Host–Guest Systems

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Solid-State Self-Inclusion: The Missing Link[**]

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Cocrystallization and polymorphism are two of the most well-documented paradigms in the fields of solid-state inclusion chemistry and crystal engineering. Such concepts are often open to interpretation, as evidenced by the recent debate regarding the differences between solvates, pseudopolymorphs, and cocrystals.[1] Self-inclusion (or, alternatively, self-hosting) in the solid state has been suggested by several authors as a distinct paradigm in supramolecular host–guest chemistry.[2] In considering the literature regarding the concept of self-inclusion, it immediately becomes clear that this topic is currently highly subjective. However, in view of the various cases that have been advanced to date as examples of self-inclusion, it is now possible to identify different levels of the phenomenon. Thus, to forestall future disagreement, it is useful to now consolidate the issue in a rational fashion and to supply the "missing piece of the puzzle".

In order of increasing constraints on interpretative freedom, the levels of solid-state self-inclusion can be listed and rationalized as follows (note that the term "molecule" is used loosely and can be substituted by "supramolecule"):

a) Any structure with $Z' = 1$. Each molecule is surrounded by like molecules and is therefore self-included.
b) Any molecular crystal with $Z' > 1$.[3] As with (a), each molecule is surrounded by other molecules of the same kind and the designation of a crystallographically unique molecule as either the host or the guest is arbitrary.[4]
c) Interpenetration or weaving of two or more hydrogen-bonded[5] or coordination[6] frameworks. Each framework "hosts" at least one other and is thus simultaneously both a host and a guest.
d) A molecular crystal in which $Z' > 1$ with the distinction between host and guest justified according to accepted

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norms,[7] but without a documented example of the same host framework with another guest.

e) A molecular crystal in which $Z' > 1$ and the identical host framework is precedented by at least one other structure with a different guest.

In discussing the above categories in turn, we concede that it is not always possible to completely eliminate subjectivity as the assignment of "host" and "guest" is generally not immune to the liberties of interpretation. Herein, we adhere to the suggestion by Cram that a host can be identified as a molecule or supramolecular motif that possesses convergent binding sites whereas a guest binds divergently.[7] It should be noted that binding may occur by means of many types of intermolecular interactions, including weak dispersive forces, such as van der Waals contacts.

Clearly (a) and (b) are cases of reductio ad absurdum and require no further discussion (namely, because any structure qualifies as self-inclusion under one of these two categories). Although the interpenetrated and interweaved frameworks[5,6] of category (c) host one another, it is not possible to unequivocally distinguish between the host and guest in such systems (for example, the structure of pure selenourea).[2c] On the other hand, identical molecules can be viewed as fulfilling two distinct roles in the structure for (d) and (e). This observation is well illustrated in a report by Bishop and Dance of a self-included alicyclic diol,[2a] in which molecules of the same kind can be assigned as either the host or guest according to Cram. However, this system must be placed in category (d) as there is no evidence that the same host framework can support the inclusion of a different guest.

In isolated examples, it is possible that a system can appear to possess characteristics of more than one category. Indeed, to illustrate the vagaries of interpretation, 4,4-bis(4-hydroxyphenyl)cyclohexanone has been described as forming a self-included structure in accordance with category (d).[2b] However, our interpretation is that the structure consists of interweaved two-dimensional hydrogen-bonded frameworks that conform to category (c).

To the best of our knowledge, no structure that conforms entirely to category (e) has been recognized as such to date. This phenomenon may be either unusual or commonplace: there could be many such systems whose structures were simply not commented on when reported. Indeed, given the obvious potential for disorder, self-inclusion may have been overlooked on many occasions. Of course this kind of inclusion behavior in molecular solids is only to be expected in host molecules that form a series of inclusion compounds that are isostructural with respect to the host packing motif (we suggest use of the term "isoskeletal" to describe this structural phenomenon). Many isoskeletal systems are now known and include host–guest complexes of Dianin's compound,[9] cholic acid,[10] *p-tert*-butylcalix[4]arene,[11] calix[4]arene,[12] hydroquinone,[13] Werner clathrates,[14] cyclodextrins,[15] Bishop's alicyclic diol molecules,[16] and many more. The importance of these types of host is that their structures can generally be predicted on the basis of their demonstrated packing preferences, which facilitates the tailoring of structure[17] as a stated goal of crystal engineering.

Although the structure of hydrated trimesic acid (TMA) almost meets the criteria of category (e), the host framework consists of a supramolecular adduct that incorporates both TMA and water, whereas the guest consists only of TMA.[18] A similar TMA/H_2O framework exists with picric acid as the guest,[18] but there are small differences in the host frameworks between the two structures. Therefore, the hydrated TMA structure can at best be described as water-assisted self-inclusion under category (d). We now report an unequivocal case of true self-inclusion under category (e) as the missing link at the extreme end of the series that represents all the possible levels.

