Molecular imprisonment: Host response to guest location, orientation and dynamics in clathrates of Dianin's compound

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ABSTRACT: Single crystal X-ray diffraction data measured at 100 K for Dianin's compound (DC) and eighteen of its clathrates formed with a wide range of guest molecules provide considerable insight into the way the host adjusts to accommodate guest molecules. Detailed information is also obtained regarding the location, orientation and dynamics of the guests in the host cavity. Although all unit cells are closely similar in size, the host undergoes significant change in response to the imprisonment of its various guests. Enclathration typically results in a larger cell and cavity volume, but for the small molecules methanol, ethanol and nitromethane the host actually shrinks significantly around the guests in the cavity. In most clathrates there is evidence of close contacts between atoms in the guest and the phenol –OH group and/or ring of the DC host. The series of clathrates formed by benzene, toluene and the halobenzenes shows the orientation of the benzene ring to be progressively modified by the increasing size of the substituent atom or group on the ring in a systematic manner that reflects functional group contributions to van der Waals volumes.

Introduction

Supramolecular chemistry and crystal engineering are among the most active and rapidly growing fields of modern chemistry. They underpin the design and development of materials for a vast number of potential applications, and many supramolecular systems function as important models for complex phenomena such as self-assembly and nucleation, crystallization, ligand-receptor binding and enzymatic catalysis. Porous organic molecular materials, in particular, have potential applications in heterogeneous catalysis, targeted drug delivery, gas storage and sequestration, and molecular encapsulation and separation, and are the recent focus of considerable experimental¹ and computational^{2,3} research activity. Host-guest chemistry, especially of clathrates, cyclodextrin inclusion compounds, calixarene and crown ether complexes, sits at the foundations of supramolecular chemistry, yet many of these simpler systems have been largely bypassed by today's researchers, equipped as they are with modern experimental and theoretical tools. The irony, of course, is that it is precisely their lesser complexity that makes these systems more attractive for, and amenable to, detailed experimental and theoretical investigation.

Scheme 1. Dianin's compound

Racemic Dianin's compound (4-(2,2,4-trimethylchroman-4-yl)phenol, Scheme 1, abbreviated here as DC) is well known to form clathrates with a very wide range of guest molecules, and is unusual in that the guest-free apohost forms a stable crystal isostructural with its clathrates. Because of this, and as recognised in earlier work,^{4,5} DC and its clathrates potentially provide an ideal system on which to investigate the distortion of the host crystal structure due to different guests, and the manner in which the host accommodates guests of different shapes, sizes and functionalities.

Named after the Russian chemist who first reported its preparation and ability to retain organic solvents,⁶ the term 'Dianin's compound' has only been in use since the mid-1950s. This is when its molecular structure was confirmed, the stoichiometries determined of many of its inclusion compounds,⁷ and the pioneering crystallographic work of Powell verified that these compounds were indeed clathrates,⁸ a term he suggested earlier be used for compounds like these "in which cage structures of suitable form imprison molecules of a second kind".⁹ A more detailed study by Baker et al.¹⁰ described more than fifty crystalline adducts formed by DC, in particular their preparation, melting points and mole ratios. Investigation of DC clathrates up to the late 1970s has been conveniently summarised.¹¹

As described by Powell and Wetters⁸ as early as 1955 the host molecules crystallize in space group $R\bar{3}$, $Z = 18$, with a hexagonal arrangement of six molecules linked by a cyclic motif of O–H...O hydrogen bonds. The alternating *R* and *S* stereoisomers crystallize with three molecules above the plane of the hydrogen-bonded six-membered ring, and the other three below (Figure 1). Stacking of these units leads to the formation of cavities that are relatively large when compared to other organic clathrates. Powell and Wetters were the first to describe the cavity formed by the six DC molecules as "roughly resembling an hour glass which has been cut horizontally across the middle of each globe", a shape that allows for the inclusion of multiple small guests or larger guests of appropriate shape. DC clathrates are generally regarded as having the same space group and crystal symmetry as the apohost, namely $R\bar{3}$ and a hexagonal cell with $a \sim 27$ Å, $c \sim 11$ Å,^{12,13} which requires most guest molecules to be disordered about the threefold axis and the inversion centre at the waist of the cavity.

Figure 1. View of the DC apohost perpendicular to c showing (a) the arrangement of six molecules forming O–H...O hydrogen-bonded rings separated by c , and the 0.0005 au procrystal electron density void surface; (b) the same view, with four molecules represented by 0.002 au promolecule surfaces mapped with the HF/3-21G molecular electrostatic potential over the range -0.05 au (red) to $+0.05$ au (blue).

Although DC host-guest chemistry has been investigated for nearly 100 years, surprisingly few structural studies have been reported. The importance of such work was highlighted by our recent study of the isopropanol adduct,¹⁴ which has the archetypal DC clathrate structure with disordered guests at room temperature, but near 182 K undergoes a transition whereby a and b axes double and guest ordering occurs in alternate cavities. A current survey of the CSD (version 5.34 with updates to May 2013) yields just 49 DC entries. No coordinates were reported for 15 of these,^{12,15} three are for the apohost in space group $R\bar{3}$,^{13,14,16} one for the S enantiomer in $P2_12_12_1$, and one is for the CCl_4 clathrate of a co-crystal formed by DC and its mercapto analogue in the polar space group $R3$.¹⁷ A further three structures are not clathrates but co-crystals of DC with the organic amines morpholine,¹⁸ piperazine and piperidine;¹⁹ none of these possess the typical trigonal clathrate structure, a consequence of the partial proton transfer from host to guest in all three structures. Twenty of the remaining 26 entries are for unique $R\bar{3}$ clathrates, all of them undertaken at room temperature (and hence generally lacking detailed information on guest location and dynamics) except for clathrates of p -xylene at 173 K,²⁰ CCl_4 at 140 K²¹ and 100 K,¹⁷ and CCl_3CN at 100 K.²²

