



Structural Studies of Guest–Host Interactions in Dianin’s Clathrates

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(Received: 21 February 2002; in final form: 9 July 2002)

Key words: inclusion compounds, clathrates, X-ray crystal structure, guest–host interactions, Dianin’s molecule

Abstract

Dianin’s compound (4-p-hydroxyphenyl-2,2,4-trimethyl chroman) forms isostructural clathrates and a clathrand which can be systematically studied to determine the microscopic origins of bulk physical properties. Due to the large number of guests that can be enclathrated in the Dianin’s system, experiments in which systematic changes of guest size and functionality can be used to probe guest–host interactions. Herein we report the structures for the 1,6-hexanediol, 1,5-pentanediol, and 1-heptanol Dianin’s clathrates deduced by X-ray crystallography. In the hexanediol, pentanediol, and heptanol clathrates, the guests’ hydroxyl groups hydrogen bond with the host cage’s hydrogen-bonded hexamer ring. The two terminal alcohol groups in the diols have different spatial orientations within the cage that result from gauche bonds between atoms in the guest’s backbone.

Introduction

Understanding guest–host interactions has become important in a number of areas. Technological applications include chemical analysis and pharmaceutical drug delivery [1, 2]. Clathrates can be used for engineering physical behavior and to model systems in order to study molecular recognition [3–5]. Perhaps most intriguing is the possibility that the guest–host interactions in these systems may inform understanding of site recognition interactions in biological molecules.

Clathrates, or “inclusion compounds”, are a wide variety of crystalline systems in which the guest is spatially incorporated into cavities created by the host lattice framework. The guest and host are associated by weak intermolecular forces such as van der Waals, hydrogen bonding, and charge transfer [6, 7]. These dynamic interactions between the guest and host have often been neglected in favor of a more simplified physical picture of noninteracting, interpenetrating lattices [8, 9]. How these guests interact with their host and the resulting changes in their macroscopic physical and chemical behaviors that result from such interactions are not thoroughly understood. Further, these systems provide useful vehicles for isolation and study of specific guest–host interactions.

Dianin’s molecule (Figure 1) clathrates are ideally suited for probing the variances in guest–host behaviors and resulting physical properties. The existence of an isostructural guest-free clathrand and a large number of guests that can

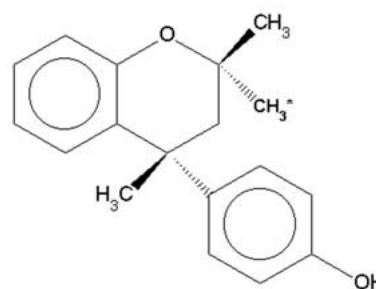


Figure 1. 4-(p-hydroxy-phenyl)-2,2,4-trimethylchroman (Dianin’s compound).

be enclathrated allows comparative studies in which similar guests with small changes in size and functional groups may be executed [10, 11]. Unlike clathrates that do not exist in the guest-free state and whose pure host properties must be inferred, the Dianin’s clathrand allows direct measurement of host behavior. The host lattice can also be changed by using analogs of Dianin’s molecule (Figure 1) [12]. This provides yet another opportunity for comparison of guest–host interactions. Recent studies of Dianin’s molecule clathrates, most notably those by White *et al.*, have attempted to correlate observed thermal conductivities with the number and type of guests [13–15]. Unfortunately, large structural differences in the guests made absolute correlation between the type and functionality of the guest and the resulting physical behavior difficult.

A study aimed at a more detailed investigation of the energetics of guest–host interactions was recently reported for the clathrand and ethanol and heptanol guests of Dianin’s inclusion compound [16]. In that investigation, the influence of the guests on the elastic properties of the respective crys-

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tals was studied. Since elastic constants may be regarded as descriptors of the “bonding” holding molecular crystals together and are directly related to the lattice potential, the investigation was able to describe the effect of guest–host interactions on these parameters. In particular, the role of competitive hydrogen bonding between guest and host molecules was found to be important. When compared to the clathrand, there was a decrease in the elasticity along the crystallographic c -direction (C_{33}) when ethanol or heptanol guests were present. The heptanol clathrate had the lowest elasticity in this direction. These decreases in elasticity were attributed to the interaction of the guest’s hydroxyl group with the hexamer ring.