2,7-Dimethyl-octa-3,5-diyne-2,7-diol (**1**) was synthesized as described below. Crystals of $\mathbf{1}_3\cdot CCl_4$ (**2**) were grown by slow evaporation of a solution of **1** in carbon tetrachloride and the structure was determined by single-crystal X-ray diffraction analysis. The binary compound crystallizes in the space group *R3*, and the asymmetric unit consists of one molecule of **1** in a general position and one-third of a molecule of CCl_4 situated on a crystallographic threefold rotation axis. The solid-state adduct can reasonably be categorized as an inclusion compound, with **1** fulfilling the role of the host and the solvent that of the guest. The C−C≡C-C≡C−C spine of the host molecule is slightly curved with four bond angles of approximately 173, 176, 176, and 176°, respectively. The host molecules are arranged in a spiral running parallel to [001] to form an infinite (convergent) channel around the (divergent) solvent guest molecules (Figure 1 a). The pitch of the spiral is 6.232(4) Å (namely, the crystallographic *c* axis). Each tube is surrounded by six identical tubes in a hexagonal arrangement and, interestingly, all of the tubes in the crystal spiral in the same direction. The hydroxy groups of **1** are situated on the exterior surfaces of the tubes and each tube is bound to all six of its neighbors by means of six infinite spiral arrangements of O−H···O hydrogen bonds (O···O: 2.733(6) and 2.657(7) Å; Figure 1 a). The guest solvent molecules in the channels are packed parallel to [001] within each tube (that is, the intrinsic threefold axis of each guest molecule coincides with that of the host tubule, as shown in Figure 1 b). Notably, the linear packing of the guest molecules along [001] is perfectly commensurate with the spiral pitch of the host molecules.

$$HO-C(CH_3)_2-C\equiv C-C\equiv C-C(CH_3)_2-OH$$

Crystals of $\mathbf{1}_3\cdot C_6H_6$ (**3**) were grown from a solution of **1** in benzene. X-ray diffraction analysis reveals that **3** is isoskeletal with respect to **2** and that the guest molecules are similarly included in the channels in a commensurate arrangement (Figure 1 c) with a packing periodicity of 6.325(5) Å. The host/guest ratio is also 1:3, and the benzene molecules are disordered about the threefold rotation axis parallel to [001].

Our primary research interest involves engineering porous crystals for gas- or vapor-sorption applications.[11,19] In this regard, we have been successful in either growing suitable crystals of metastable apohost phases by sublima-