In one of the earliest detailed structural studies on DC clathrates, Flippen et al. reported crystal structures of the ethanol and chloroform clathrates, and observed "it does seem that the cage can expand slightly to accommodate larger molecules as evidenced by the slightly larger cell dimensions for the chloroform crystal".²³ Somewhat surprisingly, and four decades later, Jacobs et al. commented about DC clathrates: "Owing to the trigonal symmetry of the host packing motif, it is usually not possible to model guest molecules that do not also possess threefold symmetry".¹⁷ In the present work we investigate in some detail the crystal structures formed by the inclusion of eighteen guest molecules, three of them reported previously and the remainder new. Contrary to the reservations expressed by Jacobs et al., guest location and orientation has been successfully modelled in all cases except one, but in only three of the systems studied does the guest's threefold symmetry coincide with that of the host. From crystal structures determined under uniform conditions and at 100 K we explore the subtle changes in host cell dimensions and crystal structure, the cavity size and the nature of the host-guest interaction, especially the host responses to the occupation, location and dynamics of the guest molecules.

Results and discussion

The structure of the apohost

The first single crystal X-ray determination of guest-free racemic DC was at room temperature (RT) (CSD refcode QQQESP¹²), but only cell parameters were reported. More complete studies

have been reported at RT (QQQESP01¹³), and at 100 K (QQQESP03¹⁶). Here we examine the structure determined at 100 K (QQQESP02) from our recent study of the isopropanol clathrate,¹⁴ as it was obtained under identical conditions to all the clathrates reported in the present study.

Because the DC apohost possesses a large fraction of void space, and in most clathrates the guest is disordered about the threefold axis and inversion centre, these structures are not readily amenable to the usual Hirshfeld surface analysis.²⁴ However, we have recently modified *CrystalExplorer*²⁵ to enable suppression of selected atoms when choosing a group of atoms for calculating a Hirshfeld surface and related fingerprint plot, etc., and results reported below for each clathrate illustrate the application of this tool. As is our standard procedure in Hirshfeld surface analysis, bond lengths to hydrogen atoms have been reset to standard neutron-derived values,²⁶ and all numerical results (Table 1) as well as d_{norm} surfaces²⁷ have been obtained with this adjustment. The d_{norm} Hirshfeld surface of the apohost DC molecule, Figure 2, is characterized by a pair of large red spots identifying the O...H–O hydrogen bonds, and a broad blue region associated with distances much greater than van der Waals contacts, and inside the cavity (bottom of the surface in Figure 2). The only other relatively close contacts are shown in the figure: a $\text{C}_{\text{Me}}\text{--H}\cdots\text{H}\text{--C}_{\text{Ph}}$ contact of 2.15 Å, and a $\text{C}_{\text{Me}}\text{--H}\cdots\text{C}_{\text{Ph}}$ contact of 2.76 Å. The latter is associated with a centrosymmetric pair of molecules, a component of the interaction between adjacent columns of molecules forming the cavities along c .

Figure 2. Semi-transparent Hirshfeld surface for one DC molecule mapped with d_{norm} . The c axis is horizontal in the figure, and dashed lines denote the closest atom-atom contacts: hydrogen bond in the O...H–O ring (green) and $\text{C}_{\text{Me}}\text{--H}\cdots\pi$ (blue and magenta).

Figure 1 shows two views of the DC apohost perpendicular to the c axis, one with a representation of the cavity formed by six DC molecules, and the other with four DC molecules mapped with the molecular electrostatic potential. The hourglass shape of the cavity is obvious, and it is bounded at each end by a narrow neck created by two cyclic six-membered O...H–O rings separated by c (~ 11 Å, Table 1). The waist separating two identical halves of the cavity is formed by the geminal methyl groups of the chroman ring (Scheme 1).

In Figure 1(a) the void surface is chosen to be the 0.0005 au ($0.0034 \text{ e } \text{\AA}^{-3}$) isosurface of the procrystal electron density. Our previous work²⁸ has shown that the 0.002 au isosurface corresponds closely to a smoothed van der Waals surface of the molecules (and hence the common Connolly surface), while a much smaller value of 0.0003 au is more appropriate for exploring porosity in materials such as MOFs. Because a choice of 0.0003 au also identifies many isolated voids in the DC crystal, here we use the slightly higher value of 0.0005 au to minimise the number of isolated voids, and for which a calculated volume refers directly to the cavities under investigation. The void volume of the apohost, $V_{0.0005}$ (Table 1), is estimated to be $\sim 420 \text{ \AA}^3$ per unit cell, or $140 \text{ \AA}^3$ per cavity. This is much smaller than estimates of $\sim 230\text{--}240 \text{ \AA}^3$, reported by Barbour, Lloyd and co-workers,^{17–19,22,29} which refer to "contact surfaces" us-

ing probe spheres with radii in the range 1.2–1.4 Å; a "solvent accessible surface" using the same probe sphere radius is much smaller.³⁰ Clearly, the precise volume depends on the method chosen for calculation, as well as assumptions about probe size, grid size (i.e. resolution), choice of "contact" vs "accessible" surface, or selection of an appropriate isovalue of electron density. This ambiguity is no different from that which arises when calculating volumes and surface areas of isolated molecules.³¹ We are interested here in the response of the host structure to the enclathration of different guests, and for this purpose $V_{0.0005}$ serves as a convenient way to quantify these changes.

Figure 3. Behaviour of various structural parameters as functions of unit cell volume, a and c axis lengths (see Table 1 for a definition of the parameters). The apohost is highlighted in red, and the DC:acetic acid clathrate in blue.

