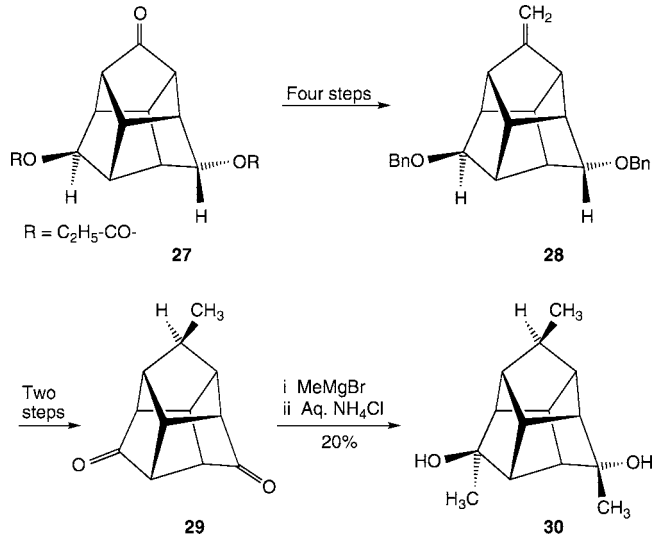
SCHEME 4. Ring Expansion Synthesis of HT Diol **21**



SCHEME 5. Synthesis of the Pentacyclic Cage HT Diols **24** and **26**

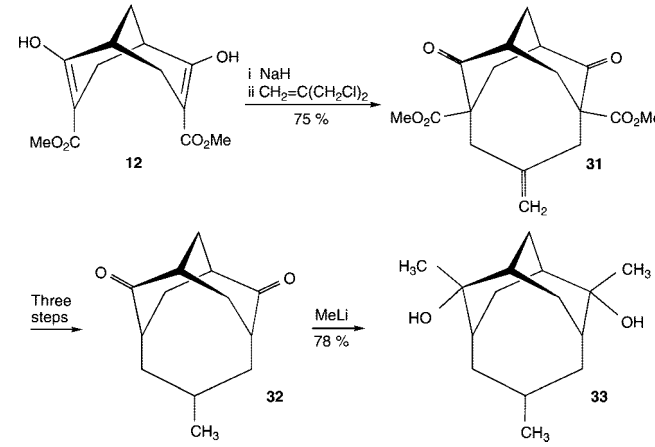


SCHEME 6. Synthesis of the Non-C_2-Symmetric HT Cage Diol **30**



being the route to diol **21** outlined in Scheme 4. The key step in this synthesis by Sungho Kim is a double Tiffeneau–Demjanov ring expansion, which allows the available bicyclo[2.2.2]octane-2,5-dione **18** to be converted into the new bicyclo[3.3.2]decane-2,6-dione **19**. Wittig reaction afforded diene **20**, which was subjected to Payne oxidation followed by reductive ring opening to yield the required diol. As anticipated, diol **21** crystallized as the helical tubulate from chloroform.[24]

SCHEME 7. The Efficient Bridging Process and Formation of HT Diol **33**



Pentacyclic Cage HT Diols

During a visit to Denton, Texas, Alan Marchand commented that the dione **23**,[25] (available *via* the well-known dione **22**) would be readily convertible into the pentacyclic cage diol **24** and that this appeared to satisfy all our molecular determinants. This compound was synthesized by Yanjun Wang and was indeed found to be an excellent HT host.[26] Unfortunately, the methylation step (Scheme 5) is indiscriminate and requires separation of all three diol products. Greatly improved facial selectivity was achieved by Paul Ahn in the analogous reaction of ethano-bridged dione **25**, and the product **26** is also a HT diol.[27] Both **24** and **26** have a rigid skeleton with no possibility of the conformational mobility present in the previous HT diols. Unlike the rigid compounds **6** and **7**, however, their pentacyclic skeletons contain built-in twist that satisfies the requirements of MD (b).