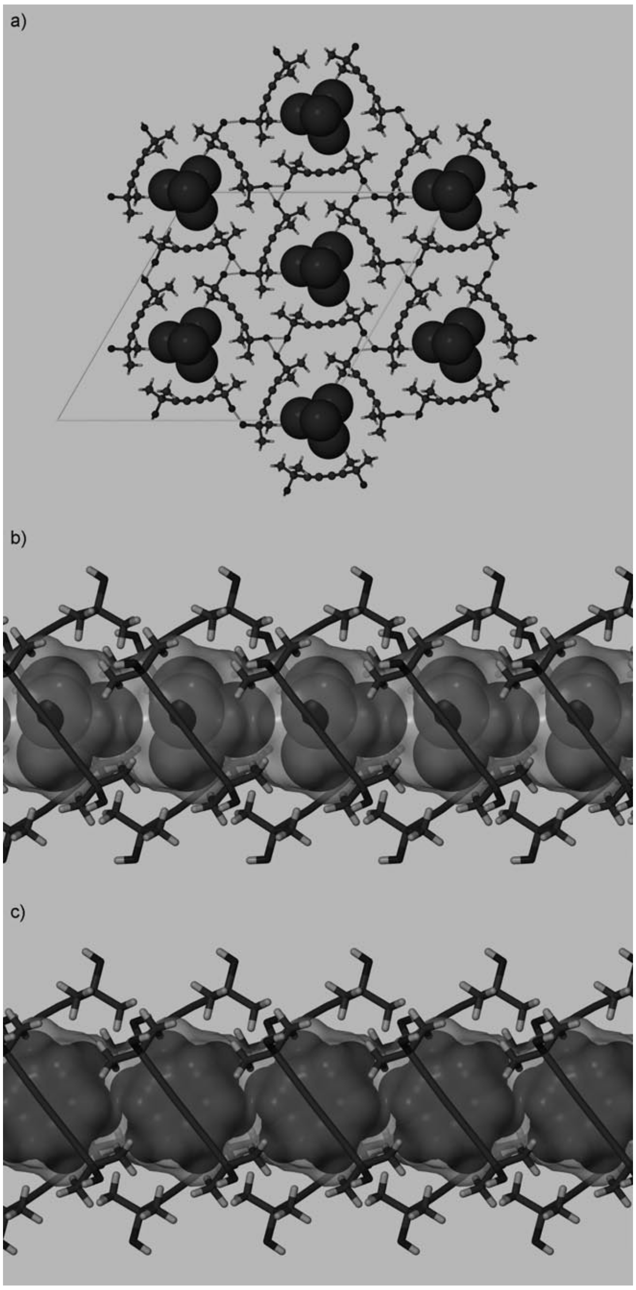

Figure 1. a) Projection of **2** along [00-1] showing the hexagonal arrangement of tubular motifs that consist of spiraling host molecules. The guest molecules are situated in the channels. b) Projection perpendicular to [001] of a tubule in **2** showing the commensurate arrangement of carbon tetrachloride guest molecules within a channel mapped using a spherical probe of radius 1.2 Å. c) A corresponding projection of **3** that shows the benzene guest molecules within a channel (also mapped using a probe of radius 1.2 Å). Hydrogen bonds are shown as fragmented cylinders, guest molecules are shown in a space-filling representation, and host molecules are shown as capped sticks.

tion[11a] and by extracting solvent molecules from guest channels without causing the collapse of the host frameworks.[19] In an attempt to remove the included solvent molecules by gentle heating, crystals of **2** and **3** were subjected to thermogravimetric analysis, which reveals that solvent loss occurs concurrently with sublimation of the host compound (onset temperature (T_{on}) = 63.5 °C). In a separate experiment, crystals were placed under vacuum for several hours, after which their structures were again determined by single-crystal X-ray diffraction analysis. These two studies show that no appreciable solvent loss appears to occur under vacuum conditions and that heating to 70 °C results in guest removal, but only with concomitant disassembly and volatilization of the host framework.

Crystals of pure **1** (**4**) were grown by vacuum sublimation at 70 °C in the hope of forming a guest-free tubular structure. Indeed, single-crystal X-ray diffraction analysis of **4** reveals an isoskeletal arrangement of **1** with respect to the structures of **2** and **3**. The tubular frameworks initially appeared to be devoid of guest molecules. However, difference maps calculated during the latter stages of refinement indicated the presence of appreciable residual electron density within the channels. It was ultimately possible to model a disordered molecule of **1** with its C−C≡C-C≡C−C spine situated on the threefold rotation axis along [001].

It is immediately apparent that the structure of **4** accords completely with category (e) of self-inclusion as delineated above. It is therefore useful in the following discussion to distinguish between the two crystallographically unique cases of **1** according to their respective roles as host $\mathbf{1_h}$ and guest $\mathbf{1_g}$. Space-group symmetry requires the hydroxy and methyl groups of $\mathbf{1_g}$ to be disordered about a threefold axis. Furthermore, application of threefold rotation symmetry to the asymmetric unit yields a molecule of $\mathbf{1_g}$ with a total site occupancy of 0.5. The model employed for $\mathbf{1_g}$ is longer than the crystallographic *c* axis and translation along [001] (that is, x, y, $z+1$) yields a second half-occupancy molecule which overlaps the first (Figure 2a). The nature of the disorder of $\mathbf{1_g}$ with regard to its possible positions along [100] is interesting and warrants further discussion. Close inspection of Figure 1b and c shows that the channels within the host tubules possess bulges and constrictions along [001] with a periodicity equal to the crystallographic *c* axis and that each bulge is occupied by one carbon tetrachloride or benzene guest molecule. However, in **4** the longer guest molecule $\mathbf{1_g}$ spans exactly two bulges and is thus packed with a periodicity of 2*c* along [001] within each channel. As X-ray diffraction analysis only reveals the average structure, it is reasonable to infer from the disordered model that two equally likely possibilities (Figure 2b and c) exist for the end-to-end stacking of $\mathbf{1_g}$ along [001] and that these two arrangements are staggered relative to one another by a distance of *c*.

Evidently the tubular framework persistently observed in structures **2**–**4** is a highly desirable arrangement of **1**, which is most likely due to the stabilizing influence of six infinite hydrogen-bonded spirals that bind each tubule to its nearest neighbors. Indeed, this kind of robust system is well known and **2**–**4** can be considered members of the helical tubuland diol family described by Bishop.[16] Using a probe of radius 1.2 Å to map the contact surface of each channel, we calculate a channel volume of approximately 205(5) Å^3 per repeat unit along the *c* axis. It follows that carbon tetrachloride, benzene, and $\mathbf{1_g}$ occupy the channels with packing coefficients of 0.44, 0.39, and 0.44, respectively. These values are significantly