Table 1. Structural details for the DC apohost and clathrates considered in this work.^a

	$a = b / \text{\AA}$	$c / \text{\AA}$	$V_{0.0005} / \text{\AA}^3$	O...O distance in ring / $\text{\AA}$	nonplanarity / $\text{\AA}$	shortest H...H / $\text{\AA}$	host:guest ratio
DC:methanol	26.691	10.888	400	2.755	0.369	2.40	3:1
DC:nitromethane	26.728	10.861	408	2.780	0.297	2.43	3:1
DC:ethanol	26.693	10.940	411	2.774	0.346	2.41	3:1
DC:dichloroethane	26.811	10.857	414	2.778	0.349	2.44	6:1
DC ^b	26.778	10.903	420	2.785	0.392	2.43	-
DC: <i>n</i> -hexane	26.793	10.892	425	2.804	0.339	2.46	6:1
DC:acetic acid	26.626	11.055	427	2.830	0.359	2.41	3:1
DC:trichloroacetonitrile ^c	26.814	10.877	430	2.803	0.334	2.49	6:1
DC:fluorobenzene	26.871	10.860	431	2.800	0.389	2.51	6:1
DC:bromoform	26.852	10.916	432	2.799	0.369	2.47	6:1
DC:carbon tetrachloride	26.867	10.870	433	2.808	0.343	2.49	6:1
DC:chlorobenzene	26.938	10.832	434	2.791	0.405	2.51	6:1
DC:iodobenzene	26.971	10.785	434	2.788	0.412	2.54	6:1
DC:bromobenzene	26.974	10.811	436	2.792	0.411	2.53	6:1
DC:acetone	26.844	10.923	440	2.848	0.276	2.49	3:1
DC:toluene	26.980	10.817	441	2.795	0.404	2.54	6:1
DC:benzene	26.904	10.885	442	2.815	0.381	2.50	6:1
DC:tetrahydrofuran	26.887	10.927	448	2.832	0.365	2.50	3:1
DC:trimethylacetonitrile	26.955	10.914	457	2.855	0.341	2.51	6:1

^a Crystal structures are ordered by increasing magnitude of $V_{0.0005}$, the volume inside the procrystal isosurface of 0.0005 au. 'O...O distance in ring' is the separation between adjacent O atoms in the puckered six-membered O-H...O hydrogen bonded ring between cavities, 'nonplanarity' is the distance between planes formed by sets of three O atoms in the ring, and 'shortest H...H' is the closest intermolecular distance between geminal methyl H atoms in the waist of the cavity. ^b CSD refcode QQQESP02.¹⁴ ^c CSD refcode WENZAR.²²

The response of the host to the guests

Table 1 summarizes cell dimensions, host:guest ratios and values for four parameters that help to shed some light on the way in which the host structure is modified by the guests, and also the nature of the guests in the clathrates. The void volume, $V_{0.0005}$, was introduced above, and Figure 3 shows that this measure corre-

To gain some insight into the electrostatic character of the inside of the cavity, Figure 1(b) maps the molecular electrostatic potential (HF/3-21G) on the promolecule surface for four of the six DC molecules involved in its creation. There are regions that are electronegative (red, associated with the π electrons of the phenol ring) and moderately electropositive (blue, adjacent to the geminal methyl groups at the cavity waist), but the most polar region is associated with the hydrogen-bonded ring at each end. We conclude that although electropositive and electronegative regions can be identified in the cavity, away from the O...H-O ring it lacks a very strong polar nature, and this is perhaps one reason for its promiscuous behaviour.

lates strongly with the volume of the unit cell; on average the void volume is ~6.3% of cell volume. The largest increase in void volume (relative to the apohost) is 8.9% for DC:trimethylacetonitrile, but of most interest is that for four of the clathrates the void and cell volumes are actually *smaller* than those for the apohost, and by as much as 4.7% for DC:methanol. At first sight this seems counterintuitive, as even though the

guests in these cases (methanol, ethanol, nitromethane and dichloroethane) are all relatively small molecules, it would be expected that the cavities would either be unaffected or expand. That the opposite is observed suggests a significant attractive interaction between host and guest molecules, and we explore this aspect below when considering each clathrate in turn.

The second plot in Figure 3 explores the possible relationship between the c axis length and the nonplanarity of the six-membered O...H–O ring. This ring of oxygen atoms has a slightly puckered chair conformation, and the distance tabulated is that between the two planes formed by alternating O atoms. This nonplanarity lies within a very narrow range of only 0.14 Å, and decreases with increasing c , although not systematically. Interestingly, for all clathrates except for DC:toluene and the heavier DC:halobenzenes, this measure is less than that for the apohost; enclathration typically makes the hydrogen-bonded ring slightly more planar. The plot also identifies the DC:acetic acid clathrate as having an exceptionally long c axis.

The remaining two plots in Figure 3 explore structural changes in the ab plane as functions of those cell edges: the O...O distance in the six-membered ring and the shortest intermolecular distance between geminal methyl H atoms in the waist of the cavity. The spread of O...O distances is very small (0.10 Å) and there is only a weak correlation with the a axis length. One significant exception is DC:acetic acid, where the distance may be regarded as either much greater than suggested by the weak trend, or alternatively the a axis appears anomalously short for that structure; this is discussed further below. Other outliers in this plot are the clathrates with the longest a axes, namely DC:toluene and the heavier DC:halobenzenes. The plot also identifies four clathrates where the O...O separation is less than observed for the apohost; these are the same clathrates for which void and cell volumes are less than for the apohost. The final plot in Figure 3, of shortest H...H distance between methyl H atoms in the waist of the cavity, reveals a very clear trend with a axis length. This particular distance reflects the extent to which the waist of the cavity "breathes" to accommodate larger guest molecules that span its two halves. The longest separation is found for DC:toluene and the heavier DC:halobenzenes and, once again, DC:acetic acid is somewhat anomalous, and this can be interpreted once more as a result of having a very short a axis.

