Host Perturbation in the β -Hydroquinone Clathrate by Combined X-ray - Neutron Charge Density Analysis: Implications for Molecular Inclusion in Supramolecular Entities

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Abstract

Combined X-ray and Neutron (X-N) diffraction data measured at very low temperature (15 K) in conjunction with *ab initio* theoretical calculations are used to model the crystal charge density (CD) of the host-guest complex of hydroquinone (HQ) and acetonitrile, **1**. Due to pseudosymmetry the information about the ordering of the acetonitrile molecules within the HQ cavities is present only in almost extinct very weak diffraction data, which cannot be measured with sufficient accuracy even using the brightest X-ray and neutron sources available, and the CD model of the guest molecule is ultimately based on theoretical calculations. The neutron diffraction data provide hydrogen anisotropic thermal parameters and positions, which are essential to obtain a reliable CD for this light-atom-only crystal. Atomic displacement parameters obtained independently from the X-ray and neutron diffraction data show excellent agreement with $|\Delta U|$ of $0.00058 \text{ \AA}^2$ indicating an outstanding data quality. The CD and especially the derived electrostatic properties clearly reveal an increased polarization of the HQ molecules in the host-guest complex compared with the HQ molecules in the empty HQ apohost crystal structure. It is found that the origin of the increased polarization is the inclusion of the acetonitrile molecule, whereas the change in geometry of the HQ host structure following inclusion of the guest has very little effect on the electrostatic potential. The fact that the guest inclusion has a profound effect on the electrostatic potential suggests that non-polarizable force fields may be unsuitable for molecular dynamics simulations of host-guest interaction (e.g. in protein-drug complexes) at least for polar molecules.

Introduction

Supramolecular chemistry is the chemistry of non-covalent interactions, and it has very broad implications in natural science. It is for instance the foundation for the design and development of a huge number of advanced materials (e.g. for gas storage, sensors, nonlinear optics etc.),^{1,2} it is the origin of self-assembly processes in nanoscience,^{3,4} and it is the key motor driving protein and drug interactions in biochemistry.⁵ Since non-covalent interactions provide the basic control of a vast number of processes, it is of fundamental importance to quantitatively understand the chemical interactions between guest molecules and host structures. The complexity of supramolecular systems, however, limits the possibilities of gaining a fundamental understanding. Indeed, it is fair to say that while chemists today can synthesize supramolecular structures with amazing complexity, often even a basic understanding of the interactions leading to such systems is lacking.⁶ Electron density (ED) level information is a potential way to provide understanding of non-covalent interactions, and molecular crystals are excellent supramolecular model entities facilitating their study.⁷

The porous host-guest systems obtained from co-crystallization of hydroquinone (HQ) and small solvent molecules are simple supramolecular entities that have been known for many years.^{8,9} HQ exists in three polymorphs (α -, β - and γ -form) at ambient conditions. In the β -modification relatively rigid spherical cages of nearly 4 Å inner diameter are formed by six HQ molecules, where potential guest molecules fit inside the cavity, see Figure 1. The general formula of these clathrates is $3\text{C}_6\text{H}_4(\text{OH})_2 \cdot x\text{S}$, with x being the fractional occupancy ranging from 0 to 1 of the guest molecule, S , such as CO_2 , CH_3OH or CH_3CN .¹⁰⁻¹² Access to the central voids of the HQ clathrate is through a “neck” formed by a ring of six hydroxyl hydrogen bonds. A particular advantage of β -HQ clathrates as a supramolecular entity is that the apohost can be formed without any enclathrated guests, and we have previously carried out a CD study of this reference system.¹³ Based on accurate low temperature synchrotron X-

ray diffraction data the CD of the HQ apohost crystal structure was modeled using the multipole method.¹⁴ Analysis of the CD provided a detailed description of the chemical bonding as well as the electrostatic properties of the cavity, which in turn determine the inclusion properties of the host system. Due to its relatively limited complexity, the hydroquinone apohost is well suited for fundamental studies of non-covalent intermolecular interactions in supramolecular entities.