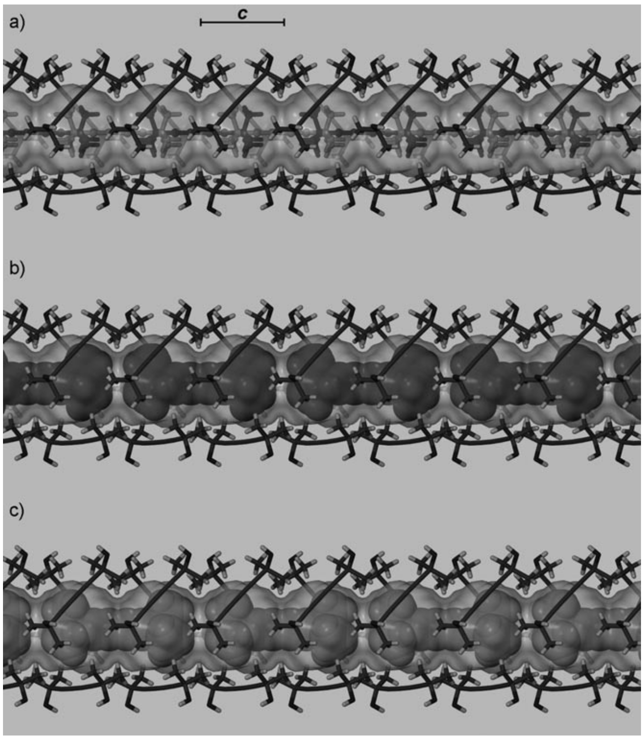

Figure 2. Three identical projections of **4** along [100] that show the two possible arrangements (light and dark) of the included examples of **1**$_g$ within each guest-accessible channel formed by **1**$_h$. a) An overlay of the guest molecules that indicates the nature of the guest disorder. The length of the crystallographic *c* axis is indicated. b) One distinct linear arrangement of the guest molecules **1**$_g$ and c) the alternative arrangement of **1**$_g$ within the same channel. The two arrangements are staggered with respect to one another by translation of 6.341(1) Å along [001]. The hydroxy groups of **1**$_g$ are threefold disordered about the linear axis of the molecule and are not shown. As both arrangements of **1**$_g$ are equally likely, it is presumed that a random arrangement is assumed within each channel and that no synchronization occurs between neighboring channels with regard to periodicity.

lower than packing coefficients normally observed for organic solids (typically 0.60–0.66) and provide further evidence for the overall stability of the host framework.

It is noteworthy that crystals of **4** can also be obtained by slow evaporation of a solution of **1** in dichloromethane.[20] Presumably **1** competes with the solvent molecules for occupancy of the channels. If included, dichloromethane would occupy the channels with a rather low packing coefficient of 0.28, and this poor efficiency may thus be used to rationalize why **1** is included in preference to dichloromethane. On the other hand, benzene is included despite possessing a slightly lower space filling efficiency than **1**. However, in the case of benzene, additional stabilization may be derived from $C_{Ar}-H\cdots\pi_{C\equiv C}$ intermolecular interactions between the guest and host.

We have described the solid-state structures of three different inclusion compounds of **1**, which have in common that they possess tubular arrangements of the host that are virtually superimposable. Remarkably, one of these structures features a host molecule as the guest. Although **4** is composed of a pure substance, the molecule clearly plays two very distinct roles in the structure. A strong case can be made that this distinction is not subjective as at least two other structures can be shown to possess the same host framework with different guests (that is, the host competes for the guest-binding void space). In the vast field of solid-state host–guest chemistry, this observation is unprecedented at the level of interpretative stringency displayed herein. The concept of self-inclusion is an important phenomenon in the field of crystal engineering that relates to porosity as it mitigates against the formation of open structures. The assembly of any porous structure represents a victory by competing factors over the natural proclivity of molecules to close pack. As discussed above, all structures exhibit self-inclusion to a certain extent, and it is the challenge of crystal engineers to understand and control this phenomenon in their quest to form low-density frameworks with minimal self-inclusion.

Experimental Section

2,7-Dimethyl-octa-3,5-diyne-2,7-diol (**1**) was synthesized by the Glaser reaction, in which 2-methylbut-3-yn-2-ol (1 mol) and pyridine (0.25 mol) were heated at 35°C for 4 h in methanol with 1.2% cuprous chloride as the catalyst and oxygen being passed through. The product was extracted from aqueous ammonium chloride with diethyl ether and recrystallized from benzene in 90% yield (m.p. 127–129°C). Further purification was achieved by sublimation. Solvated crystals were grown by slow evaporation of a solution of **1** in the relevant solvent, whereas crystals of the pure form were grown by sublimation at 70°C under vacuum. X-ray diffraction data were collected on a Bruker SMART Apex diffractometer and corrected for Lorentz-polarization effects. Structures were solved by direct methods using SHELXS-97 and expanded/refined on F^2 by difference electron density synthesis using SHELXL-97 and the X-Seed graphical user interface.[21–23]

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[23] The crystal data, thermoanalytical, and complementary analyses can be found in the Supporting information. CCDC 605735–605737 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.