To further test the role of hydrogen bonding in the elastic response of Dianin’s clathrates, 1,5-pentanediol and 1,6-hexanediol have been included as guests. These diols were chosen because they have the potential to competitively hydrogen bond with the hexamer rings at the top and bottom of the cage.

In the solid state, six molecules of Dianin’s compound form an hourglass-shaped cage (Figure 2a) [17]. This supramolecular enclosure is held together at the top and bottom by a nearly planar, hydrogen-bonded, hexamer ring consisting of six phenolic hydroxyl groups (Figure 2b). The phenol groups alternate above and below this hexamer plane such that the attached chromans, three from the top and three from the bottom, form the sides of the cage. The chromans in these two different groups are of opposite chirality. The methyl group marked by an asterisk in Figure 1 forms the equatorial waist. Unlike inclusion compounds that form open channels, Dianin’s compound forms discrete columns of independent cages.

Dianin’s clathrates for which structures are available, and the associated clathrand, crystallize in the $R\bar{3}$ space group [10, 17–20]. Due to the isostructural nature of the host, physical properties such as elasticity, thermal conduction, and melting point can be used to investigate variations in guest interaction with the host lattice. Knowledge of the structure of these systems is invaluable for elucidating guest–host interactions. We report herein the structure of two previously undetermined Dianin’s clathrates with 1,6-hexanediol and 1,5-pentanediol guests and the structure for the 1-heptanol clathrate for which the guest’s location and structure has been assumed but not determined experimentally [19].

Single-crystal X-ray diffraction

Lattice constants, space groups, and other relevant crystallographic data are presented in Table 1. Enclathrated molecules of 1-heptanol, 1,5-pentanediol, and 1,6-hexanediol thread through the waist of the Dianin’s cage. Their backbones lie along the crystallographic c -axis with the terminal alcohol group(s) interacting with the nearly planar, hexameric, hydrogen-bonded ring. Due to the lack of threefold and inversion symmetry in the guests, rotational and inversion disorder were present. Table 2 lists the fractional atomic coordinates for terminal atoms of the guests

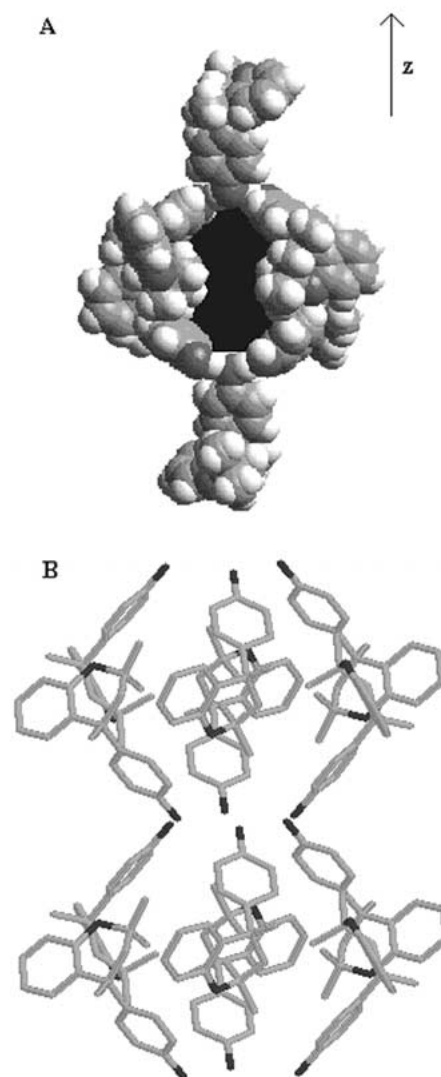


Figure 2. (A) The ac -plane projection of the supramolecular structure formed by six Dianin’s molecules. The front and back molecules of a single cage have been removed to show the hourglass shape. (B) A view of the hydrogen-bonded hexamer ring between two cages.

and the host’s hexamer ring phenolic oxygen. The equivalent isotropic atomic displacement parameters, U_{eq} , are also presented. Thermal ellipsoid drawings of the asymmetric units of the heptanol, pentanediol, and hexanediol clathrates are shown with atomic labeling in Figures 3–5 [21].