DC:methanol

For this clathrate both cell axes are shorter than for the apohost, suggesting significant attractions between guest molecules and the host. The mole ratio of 2:1 for DC:methanol established by Baker and co-workers^{7,10} implied three methanol molecules per cavity, but the later analysis performed by Davies and Child,³² based on a measured weight loss of $3.8 \pm 1.0\%$ by heating to the melting point, implies a guest occupancy of 1.9 ± 0.5 per cavity. This result is supported by analyses using vapour phase chromatography,³³ which determined a weight loss of 3.8% for the methanol clathrate (although there was a suggestion that the guest content depended on the crystallization conditions). In the present refinement it was not possible to resolve methyl or OH hydrogen atoms of the guest molecules, but guest occupancy was modelled with two disordered guests per cavity, one with its methyl group facing the O...H–O ring, and the other further inside the cavity, and of indeterminate orientation. This model is consistent with recent molecular dynamics simulations by Nemkevich et al.,³ which also suggested that the stoichiometry is likely to depend on the temperature at which enclathration occurs, with two molecules per cavity likely to be favoured above 160 K.

Figure 4. DC:ethanol. Left: possible orientations of guest molecules inside the 0.0005 au void surface (the internal surface of the cavity is grey, the outside surface gold and guests are necessarily disordered about the centre of inversion in the waist of the cavity as well as the threefold axis along c). Right: Hirshfeld surface mapped with d_{norm} (range between -0.2 and 2.0) for an ethanol guest molecule nearest the hydrogen-bonded ring.

DC:ethanol

This is arguably the most studied of all DC clathrates. Originally reported by Dianin, its 3:1 stoichiometry (i.e. two molecules per cavity) is well established.^{10,12,23} The 1970 room temperature X-ray structure of Flippen et al. (DIANET²³) concluded that the guest molecules lie roughly perpendicular to the c axis and occupy the largest cross-sections of the cages. Since that report the DC:ethanol clathrate has been studied by dielectric relaxation,³⁴ ¹³C NMR, IR spectroscopy,³⁵ and ²H NMR,^{36,37} and its heat capacity,^{38,39} thermal expansion,⁴⁰ elastic constants,⁴¹ thermal conductivity^{38,42} and melting behaviour⁴³ have been determined experimentally. Figure 4 depicts two possible locations and orientations of the guest molecules; many more mutual arrangements are possible when disorder is taken into account. The present structure refinement resulted in a ratio of 3:1 for the occupancy of the guest molecule perpendicular to the c axis, relative to that in the waist of the cavity. The arrangement depicted in Figure 4 suggests a possible hydrogen-bonded dimer, as originally proposed by Davies³⁵ on the basis of IR difference spectra, however the ¹³C NMR study concluded that guest motion in DC:ethanol is quite rapid.⁴⁴ Most relevant to the present study is the detailed single crystal ²H NMR study by Bernhard et al. over the temperature range 10 – 310 K, which confirmed that "(essentially) all cages are occupied by *two* guests" and that both ethanol molecules are "at least approximately in a staggered conformation".³⁷ That work also deduced the most likely orientations of the two guest molecules: one roughly aligned along c and the other perpendicular to c , and that the two molecules form a weakly bound dimer for $T < 55$ K. The present structure supports all of those conclusions. Exchange between these two guest positions was also deduced from the ²H NMR study, which seems unlikely to occur within a single cavity, but could be a result of diffusion from one cavity to another, through the hydrogen-bonded ring at each end. DC:ethanol was also studied recently by molecular dynamics,³ and those simulations suggested an energy for reorientation of guest molecules to be only 5 kJ mol⁻¹, and barriers for transport along the cavity to be ~ 20 kJ mol⁻¹ through the waist of the cavity, but as much as ~ 70 kJ mol⁻¹ through the hydrogen-bonded ring. Figure 4 also depicts the Hirshfeld surface for an ethanol guest molecule closest to the hydrogen-bonded ring. The interaction suggested by a single red spot on the d_{norm} surface is due to a close contact between the ethanol O–H and the carbon atoms of the DC phenol ring – an O–H... π interaction.

Figure 5. DC:nitromethane. Left: possible orientations of two guest molecules. Right: Hirshfeld surface mapped with d_{norm} for a guest molecule. (See Figure 4 for details).

DC:nitromethane

This clathrate has been described previously and found to have a mole ratio of 3:1,^{7,10} consistent with two molecules per cavity, and a 97% occupancy.⁴⁵ In agreement with this, the structure determined in this work consists of two guests incorporated into each cavity (Figure 5). The C–N bond of the guest is canted with respect to the c axis, with one oxygen oriented towards the phenolic hydrogen-bonded ring and the other towards the center of the cavity. The two red spots on the d_{norm} surface in Figure 5 reflect relatively close N=O...H contacts (2.69 Å and 2.90 Å) between a nitromethane O atom and two adjacent phenol H atoms of the ring. With a molecular dipole moment of 3.52 D⁴⁶ the mutual orientation of the two guest molecules in Figure 5 suggests a significant attractive antiparallel dipole-dipole interaction. The intermolecular C_{Me}...N separation for the pair depicted in Figure 4 is 4.56 Å, only slightly longer than the separation of 4.36 Å for a pair of molecules similarly oriented in the nitromethane crystal.⁴⁷

Figure 6. DC:dichloroethane. Left: one orientation of the single guest molecule. Right: Hirshfeld surface of guest mapped with d_{norm} . (See Figure 4 for details).