Further, a related non-C_2-symmetric HT diol **30** was prepared by Zenghui Liu as shown in Scheme 6. The ketone functionality of **27**[28] was first elaborated into the methylidene derivative **28**, and thence to the methyl dione **29**. Once again methylation was stereochemically indiscriminate, but the required isomer **30** could be separated, and this diol also had a HT crystal structure.[29]

This key compound was targeted to probe the nature of MD (f) because, initially, it was thought that C_2 symmetry was obligatory. Although the HT diols **15** and **17** have average C_2

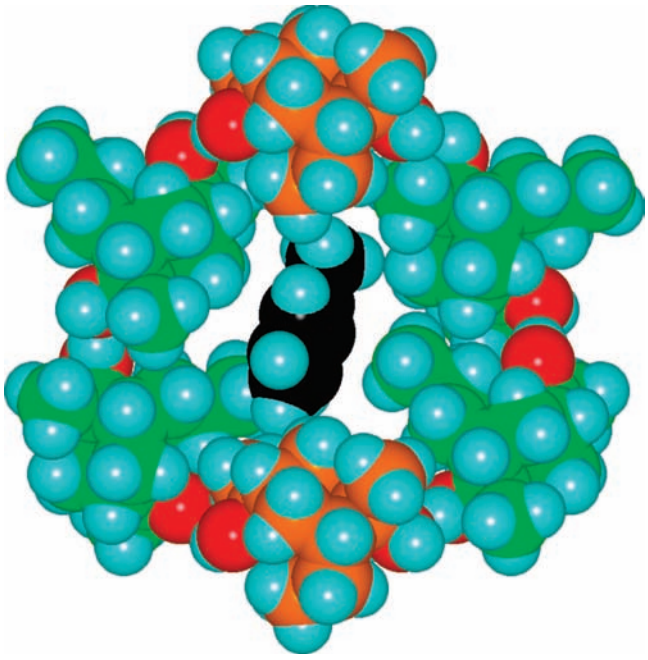


FIGURE 8. Projection in the *ab* plane of one tube of (**15**)·(**33**)$_2$·(toluene) showing the guest template tightly surrounded by the two different HT diols. Color code: **15** C orange; **33** C green; guest C black.

symmetry in solution, this is impossible to achieve in the solid state due to the required folding of the propano bridge. The additional methyl group of **30** makes this diol non-C_2-symmetric. It participates in the HT lattice using crystallographic disorder, as do **15** and **17**, to achieve average C_2 symmetry in the solid state. The two "halves" of the diol are related by a 2-fold axis with the molecules randomly orienting their symmetry-breaking functionality up or down in the crystal.

Improved Bishomoadamantane Diol Synthesis

The bishomoadamantane ring system of diols **15** and **17** was not easily accessed, with the weak spot in these syntheses being the poor yield obtained for the bridging reaction **12** to **13**. The alternative bridging process to form **31**, carried out by Weimin Yue (Scheme 7), overcomes this difficulty and permits simple access to 5-substituted derivatives of the ring system, such as the new HT diol **33** from dione **32**.[30,31]

Many attempts to add groups to the molecular periphery led to non-HT crystal structures. Diols **30** and **33** are notable exceptions to this requirement of MD (e). Such cases have only been successful where the pendant group protrudes into the host canal space. It should also be located remote from the hydroxy groups and not interfere with their hydrogen bonding. Somewhat surprisingly, it appears that the alkene functionality is deleterious in this respect. Diol **33** is also non-C_2-symmetric and incorporates within the HT lattice using crystallographic disorder.[30]

Mixed HT Diol Crystals

What would happen if a solution containing two different HT diols were allowed to crystallize? Our early investigations just led to one of these precipitating first. The outcome can be dif-