The carbon atoms of the methyl groups which form the waist of the Dianin’s cage are 4.17 Å from the c axis in the hexanediol, pentanediol, and heptanol clathrates. The increase in the a axis by 0.03 Å in the heptanol and hexanediol clathrates is attributed to the expansion of the chroman cavity due to steric effects. The center of the C3S–C4S bond (atomic designations shown in Figures 3–5) in hexanediol and the C3S atom of pentanediol are centered at the waist of the host cage. The hydrogen bond between the hexamer ring and heptanol’s single hydroxyl group pulls the guest off center within the cage. This interaction may account for the center of the C3S–C4S bond being offset from the center of the cage by one third of that bond’s length.

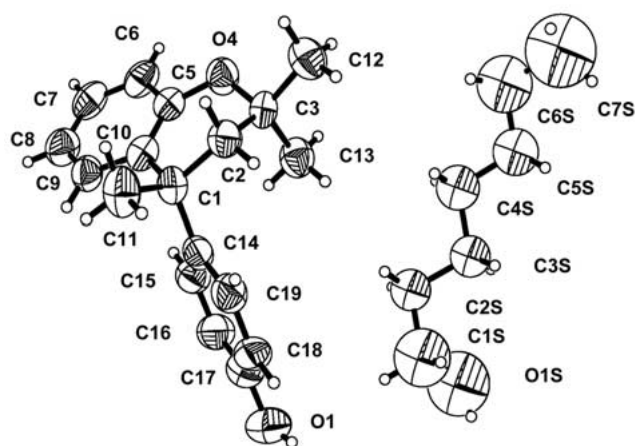


Figure 3. Perspective view of 1-heptanol and an associated Dianin's molecule illustrating the atomic numbering scheme. Thermal ellipsoids are drawn at 50% probability.

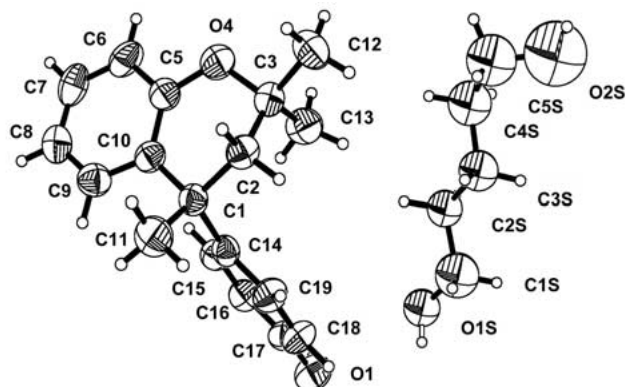


Figure 4. Perspective view of 1,5-pentandiol and an associated Dianin's molecule illustrating the atomic numbering scheme. Thermal ellipsoids are drawn at 50% probability.

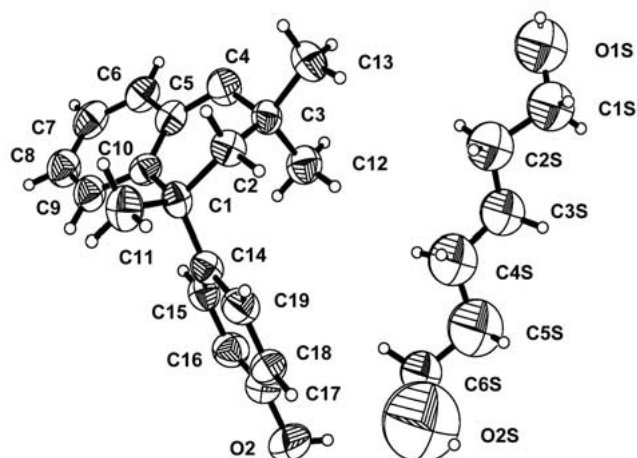


Figure 5. Perspective view of 1,6-hexanediol and an associated Dianin's molecule illustrating the atomic numbering scheme. Thermal ellipsoids are drawn at 50% probability.

Table 1. Crystallographic data and parameters for the structural analysis of the 1,6-hexanediol, 1,5-pentandiol, and 1-heptanol clathrates of Dianin's compound