DC:dichloroethane

The preparation of this clathrate was reported by Baker in 1956;¹⁰ the 6:1 stoichiometry (one molecule per cavity) reported therein is supported by the present study. There appear to be no other reports, structural or otherwise, of this clathrate. The chlorine atoms of the guest molecule are arranged *anti* with respect to the ethane backbone, resulting in an extended conformation along the c axis. One chlorine is close to the hydrogen-bonded ring of the host, and the other close to the methyl groups that form the waist of the cavity (Figure 6). Host structural details for DC:dichloroethane are very close to those of the apohost (Table 1), most likely a consequence of the relatively small size of the guest and its limited interaction with the host, and this is also reflected in the very small red spots on the d_{norm} surface (Figure 6) due to two Cl...O separations of 3.27 and 3.28 Å, commensurate with the sum of van der Waals radii, 3.27 Å.

Figure 7. DC:hexane. Left: one orientation of the guest molecule. Right: Hirshfeld surface of guest mapped with d_{norm} . (See Figure 4 for details)

DC:*n*-hexane

No previous single crystal studies have been performed for this clathrate, although Goldup and Smith¹² reported its formation and a mole ratio of 5.9:1 (i.e. one guest per cavity). Imashiro⁴⁸

investigated the conformation of *n*-alkanes (pentane to nonane) in DC using MM2 calculations and ¹³C NMR. The MM2 calculations concluded that the all-*anti* configuration is by far the most dominant for DC:*n*-hexane, and Imashiro suggested that "This inherently stable, all-*anti* conformer fits into the cavity so well that it should bring about the largest Δ*E* [stabilization of steric energy] among all of the present clathrates"; Δ*G* for clathrate formation was estimated to be −38 kJ mol^{−1}, the largest for the *n*-alkanes studied. Solid state ¹³C NMR results also suggested rotation of the guest molecules about the c axis. Further MM/MD calculations by Zaborowski⁴⁹ on dynamics of *n*-hexane in DC predicted an all-*anti* conformation for the guest molecule, which is rotating about its long molecular axis, a result also supported by temperature-dependent ¹H NMR results. The present crystal structure is in agreement with these earlier computational and NMR studies. Figure 7 illustrates the excellent fit of a single guest molecule spanning the entire DC cavity. The separation between carbon atoms at opposite ends of the hexane molecule is 6.31 Å, in line with the separations typical of low-temperature structures in the CSD (e.g. crystalline *n*-hexane at 90 K, where the separation is 6.40 Å⁵⁰). Together with the absence of close contacts on the d_{norm} Hirshfeld surface (Figure 7) and the observation that cell parameters for the clathrate differ very little from those of the apohost (Table 1), this suggests that neither guest nor host geometry are greatly affected by enclathration.

Figure 8. DC:trichloroacetonitrile (top) and DC:carbon tetrachloride (bottom). Left: orientation of the guest molecule. Right: Hirshfeld surface of guest mapped with d_{norm} . (See Figure 4 for details).

Figure 9. Close Cl...C contacts between host and guest molecules in DC:trichloroacetonitrile (left) and molecular electrostatic potential (range −0.025 au (red) to +0.025 au (blue)) mapped on 0.002 au promolecule surfaces for the same pair of molecules (right).

DC:trichloroacetonitrile

This 100 K structure is from the study by Jacobs et al. (WENZAR²²), who attributed ordering of the guest molecule to "strong Cl... π interaction between the Cl groups of the guest and

the benzene rings of the host, represented by the short Cl1...C2 and Cl1...C3 distances of 3.08 and 3.30 Å, respectively". Figure 8 shows how the chlorine atoms fit snugly into the broadest part of the cavity, with the nitrile group spanning the waist and pointing towards the opposite end of the cavity, and the mapping of d_{norm} on the Hirshfeld surface of the guest clearly identifies the close Cl...C contacts as three large red spots. Figure 9 highlights those Cl...C close contacts between host and guest molecules identified by Jacobs et al., beside promolecule surfaces for the same pair mapped with HF/3-21G molecular electrostatic potentials. The close Cl...C contacts arise from the very obvious electrostatic complementarity between the host and guest, namely the electropositive (blue) region beyond the Cl atoms and the broad electronegative (red) region above the electron-rich benzene ring.

DC:carbon tetrachloride

Dianin's compound was originally reported to enclathrate two CCl_4 guests per cavity,^{7,10} but subsequent single crystal measurements (SIHJEY at RT;⁴ SIHJEY01 at RT and SIHJEY02 at 140 K;²¹ SIHJEY03 at 100 K¹⁷) have confirmed that the cavity only allows the inclusion of a single guest. The DC:carbon tetrachloride clathrate has been studied extensively, with publications focusing on thermal expansion coefficients from lattice parameters measured between 10 – 300 K and rigid body analysis of thermal motion of the guest,⁴ ^{35}Cl NQR spectra,⁵¹ heat capacity measurements compared with bulk CCl_4 ,³⁹ thermodynamic properties,⁵² atom-atom potential calculations on host-guest energetics including the barrier to guest rotation,⁵³ melting behaviour⁴³ and thermal conductivity and heat capacity under pressure.³⁸