Supramolecular processes are dynamic, and molecular dynamics (MD) simulations have become a widely used method to probe processes ranging from molecular motion in ion channels of membrane proteins, to uptake of gas molecules in porous host materials. Such simulations are ultimately dependent on the accuracy of the force fields used in solving the equations of motion. In the case of HQ clathrates recent interest has concerned the phenomenon of flip-flop hydrogen bonding in which individual hydrogen atoms can alternate between hydrogen bonding to two acceptors.¹⁵ Flip-flop hydrogen bonding is also believed to be of significant importance in many biological systems (e.g. hydrated saccharides, nucleic acids, resveratrol and cholic acid),¹⁶⁻²¹ and understanding the mechanism of the reorientation of such networks of hydrogen bonds is a fascinating challenge. In the HQ system the flip-flop hydrogen bonding is an important factor affecting the access of guest molecules to the voids. By comparing MD simulations on the empty host and the host with ethanol inclusion in a similar host-guest system, Dianins compound, it was found that the guest molecule significantly affects the energy landscape of hydrogen bond reorientation. However, in such simulations one main approximation is that the force field is unchanged with and without guest molecule inclusion. Thus, even though the host and the guest molecules in reality might have significant chemical interactions leading to polarization of the ED, this is not accounted for in the modeling of the dynamical system. This is a general limitation in numerous MD studies and it is not known precisely how this affects the predictive power of the MD method.

In the present experimental study we report the accurate CD of HQ:acetonitrile, **1**. By comparing it with our previously determined CD of the HQ apohost, **2**, we can experimentally quantify the polarization of the host due to inclusion of a polar guest molecule, and thereby evaluate whether its omission in MD simulations could be important.

Figure 1. (a) The asymmetric unit of β -type hydroquinone clathrate with molecular labeling. (b) The cavity generated by six HQ molecules enclathrating an acetonitrile molecule. (c) Packing diagram illustrating the hydrogen-bonded hexagons viewed along the c -axis of the unit cell of **1**. The thermal ellipsoids are drawn at a 90% level.

There is a rich and varied crystal chemistry of the HQ-clathrates. Depending on the ordering of the enclathrated solvent, the β -HQ clathrate is reported to crystallize in three different structure types.²² In the type I clathrate the guest molecules are completely disordered leading to the highest symmetry, space group $R\bar{3}$. Removing the inversion center at the cage center gives rise to the type II clathrate in the polar space group $R3$ having

partially ordered solvent molecules. Type III clathrates are obtained by reduction in lattice symmetry from rhombohedral to trigonal leading to the polar space group P3, which is caused by further solvent ordering. Acetonitrile enclathrated in the β -HQ apohost,¹⁰ **1**, is a type III clathrate in which only the ordered enclathrated acetonitrile molecules break the rhombohedral symmetry leading to trigonal symmetry. This means that the $-h + k + l \neq 3n$ Bragg reflections are no longer extinct, but contain contributions that are related to the relatively small difference between the density distributions of the ordered and the disordered guest molecules as well as the perturbations of the host network. These reflections are inherently extremely weak, but nevertheless of significance for the ED of the pseudo-rhombohedral structure of **1**. In the present study great efforts have been invested into precisely measuring these weak reflections using an extremely intense synchrotron X-ray beam combined with very low experimental temperature. In order to experimentally determine the very fine details of the ED, we furthermore combine the synchrotron X-ray diffraction data with independent neutron diffraction data to obtain unbiased hydrogen positional and thermal parameters. The combined X-N data provide an experimental CD, which is not biased by the charge shift of the covalently bonded hydrogen atoms. However, it is found that addition of theoretical calculations is necessary since the noise in the very weak reflections limit the modeling of the ED of the solvent molecule.

Experimental Section

Synthesis

The synthesis of β -HQ clathrates, $3\text{C}_6\text{H}_4(\text{OH})_2 \cdot x\text{S}$, is rather simple as evaporation of the solvent from a HQ solution results in the clathrate crystals. For the synthesis of **1**, several batches were prepared to accommodate the different crystal sizes needed for both neutron and synchrotron X-ray experiments, see the supporting information for further details.