	1,6-hexanediol	1-5-pentandiol	1-heptanol
Melting Point ($^{\circ}\text{C}$)	178	171	165
Crystal System	Trigonal	Trigonal	Trigonal
Space Group	$R\bar{3}$	$R\bar{3}$	$R\bar{3}$
a (\AA)	27.185(17)	27.1519(16)	27.1896(6)
c (\AA)	11.050(11)	10.8562(17)	11.0928(7)
$Z_{\text{dianin's}}$	18	18	18
Z_{guests}	3	3	3
Density _{calc} (g/cm^3)	1.217	1.231	1.211
Source	MoK α	CuK α	MoK α
Theta _{min/max}	2.04/25	1.50/55.00	4.41/25
Reflections _{tot}	3370	2362	3448
Reflections _{uniq}	2665	1817	2715
Reflections _{observed}	1233	1064	1246
Data/Parameters	213	210	216
R_1	0.0874	0.0777	0.0860
wR2 (all reflections)	0.2385	0.2185	0.2318
μ (mm^{-1})	0.078	0.628	0.077
S = goof	1.176	1.224	1.219
Diff. Density _{max/min}	0.238/−0.212	0.342/−0.287	0.354/−0.287

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for selected atoms of clathrate guests of 1,6-hexanediol, 1,5-pentandiol, and 1-heptanol

	x	y	z	U_{eq}
1,6-Hexanediol				
O(1S)	−40 (70)	0 (90)	3810 (20)	139 (10)
C(1S)	−193 (19)	160 (20)	2720 (30)	109 (15)
C(6S)	170 (20)	60 (20)	−2870 (30)	88 (19)
O(2S)	210 (30)	490 (20)	−3640 (40)	290 (30)
O(2)	1242 (2)	672 (2)	−4797 (3)	97 (1)
1,5-Pentandiol				
O(1S)	−100 (30)	−128 (19)	3453 (16)	79 (10)
C(1S)	100 (50)	182 (19)	2360 (20)	110 (50)
C(5S)	170 (30)	30 (20)	−2260 (40)	130 (60)
O(2S)	180 (20)	513 (18)	−2700 (20)	200 (20)
O(1)	636 (2)	−559 (2)	4813 (3)	68 (1)
1-Heptanol				
O(1S)	290 (20)	488 (17)	−2920 (40)	220 (18)
C(1S)	−150 (30)	−50 (20)	−2580 (30)	170 (30)
C(6S)	60 (60)	−70 (40)	3040 (40)	170 (20)
C(7S)	−160 (40)	190 (50)	3970 (30)	260 (40)
O(1)	−678 (2)	−1261 (2)	−4807 (3)	109 (2)

Hexamer ring $\text{O}_r \dots \text{O}_r$ bond distances and the distance of the closest guest oxygen atom(s) of Dianin's clathrates and clathrand are given in Table 3. Not including their three-fold rotationally disordered positions, the two terminal hydroxyl groups of the pentandiol and hexanediol guests have different conformations. Figure 6 depicts the varied structures arising from the orientations of the terminal hydroxyl group oxygens and those of the hexameric ring. One of the oxygen atoms in each guest is centered below the

Table 3. $O_r \dots O_r$ hexamer ring hydrogen bond distances and distance to nearest hydrogen bonding neighbor(s) (O_g – off-axis oxygen, O_a – on-axis oxygen)

Guest	$O_r \dots O_r$ Distance Å	$O_r \dots O_g/O_a$ Distance Å
None (Clathrand)	2.798 [11]	–
CCl_4	2.857 [19]	–
$CHCl_3$	2.85 [18]	–
Ethanol	2.85 [18]	NR*
1,5-Pentanediol	2.841	3.141/2.969
1-Heptanol	3.003	3.111/–
1,6-Hexanediol	2.961	2.881/3.032

* The ethanol guest coordinates were not reported.

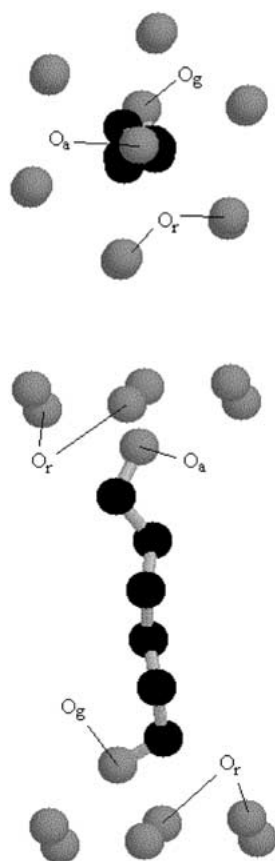


Figure 6. (Top) View down the z -axis of the 1,6-hexanediol Dianin's clathrate. All atoms, except the guest and the hexamer-ring oxygen atoms of the host, have been omitted. The hexamer-ring oxygen atoms, O_r , for the top and bottom of the cage are overlapped. The on-axis guest oxygen, O_a , is centered below the upper hexamer ring. The off-axis guest oxygen, O_g , is above the lower hexamer ring. (Bottom) View perpendicular to the z -axis.

middle of the ring on or near the c -axis. The other guest's oxygen atom is off center between and below two of the hexamer-ring's oxygen atoms. In each case, the off-center oxygen is the result of a gauche bond conformation between the first carbon and the off-center oxygen.