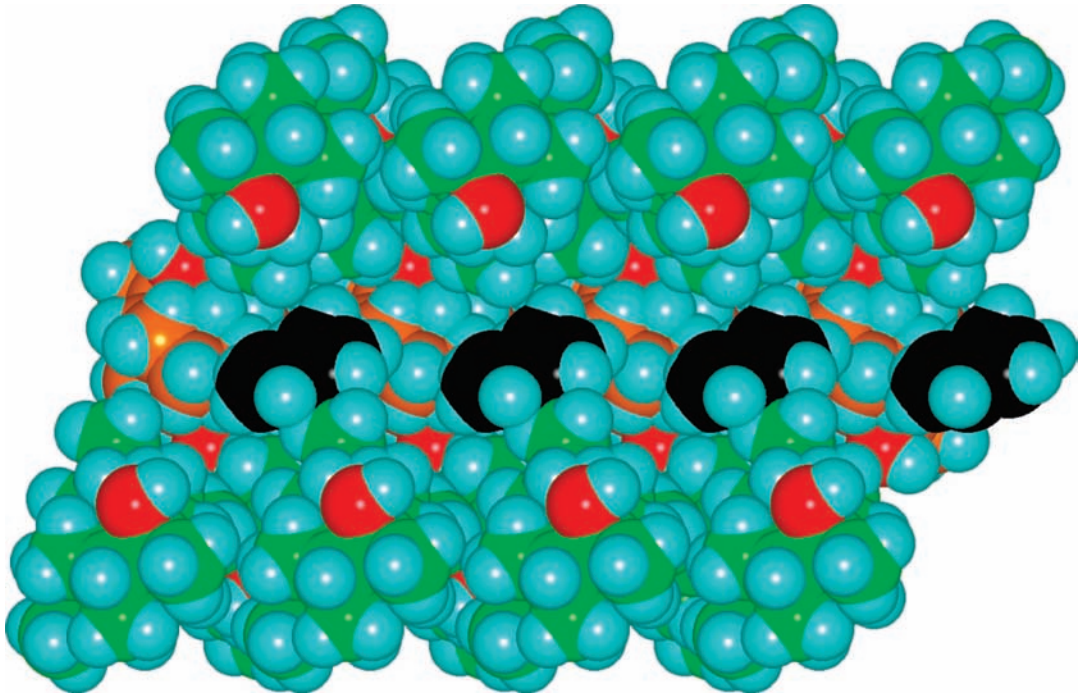
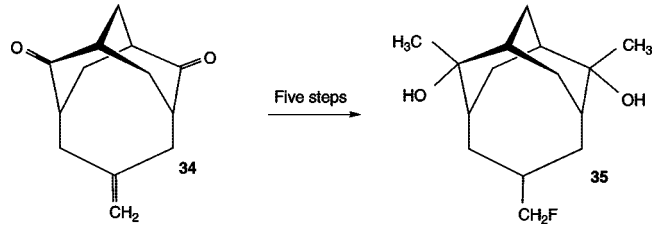


FIGURE 9. Side view of one tube of (**15**)·(**33**)$_2$·(toluene) with the *c* axis horizontal and the three front columns of host molecules removed. The host–guest ordering is seen readily in this cut-away view.

SCHEME 8. Synthesis of the Functionalized HT Diol **35**



ferent, however, if the molecular structures of the two diols are very similar. When a solution of racemic diols **15** and **33** in hot toluene was allowed to cool and concentrate, crystals of the mixed helical tubulate (**15**)·(**33**)$_2$·(toluene) were produced.[32] This is an astonishing outcome in molecular self-assembly. Two simultaneous self-resolutions take place and a five-component mixture spontaneously yields stoichiometric, chirally pure, three-component crystals (Figures 8 and 9).

One can speculate that, during aggregation, all reasonable combinations of weak forces are in equilibrium and that the guest plays a major templating role. The most suitable combinations eventually lead to the product combination of best fit; for example, the resulting tube cross-sectional area lies between those of pure **15** and pure **33**. Molecules participating in assembly and recognition processes can be regarded as programmed information carriers, and this result offers a glimpse of how mixtures of apparently simple molecules of low molecular mass can have the inherent capability of generating complex helical and chiral aggregates. Further research is in progress into this fascinating phenomenon.

Functionalized HT Tubes

The first HT diols carried no pendant groups of any sort, but later, it was demonstrated that the methyl-substituted compounds **30** and **33** also were members of this family. In all examples, however, the HT tubes were lined with hydrocarbon functionalities and offered a uniformly hydrophobic environment to any guest molecules. Thus guest selectivity is based on guest size and shape, and the host–guest interactions in these compounds are generally weak and ill-defined.