The present structure supports those reported earlier, with one chlorine atom directed towards the waist of the cavity and the other three closer to the hydrogen-bonded ring (Figure 8). The present lattice parameters at 100 K (Table 1) fit neatly within the range determined by powder diffraction between 10 and 300 K.⁴ The mapping of d_{norm} on the Hirshfeld surface reveals a pattern of close Cl...C contacts almost identical to that seen for DC:trichloroacetonitrile. Clearly, in both structures the guest molecule is not entirely free to rotate, but will exhibit hindered rotation about the c axis. For these molecules with threefold symmetry there are two libration modes: one is axial about the c axis, and the other a degenerate equatorial mode about axes perpendicular to c . In their combined ^{35}Cl NQR and crystallographic study of DC:carbon tetrachloride, Pang et al.²¹ deduced libration frequencies of 39.4 cm^{-1} (axial) and 49.2 cm^{-1} (equatorial) from the temperature dependence of NQR frequencies between 4 K and 200 K. They also reported rms amplitudes for libration and translation from rigid-body analysis of anisotropic displacement parameters (ADPs) for CCl_4 in its clathrate at 140 K and 293 K, and similar results have been reported by Abriel et al.⁴ from ADPs determined at 293 K. The same analysis⁵⁴ applied to ADPs from the present structure refinement at 100 K yields rms libration amplitudes of 5.4° (axial) and 3.8° (equatorial) and rms amplitudes of translation of 0.134 Å (axial) and 0.120 Å (equatorial). As expected, these values lie below those reported earlier at 140 K and 293 K.^{4,21} We have also computed normal mode frequencies of libration from the present rigid body analysis. The results of 32 cm^{-1} (axial) and 45 cm^{-1} (equatorial) are in excellent agreement with those reported previously. Unfortunately, the ADPs reported by Jacobs et al. from their study of DC:trichloroacetonitrile (WENZAR²²) are not amenable to a meaningful rigid body analysis.

Figure 10. DC:acetic acid. Left: one orientation of the guest molecular dimer. Right: Hirshfeld surface of a guest molecule mapped with d_{norm} . (See Figure 4 for details).

DC:acetic acid

Also reported by Dianin, the 3:1 stoichiometry (i.e. two molecules per cavity) of this clathrate has been well established by a variety of techniques.^{7,10,32,45,55} The dimeric nature of the two guest molecules was suggested by Davies and co-workers on the basis of IR spectra³² and later confirmed by dielectric permittivity measurements.⁴⁵ Small has reported room temperature X-ray structures of DC clathrates with eight straight-chain carboxylic acids, as well as trifluoroacetic and isobutanoic (dimethylacetic) acids.⁵⁶ In that work low resolution electron density difference maps (i.e. Fourier maps of clathrate minus host electron densities) for the DC:acetic acid structure (HUSXUO) revealed guest locations in the cavity, supporting a cyclic hydrogen-bonded dimer. The present structure at 100 K clearly shows two guests included in each cavity, each disordered around both the three-fold axis and between two possible positions. The guests form two slightly different centrosymmetric hydrogen-bonded dimers with O...O separations of 2.621(7) and 2.595(7) Å; Figure 10 shows one of these dimers. Curiously, the centrosymmetric dimer is not observed in the crystal structure of acetic acid. Instead, infinite hydrogen-bonded chains of molecules are observed in both ambient and high pressure polymorphs.⁵⁷ Propionic acid does, however, form centrosymmetric dimers in its two known polymorphs.^{58,59} The monoclinic polymorph has an O...O separation of 2.64 Å at ambient pressure,⁵⁹ shortening to 2.62 Å at 0.9 GPa.⁵⁸ This suggests that the guest dimer in DC:acetic acid experiences compression in the cavity, and further evidence for this comes from the earlier observation that DC:acetic acid has by far the longest c axis and the shortest a axis of all clathrates in the present study (Table 1 and Figure 2). Given these observations, the two-dimensional nature of the dimer, and our report of guest ordering in the isopropanol clathrate,¹⁴ we postulate that DC:acetic acid may be an excellent candidate for further very low-temperature or high-pressure single crystal studies. The d_{norm} Hirshfeld surface for one guest molecule (Figure 10) suggests close contacts occur between two of the guest methyl hydrogens and two DC phenol oxygen atoms.

Figure 11. DC:benzene (top) and DC:toluene (bottom). Left: orientation of the guest molecule. Right: Hirshfeld surface of guest mapped with d_{norm} . (See Figure 4 for details).

DC:benzene and DC:toluene

These clathrates were first reported by Baker and McOmie⁷ in 1955 and the 6:1 ratio of host to guest (i.e. one molecule per cavity) is firmly established.^{10,12,45} Goldup and Smith¹² investi-

gated selective clathration of DC with various hydrocarbons and binary hydrocarbon mixtures, and reported results from powder X-ray diffraction for a number of clathrates with aromatic molecules, including toluene (QQQESV) and benzene; single crystal X-ray cell data were also reported for DC:benzene (QQQESA). That study reported no obvious correlation between the cell parameters and the shape of the aromatic guest. In both clathrates the phenyl rings of the guest molecules are similarly oriented in the widest part of the cavity, and the methyl group of DC:toluene is oriented towards the waist of the cavity (Figure 11). Hirshfeld surfaces mapped with d_{norm} indicate several close C-H...O contacts and a C-H... π contact for DC:benzene, but only a single, and apparently much closer, C-H... π contact for DC:toluene. The closer contact for DC:toluene results from the subtle tilt of the benzene ring with respect to that in DC:benzene in order to accommodate the methyl group in the waist of the cavity. In this regard we note that DC:toluene has the greatest H...H separation listed in Table 1. Another perspective on this can be obtained by comparing the angle between the $\text{C}_{\text{Ph}}\text{-C}_{\text{Me}}$ bond and the c axis in toluene (13.6°), with that for the comparable $\text{C}_{\text{Ph}}\text{-H}$ bond in benzene (21.6°).

Figure 12. Top to bottom: DC:fluorobenzene, DC:chlorobenzene, DC:bromobenzene and DC:iodobenzene. Left: one orientation of the guest molecule. Right: Hirshfeld surface of a guest molecule mapped with d_{norm} . (See Figure 4 for details).