In a previous study of the 1-heptanol clathrate, the heptanol guest was assigned a folded gauche configuration, but its atomic positions were not reported [19]. Refinement of the heptanol clathrate used in this work confirmed this configuration. Because of its single hydroxyl group, heptanol can be enclathrated in two equally probable con-

formations with respect to the direction of the threefold axis. The resulting inversion and rotational disorders lead to larger atomic displacement parameters for the terminal groups of the heptanol compared to the terminal groups of both diols.

Molecular mechanics calculations for the inclusion of n -alkanes within the Dianin's cage found the most energetically favorable conformation of n -heptane has a single terminal gauche bond [22]. This geometry was also observed in this study of the pentanediol guest. The heptanol guest's terminal gauche bonds were modeled well by the most favored (within error) conformation of n -octane [22]. However, the conformation of the hexanediol guest, with its axis-centered oxygen resulting from a gauche bond conformation between C1S and C2S, was not well-modeled by other energetically favorable n -octane conformers. This conformational disparity likely results from the increased hydrogen bond interaction found in the diol clathrate. In the calculation, the hexamer ring geometry was fixed at the ethanol clathrate's $O_r \dots O_r$ bond distance and planarity.

Guest dynamics

Comparison of the isotropic atomic displacement parameters, U_{eq} , in Table 2 for the guest terminal groups of the hexanediol, pentanediol and heptanol clathrates shows increased motion in the hexanediol and heptanol guests. Whether this is due to static or dynamical motion was not experimentally elucidated through low temperature studies. However, recent reports on the dynamics of various guests in the Dianin's system would seem to indicate that these should be dynamically disordered. Zaborowski *et al.* in reporting molecular modeling and NMR studies on the clathrates of n -hexane and n -pentanol concluded that the motion of these guests was dynamic about the three-fold rotational axis at room temperature [23]. Also, NMR studies on n -alkanes with 5–8 carbons suggested that the enclathrated molecules undergo rotation about the c -axis [22]. Studies involving smaller guests have shown them to be rotationally dynamic at room temperature [24–26] In particular, the NMR study on Dianin's ethanol clathrate by Bernhard *et al.* showed that the cage distorts enough to allow the two ethanols within different lobes of the cage to exchange positions [25]. There is, apparently, only one reported Dianin's clathrate in which the guest, p -xylene, is statically disordered at room temperature [27] However, this appears to result from the large xylene phenyl ring passing through the waist of the cage. Therefore, we infer that the smaller diameter n -alkane chains of the guests discussed in this report would not pose enough of a barrier to rotation for them to remain statically disordered.

As hydrogen-bond strength between the guest and host increases, atoms which make up the bond should exhibit less motion [28]. In contrast, the off-center hydrogen bond in the hexanediol clathrate is shorter and thus presumably stronger than the pentanediol clathrate, but its $U_{eq}[O2S]_H$ is larger. The atomic displacement parameters for the off-center oxygen atoms are also influenced by their positional interchange around the energetically equivalent sites produced by the hexamer ring.

For each of the clathrates listed in Table 2, and depicted in Figures 3–5, the isotropic displacement parameters for the guests' terminal groups are larger than those of the guests' central atoms (C3–C4 or C3). This can be attributed to steric hindrance and stabilization by the waist of the cage.

Guest–host interactions

The effect of hydrogen bond cooperativity in branched-cyclic methanol clusters has been calculated by Hagemester *et al.* [29]. The addition of a branched hydrogen bond to a cyclic hydrogen-bonded ring was shown to increase the overall binding energy of the system while slightly increasing the ring size. However, the increase in $O_r \dots O_r$ hexamer ring distance in the Dianin's clathrates seems to be not solely dependent on hydrogen-bond cooperativity. The hexanediol clathrate has the closest $O_r \dots O_g$ distance with the heptanol guest exhibiting the largest separation. The cholorcarbon clathrates display essentially the same ring-atom separation.