Heat capacity

The heat capacity (C_p) of **1** was measured from 2 to 300 K on a Quantum Design Physical Properties Measurement System (PPMS) using pellets pressed from finely ground powder. The data are shown in the supporting information.

Neutron diffraction data collection

Single crystal neutron diffraction data on **1** were collected at the D19 instrument at the Institute Laue-Langevin, France, using monochromatic thermal neutrons with a wavelength of 0.9458 Å. A hexagonal prism-shaped crystal with dimensions $1.5 \times 1.5 \times 2.5 \text{ mm}^3$ was wrapped in alu-foil and mounted on the tip of an aluminum pin. The sample was placed in a two-stage closed cycle refrigerator, cooled to 15 K, and the data were subsequently collected with a large position-sensitive detector. A total of 43696 reflections were collected to a maximum resolution of 0.929 Å^{-1} . The crystal faces were indexed as $\{100\}$, $\{-1\ 2\ 0\}$ and $\{1\ 0\ 1\}$ and the data were integrated and corrected for absorption using locally developed programs and a calculated absorption coefficient of 1.8 cm^{-1} .²³ Outlier rejection and merging using the program SORTAV gave a total of 5699 unique reflections with an internal agreement factor of $R_{\text{int}} = 3.26\%$ and an overall completeness of 94.9% .²⁴ Further experimental details are listed in Table 1.

X-ray diffraction data collection

A single crystal of **1** was mounted on the Bruker D8 diffractometer at the ChemMatCARS beamline at the Advanced Photon Source in Chicago. The transparent crystal ($0.040 \times 0.040 \times 0.050 \text{ mm}^3$) was cooled to 15(2) K using an open flow liquid Helium cryostat. The data collection was carried out using a wavelength of 0.41328 Å yielding a maximum

resolution of $1.20 \text{ \AA}^{-1}$. A combination of exposure times of 0.5 s, 1 s and 3 s was chosen in order to obtain accurate intensities of the weak reflections without compromising the intensities of the strong reflections due to the finite dynamic range of the Bruker APEXII CCD detector. A total of 144185 reflections were collected and integrated with SAINT+.²⁵ Subsequently the data were corrected for the imperfect detection by the CCD phosphor using a transmission factor of 0.6041 in the program SADABS.^{25,26} This program also corrects for slight misalignment of the crystal with respect to the ϕ -axis, as well as absorption and other systematic effects. The weak reflections are expected to be important for the accurate modeling of the ED of the guest molecules. The subgroup of weak reflections breaking the rhombohedral symmetry, $-h + k + l \neq 3n$, was taken only from the 3s runs to avoid poorly determined intensities from the measurements with shorter exposure time. The remaining 131229 reflections were averaged and outliers were rejected in the program SORTAV giving a total of 21872 unique reflections with $R_{\text{int}} = 4.40 \%$.²⁴ Only reflections measured three times or more were used in the subsequent multipole refinements. Selected experimental details are listed in Table 1.

Theoretical calculations

A wave function was calculated using *ab initio* periodic density functional theory employing the B3LYP exchange and correlation functional^{27,28} implemented in the program CRYSTAL06.²⁹ The basis set used in the calculations was a standard Pople 6-311G** all electron basis. The calculations were performed using the present experimental geometry and the geometry of the apohost from Clausen *et al.*¹³ The SCF (self-consistent field) energy convergence threshold was set to $\Delta E < 10^{-6}$ hartree. The topology of the density was analyzed using the program TOPOND08.³⁰

Refinement of neutron data

It became immediately clear that the guest molecules in **1** are ordered with two acetonitrile molecules pointing up and one pointing down, Figure 1a. The model which was used to describe the molecular structure included an inversion center for the host atoms (adhering to P-3 symmetry), while the individual guest molecules were allowed to differ (P3 symmetry). The atomic displacement parameters (ADPs) for the host structure atoms were constrained to follow point group symmetry -3. The geometry and ADPs of the three unique acetonitrile molecules were constrained to be identical. Details of this constrained refinement are shown in Table 1.