This situation will change if the interior of the tubes can be functionalized. Placement of an oxygen atom, for example, would result in a novel three-dimensional crown ether type of host structure. The inclusion properties of such a structure would be considerably different from those observed previously. This particular objective has not yet been achieved despite a great deal of effort and some progress. The problem is simply that many substituent atoms or groups disrupt the hydrogen bonding of the diol molecule. If this happens, then formation of the HT lattice is no longer possible.

Scheme 8 shows the synthesis by Weimin Yue of the first HT diol with a functionalized tube interior. The bridging methodology shown in Scheme 7permits synthesis of compounds bearing a small pendant group. This approach was utilized to produce the dione **34**, which was then elaborated into diol **35**. The choice of a fluorine substituent was made in the knowledge that C–F bonds almost never hydrogen bond to hydroxy groups.[33] Further, the earlier behavior of diol **33** had shown

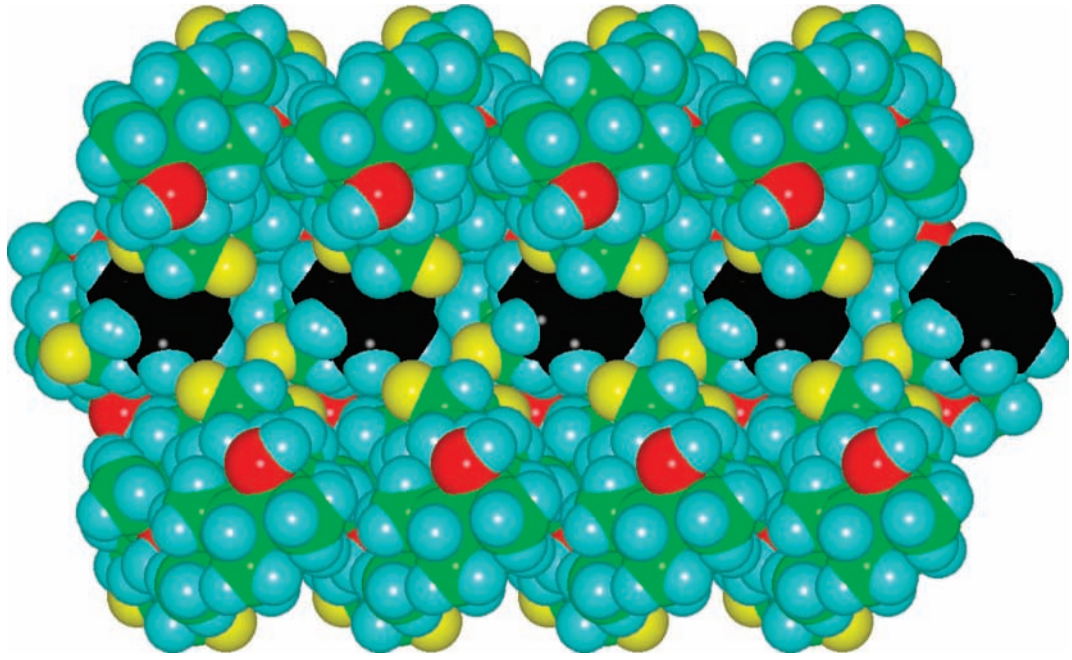


FIGURE 10. Side view of one tube of (**35**)$_3$·(benzene) with the *c* axis horizontal and the three front columns of host molecules removed. Color code: guest C black; host F yellow.