The n-pentanediol guest was included to determine the effect of guest size and hydrogen bonding on cage structure. The hexanediol and heptanol clathrates have similar *c*-axis distances that contract by nearly 2% in the pentanediol clathrate. Similar contraction of the pentanediol clathrate $O_r \dots O_r$ bond distances is also observed. Although the lightest of the three guests studied, pentanediol causes an increase in the clathrate density implying stronger packing forces are created by the bifunctional guest.

Comparison of the pentanediol clathrate to the guest-free clathrand [10] shows that the pentanediol guest may slightly contract the *c*-axis of the clathrate while definitely increasing the $O_r \dots O_r$ bond distances. The interactions of hydroxyl groups of the pentanediols on either side of the hexamer ring and those of the ring itself may cause contraction along the cage axis with a concomitant transverse dilation.

Materials and methods

Dianin's compound was prepared according to the method of Baker *et al.* [11]. The resulting ethanol adduct was sublimed three times and purity was checked by mass spectroscopy and thin layer chromatography. Clathrates of 1-heptanol, 1,5-pentanediol, and 1,6-hexanediol were prepared by slow cooling saturated solutions of Dianin's compound using the desired guest as the solvent. Because 1,6-hexanediol is a solid at room temperature, residual solvent was removed by wicking at temperatures above 70 °C. Single crystals of all clathrates were used in the X-ray measurements. The large crystals (~2 mm × 2 mm × 5 mm) were cut and ground to a spherical shape appropriate for X-ray crystallographic measurement.

X-ray data were collected on a Bruker P4 four-circle diffractometer using either copper or molybdenum $K\alpha$ sources. Data was collected by XSCANS [30]. Initial cell constants were found by centering reflections located on rotation photos. The crystal system and Laue symmetry were determined from low-angle reflections. Precise unit cell constants were found by centering of high angle reflections picked from the

(*hkl*) reflection data. The data were reduced with SHELXTL [31]. The structures were solved in all cases by direct methods without incident. Guests were located in difference Fourier maps and refined using the following geometric constraints: (a) all guest C_x-C_y bond lengths were idealized using the 1,2-distance constraint "DFIX 1.54 0.01 $C_x C_y$ ", (b) all guest C_x-O_y bond lengths were idealized using the 1,2-distance constraint "DFIX 1.40 0.01 $C_x O_y$ ", (c) $C_x-C_y-C_z$ bond angles were idealized using the 1,3-distance constraint "DFIX 2.52 0.01 $C_x C_z$ ", (d) $C_x-C_y-O_z$ bond angles were idealized using the 1,3-distance constraint "DFIX 2.44 0.01 $C_x C_y O_z$ ". No constraints were applied for torsion angles. After refinement, constrained distances were generally within 0.01 Å of their target values. In all cases the guest sat on a $\bar{3}$ special position with site multiplicity of 6. Within experimental limits of sensitivity, there was no evidence of either (a) superlattice reflections, (b) violation of Laue symmetry, or (c) thermal diffuse scattering. For this reason, the required partial occupancy of the guest on the $\bar{3}$ site was treated as simple random 1/6 occupancy. Attempts to allow the guest to refine without geometric constraints were unsuccessful. Hydrogens were assigned to idealized positions and were allowed to ride. Heavy atoms, other than those of the guests, were refined with anisotropic thermal parameters.

Conclusions

We have reported the structures of the 1,5-pentanediol, 1,6-hexanediol, and 1-heptanol Dianin's clathrates determined by X-ray diffraction methods. From these a consistent picture of guest–host interactions has been established. In each case, steric effects have explained the structural changes to the host cage or hydrogen bonding between the guest and the hydrogen-bonded hexamer ring that makes up the top and bottom of the cage. Specific guest-dependent interactions were analyzed by enclathrating guests with small differences in size and functionality. Each of the guests used in this study adopted gauche conformations that decreased their overall length. The shortest guest, the pentanediol, also caused contraction in the cage length along the *c*-axis. Further work on these clathrates using other methods is necessary to understand the dynamical motion of the guests. However, this study indicates that a hydrogen-bond-forming guest that is stabilized by passing through the waist of the cage will affect the packing energetics in the Dianin's system.

Supporting information available

The X-ray structures have been deposited with the Cambridge database (CCDC 176840, CCDC 176841, and CCDC 176842).

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