DC:fluorobenzene, DC:chlorobenzene, DC:bromobenzene and DC:iodobenzene

Clathrates of DC with bromobenzene and iodobenzene were first reported by Baker *et al.* in the 1950s,^{7,10} who determined a 6:1 ratio of host to guest (i.e. one molecule per cavity). DC:fluorobenzene and DC:chlorobenzene appear not to have been reported previously. The present structural studies on this series of halobenzene clathrates confirm the inclusion of a single guest molecule in all cases, with only one orientation, disordered as expected, and with the halogen atom in the waist of the cavity. Figure 12 clearly shows how the location and orientation of these guest molecules reflects a compromise between fitting the benzene ring into one half of the cavity, and the halogen in the other half. Very subtle trends are evident as the halogen increases in size. For example, the angle between the $\text{C}_{\text{Ph}}\text{-X}$ vector and the c axis decreases systematically: 19° (F), 17° (Cl), 15° (Br) and 11° (I). The orientation of the benzene ring observed in DC:fluorobenzene is most similar to that observed for DC:benzene ($\text{C}_{\text{Ph}}\text{-H}$ angle of 22°), suggesting that it is the benzene:host interactions that dictate the orientation of the guest in DC:fluorobenzene; although the fluorine atom is quite small and could readily sit closer to the c axis, it does not. Further evidence for this comes from the d_{norm} Hirshfeld surface for the guest, which closely resembles that for DC:benzene with a large red spot due to a $\text{C}_{\text{Ph}}\text{-H}\cdots\pi$ close contact, and two smaller spots reflecting $\text{C}_{\text{Ph}}\text{-H}\cdots\text{O}$ contacts to the hydrogen-bonded ring. As the size of the halogen atom increases, the halobenzene molecule rotates progressively away from the wall of the cavity and closer to the c axis. Accompanying this rotation, the two red spots due to $\text{C}_{\text{Ph}}\text{-H}\cdots\text{O}$ contacts evident for DC:fluorobenzene reduce to one smaller one for DC:chlorobenzene, a very faint one for DC:bromobenzene and, finally, none for DC:iodobenzene. There is no evidence of any close contacts between the halogen atoms and those in the wall of the cavity. However, like DC:benzene and DC:toluene, all DC:halobenzene structures show a short H...H distance between a benzene hydrogen atom and one of the methyl hydrogens in the cavity waist (although not visible in the d_{norm} surfaces in Figs. 11 and 12, there is evidence of it, as the bottom H atom on the benzene rings does not fit inside the 0.0005 au void surfaces). Although anomalously short if the structure was static, we note that these structures are inescapably dynamic, and this contact could be readily accommodated by a small cooperative rotation of the methyl group.

Figure 13. DC:bromoform. Left: orientation of the guest molecule. Right: Hirshfeld surface of the guest molecule mapped with d_{norm} . (See Figure 4 for details).

DC:bromoform

This clathrate appears not to have been reported in any of the previous literature, although the crystal structure of DC:chloroform (DIANCH) was one of the earliest reported in the study by Flippin *et al.*²³ In that pioneering study the guest chloroform molecules were found in two different orientations with approximately equal occupancies. One orientation takes advantage of the cavity's threefold symmetry (i.e. with the H atom along the c axis and in the waist of the cavity) and the other has one Cl atom in the waist of the cavity, and hence the H atom is disordered over three sites. These two orientations are readily understood from the present DC:carbon tetrachloride structure (Figure 8). Despite the bromoform guest having threefold sym-

metry, the larger size of the bromine atoms precludes the molecule from taking advantage of the threefold symmetry of the host cavity, and as a consequence only one (disordered) orientation is observed for the guest molecule in DC:bromoform (Figure 13). The d_{norm} Hirshfeld surface for the guest shows two large red spots in an arrangement closely similar to those seen for DC:trichloroacetonitrile and DC:carbon tetrachloride (Figure 8), and in this case due to two close Br...O contacts of 3.21 Å and 3.28 Å, compared with the sum of vdW radii of 3.37 Å.

Figure 14. DC:acetone. Top: two possible orientations of the guest molecules. Bottom: Hirshfeld surfaces for each of the two guest molecules mapped with d_{norm} . (See Figure 4 for details).

DC:acetone

This was one of the adducts first reported by Dianin,⁶ and its preparation and stoichiometry of 3:1 (two guest molecules per cavity) were reported by Baker et al. in the 1950s.^{7,10} Guest molecules are disordered, with two possible orientations (Figure 14), one with the oxygen atom directed towards the hydrogen-bonded phenol ring, and the other with the oxygen near the cavity waist. The occupancy of an individual cavity could therefore be such that dipole moments of the two molecules roughly add, or cancel one another (i.e. $\rightarrow \rightarrow$ or $\rightarrow \leftarrow$). The dielectric measurements by Davies and Williams⁴⁵ suggested an effective dipole moment per cavity of 5.6 ± 0.3 D, twice the gas phase monomer value of 2.90 D,⁶⁰ indicating an ordering of guest molecules in an individual cavity, more or less in the manner depicted in Figure 14. Host-guest interactions can be readily seen in Figure 14 from the d_{norm} Hirshfeld surfaces for the two guest orientations; in both cases the largest red spots correspond to C_{Me}-H... π contacts.

Figure 15. DC:tetrahydrofuran. Top: two possible orientations - and conformations - of the guest molecules. Bottom: Hirshfeld surfaces for each of the two guest molecules mapped with d_{norm} . (See Figure 4 for details).

DC:tetrahydrofuran

The inclusion of tetrahydrofuran (THF) as a guest in DC has not previously been reported. Two guest molecules are accommodated in the cavity, with two similar but different conformations, each disordered about the threefold and inversion centre. Both conformers have oxygen atoms nearest to the hydrogen-bonded ring, were refined with equal occupancies, and have approximate C₂ symmetry (twist form). This conformation is also observed in crystalline THF,⁶¹ although the degree of twist is considerably greater in the present clathrate. The C_s (envelope) conformer appears to be the most populated in the gas phase, but interconversion (pseudorotation) requires only ~ 0.3 kJ/mol at B3LYP/6-311++G** level of theory.⁶² The Hirshfeld surfaces for the two conformers (Figure 15) indicate only a single close C-H... π contact with the phenol benzene ring, but viewed from the side both surfaces show large red spots due to very close contacts between THF methylene hydrogen atoms and the methyl groups of the host at the cavity waist. In this context we note that DC:tetrahydrofuran has some of the longest O...O and H...H separations in Table 1 and the second largest void volume, $V_{0.0005}$.