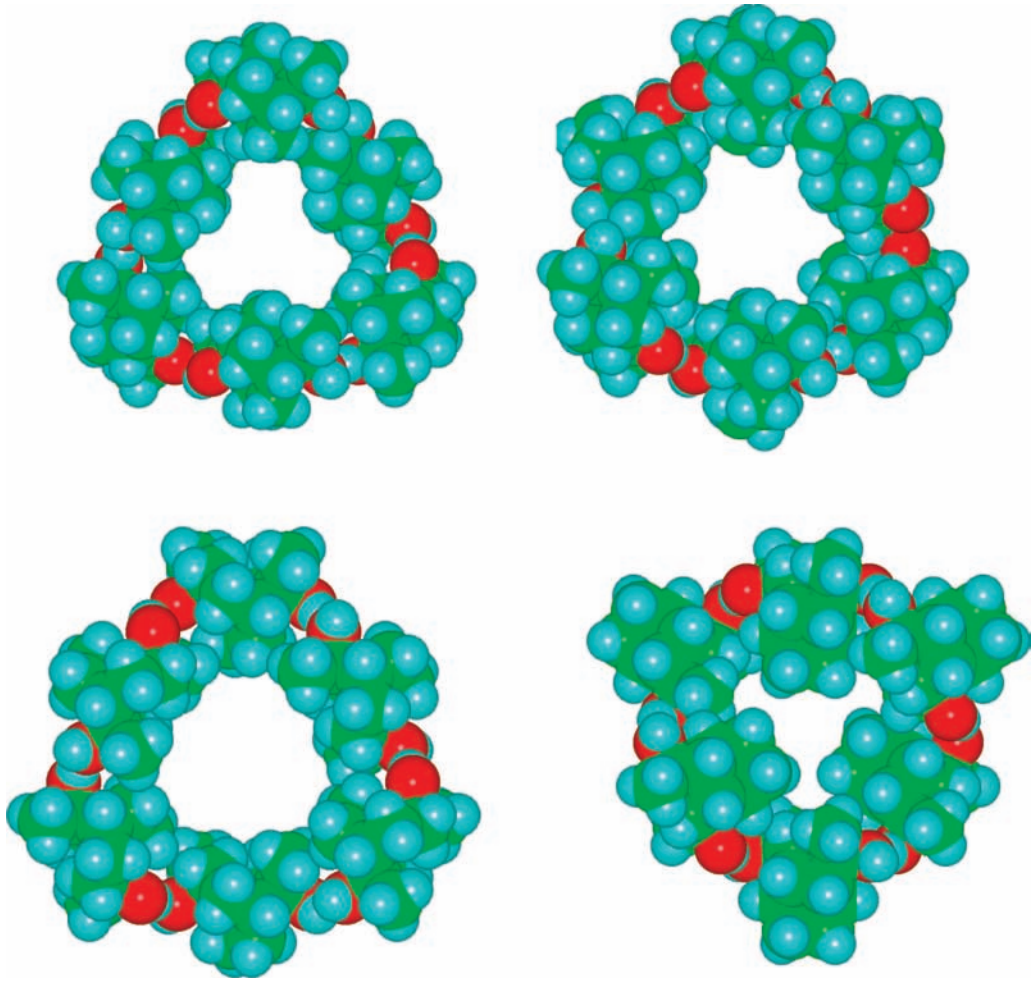


FIGURE 11. Examples of differing HT tube unobstructed cross-sectional areas: diol **9** 29.2 Å^2; diol **15** 32.3 Å^2; diol **21** 34.0 Å^2; diol **26** 9.9 Å^2.

that small pendant groups at this particular ring position can be accommodated within the tubes. Consequently, we were gratified to obtain crystals of the helical tubulate (**35**)$_3$·(benzene) shown in Figure 10. Within the tube, two different fluoromethyl groups cup each benzene guest by means of C−F···π and C−F···H−Ar contacts, in an action similar to that of a pair of hands.[34]

Having now demonstrated that functionalized HT tubes are structurally possible, work is currently in progress toward the synthesis of further examples and the investigation of their properties.

Other HT Diol Behavior

Our synthetic program has provided a family of HT diols with a range of tube cross-sectional areas, a selection of which is shown in Figure 11. These views are analogous to looking along an indented pipe. The larger tubes enclose guests of many functional types,[35] but small phenols instead produce quite different cocrystals.[36] Generally, the hydrogen-bonded 3-fold-screw spines are retained, but the phenolic molecules replace one of the three stacks of diol molecules. This results in a nonresolved structure built up from homochiral layers of alternating handedness.[37,38] Recently we have found that some HT diols show almost identical cocrystalline behavior when crystallized from alcohols and carboxylic acids.[39−41] This is the case for **9** and **33**, but not for diol **3**, which includes both alcohols and carboxylic acids inside its HT tubes.