Figure 16. DC:trimethylacetonitrile. Left: two possible orientations of the guest molecule. Right: Hirshfeld surface of guest molecules for each orientation mapped with d_{norm} . (See Figure 4 for details).

DC:trimethylacetonitrile

The only previous reference to this clathrate is found in the study of dielectric relaxation of DC clathrates by Davies and Williams⁴⁵ (where it is referred to as tert-C₄H₉CN). Loss of weight on heating suggested a 6:1 ratio of host to guest (i.e. one guest molecule per cavity), and that is borne out by the present structure determination. The clathrate with the related and smaller guest, DC:acetonitrile, has been reported to have a 3:1 ratio,³² with two guests per cavity, but no structural studies have been reported. There are two possible orientations of guest molecules (Figure 16), both disordered about the inversion centre, and with approximately equal occupancies. One of these is similar to that observed for DC:trichloroacetonitrile, with the nitrile group directed towards the cavity waist; no close contacts with the host atoms are evident from the d_{norm} surface in Figure 16. The other points in the same direction, with the nitrile group close to the hydrogen-bonded ring, and the respective d_{norm} surface highlights six close N...H contacts of 2.60 or 2.62 Å. Dielectric permittivity measurements suggest a guest molecule dipole moment of 3.3 D which compares well with the literature value of 3.6 D for an isolated molecule.⁴⁵

Conclusion

Detailed structural analysis of single crystal X-ray diffraction data measured at 100 K for DC and eighteen clathrates formed with a wide range of guest molecules has provided considerable insight into the way in which the DC host adjusts to accommodate guest molecules. It has also provided, for the first time in many instances, important information about the location, orientation and dynamics of the guests in the host cavity. All clathrates studied in this work have the same space group as the apohost, $R\bar{3}$, with guests in most cases disordered about the threefold axis along c as well as the inversion centre in the waist of the cage. Although all cells are closely similar in size, the host structure displays significant changes in response to enclathration of its various guests, with a spanning a range of 0.35 Å and c a range of 0.27 Å. Cavity volume, as measured by $V_{0.0005}$, is found to closely follow the trend in unit cell volumes, spanning a range of 57 Å³, or almost 14% of the cavity volume of the apohost. Enclathration typically results in a larger cell and void volume, but notable exceptions are observed with some small molecule, especially methanol, ethanol and nitromethane, where the host actually shrinks significantly around the multiple guest molecules in the cavity.

A considerable amount of information has been revealed about the location and orientation of the guest molecules. Although it is not straightforward to draw conclusions for all clathrates, a number of patterns and trends do emerge. In most clathrates there is evidence of close contacts - and attractive interactions - between atoms in the guest and the phenol -OH group and/or ring of the DC host. Exceptions are found for hexane, which fits almost perfectly within the entire DC cavity and makes no close contacts with the host, and dichloroethane, which sits comfortably at one end of the cavity. A cyclic hydrogen-bonded dimer of acetic acid also spans the entire cavity, although there is a suggestion of compression in this case as DC:acetic acid appears as an outlier in trends displayed by several structural parameters. The clathrates formed by benzene, toluene and the halobenzenes provide a fascinating series where the host:guest interactions between the benzene ring and the DC host molecules - largely C_{ph}-H... π and C_{ph}-H...O - dictate the location and orientation of the molecules in the cavity, but this is progressively modified by the increasing size of the substituent atom or group on the ring. The angle formed by a reference C_{ph}-X bond and the c axis decreases from 22° for benzene to 11° for iodobenzene; the angle for toluene (14°) is found to be similar to that for bromine (15°), and some-

what smaller than for chlorine (17°), a trend that follows closely that tabulated for functional group contributions to van der Waals volumes by Bondi.⁶³

A final comment is worthwhile concerning the concept of a "crystal structure" for DC clathrates. We have already noted that for all examples studied in this work the space group and cell dimensions of the clathrates are essentially the same as those for the apohost, and this is generally accepted to be the case in the current literature. However, our recent study of DC:isopropanol showed that, in some instances, the observed structure depends on temperature.¹⁴ In that work partial ordering of guest molecules was observed with lower temperature, and below 180 K the a and b axes of the clathrate doubled to accommodate this ordering. Accompanying this transition, the isopropanol guest molecules were shown to interrupt and participate in the cyclic hydrogen-bonded ring at the end of the cavity. As noted in the Introduction, structures of DC with three organic amines actually display partial proton transfer from host to guest, and are not clathrates but co-crystals; that with ethylenediamine¹⁹ has a crystal structure remarkably similar to that for DC:isopropanol at 100 K. In the process of our current studies we also determined the crystal structure of DC:*p*-xylene and found that at 100 K it also shows a doubling of a and b , although there would not be expected to be any hydrogen bonding (let alone proton transfer) between host and guest. The temperature dependence of that clathrate will be reported in some detail in the future, but it highlights once more that there remains a great deal to be learned about the nature of these apparently simple archetypal inclusion compounds.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and details of crystallography. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Molecular imprisonment: Host response to guest location, orientation and dynamics in clathrates of Dianin's compound

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Synopsis

Crystal structures of clathrates of Dianin's compound reveal that imprisonment typically expands the cavity volume but, somewhat surprisingly, for some small molecules the host actually shrinks around the guests. Guest molecules typically interact with the phenol ring of the host, and for substituted benzene guests the orientation of the benzene ring changes systematically with increasing size of the substituent.