The racemic HT diol **9** is unique in forming two alternative clathrate structures. This property may arise from the similarity of the two molecular bridges on the C_2 axis. Larger guest molecules form the usual HT structure, but smaller guests are included as a racemic ellipsoidal clathrate structure in space group $I4_1/acd$. The latter structure encloses its guests in a cavity between two identical, inversion-related, interpenetrating sublattices.[42,43] This group of isostructural compounds[44] is ideal for the storage of volatile or odorous host molecules.[45] These interpenetrated structures have recently been compared with other organic hydrogen-bonded nets in a comprehensive survey carried out by Blatov and Proserpio.[46] Although Desiraju has described poly-

morphism[47,48] as *The nemesis of crystal design?*,[49] prediction of these ellipsoidal clathrate or HT structures can be made with ease, as can isolation of *both* crystal types in the guest cross-over region.[50,51]

Preresolved HT Diols

All the HT diols described in this Account were prepared as racemic compounds that then underwent self-resolution to produce conglomerates during crystallization. It is also possible to make homochiral samples in the first place, and this has been done in the cases of **3** and **9**. Such syntheses are longer, more expensive, and usually unnecessary given the spontaneous self-resolution that occurs. Nonetheless there can be advantages in this additional effort.

We have observed, using racemic **3**, that there are differences in the efficiency of including guests of varied size. Some larger guests are reluctant to yield inclusion crystals, and some smaller guests give poorer quality crystals. These technical difficulties at the extremities of guest size can be overcome if chirally pure diol samples are used. Conglomerate formation involves an enormous entropic reorganization that is partly circumvented if the preresolved diol is used instead.

Furthermore, we should not assume that *all* racemic target molecules will necessarily self-resolve. There are likely to be cases where this does not occur, but where the chirally pure diol would form the HT lattice. A possible indicator of such wider behavior is the special case of diol **9**. The use of preresolved diol **9** rules out formation of the racemic ellipsoidal structure, and as we predicted, small guests now become included in the HT lattice.[52]

Concluding Remarks

This Account has deliberately concentrated on synthetic and crystal engineering aspects of the helical tubuland diols, but all members of the family with sufficiently large tubes show rich inclusion chemistry. These important properties have been reviewed elsewhere.[6] The host topology is akin to those of unidirectional zeolites such as laumontite, and we have shown that the tube dimensions can be engineered.

The concept for developing the HT diol family has many similarities to preparing analogues of a newly discovered bioactive molecule. This is for sound reasons. Both types of molecule require a combination of molecular structure and supramolecular interaction to achieve their properties. Hence, just as a search for the pharmacophore is the aim of the bioactive case, similarly it was possible here to determine a set of molecular determinants that govern the HT diol properties. It should be emphasized that, in both cases, apparently unimportant parts of the molecular structure can actually be playing a critical role in the supramolecular behavior.

This methodology worked particularly effectively in this case, even for the repeated synthesis of a specific space group. Our investigation confirms that crystal engineering is underpinned by definite supramolecular properties that are capable of being uncovered and exploited. The discipline is now sufficiently mature for investigators to design and synthesize new target compounds that will provide proof for their theories.

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BIOGRAPHICAL INFORMATION

Roger Bishop was born in Leicester, U.K. (1944), and was educated at George Heriot's School in Edinburgh, the University of St. Andrews (B.Sc. 1966), and the University of Cambridge (Ph.D. 1970). Later, he joined The University of New South Wales in Sydney, Australia, where he is currently a Professor in the School of Chemistry. "Ritter-type Reactions", his review article published in *Comprehensive Organic Synthesis*, won the Royal Australian Chemical Institute Ollé Prize in 1993. His research interests focus on synthetic organic chemistry, crystal engineering, inclusion compounds, and molecular chirality.

FOOTNOTES

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