Table 1. Crystallographic details and refinement residuals

	Neutron	Synchrotron X-ray
Empirical formula	(C ₆ H ₆ O ₂) ₃ CH ₃ CN	(C ₆ H ₆ O ₂) ₃ CH ₃ CN
<i>T</i> (K)	15(2)	15(2)
<i>a</i> (Å)	15.7845(2)	15.7807(5)
<i>c</i> (Å)	6.1736(1)	6.1683(2)
<i>V</i> (Å ³)	1332.08(3)	1330.30(7)
λ (Å)	0.9458	0.41328
μ (mm ⁻¹)	0.18	0.011
<i>T</i> _{min} / <i>T</i> _{max}	0.6783 / 0.8028	0.89 / 1.00
<i>N</i> _{measured} / <i>N</i> _{unique}	43696 / 5699	144185 / 21872
<i>R</i> _{int}	0.0326	0.044
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.93	1.20
		<i>X-N Multipole Model</i>
Space group	<i>P</i> 3	<i>P</i> 3
<i>N</i> _{obs}	5699	4276 (2 σ level)
<i>N</i> _{par} / <i>N</i> _{restraints}	157 / 12	192
<i>R</i> _{all} (<i>F</i>), <i>R</i> _{2σ} (<i>F</i>)	0.0892 / 0.0511	0.1134 / 0.0221
w <i>R</i> (<i>F</i> ²)	0.0825	0.0610
Residual	−1.44 / +2.12	−0.66 / +0.71 (acetonitrile) <0.17 (HQ)
GoF	1.541	0.7510

A Hirshfeld rigid bond test was satisfactorily fulfilled for the structure^{32,33} with a mean value of the difference of mean-square displacement amplitudes (DMSDA) of $\Delta_{A-B} = 5.9 \text{ pm}^2$.

The maximum Δ_{A-B} value of the host was 10 pm², whereas in the cyano group of the solvent molecule the DMSDA value rises to 21 pm².³⁴ The positions and (scaled) ADPs of the hydrogen atoms were used in the combined X-ray and neutron multipole refinement (see below).

X-ray multipole refinement

The neutron model obtained from SHELXL (atomic positions and ADPs for all atom types, including hydrogen) was chosen as a starting point for the multipole refinement. The model was imported into the XD program,³⁵ and non-H atom parameters were refined against the high order part of the synchrotron data with $\sin\theta/\lambda > 0.8 \text{ \AA}^{-1}$. The constraints used for the neutron model, e.g. centrosymmetry on the coordinates and ADPs of the hydroquinone host, and restraints on the geometry and ADPs of the acetonitrile guest molecules, were also used in the subsequent multipole refinement. In addition, the bond distances from the heavy atoms to the hydrogen atoms were fixed to the values obtained in the neutron data refinement. To optimize the starting model, non-zero multipole populations were retrieved from invariom atoms using InvariomTool.^{13,14} After convergence, a multipole model was refined with gradually increasing complexity,¹⁴ while maintaining the symmetry restrictions. The imposed constraints reduced the number of refinable parameters to those of half a hydroquinone molecule while only one unique acetonitrile was refined and the other two acetonitrile molecules were constrained to have the same multipole parameters.

It is likely that forcing identical electronic distributions on the two different orientations of the acetonitrile molecules (up and down) is incorrect; however, as already discussed, information about the differences between the three acetonitrile molecules is restricted to the very weak intensities breaking the rhombohedral symmetry ($-h + k + l \neq 3n$), which makes it difficult to assess the severity of this approximation. Attempts to distinguish the ED of the

solvent molecules resulted in unrealistically large charge transfers between the atoms of the acetonitrile molecules, and hence the monopole populations of the acetonitrile guest was fixed to the invariom values. Experimental noise has a tendency to accumulate on the high symmetry axis,³⁶ which in this structure coincides with the 3-fold axis of the acetonitrile molecules, and hence this noise will significantly bias the refinement.

After co-refinement of all parameters (structural, thermal and electronic parameters for the host, electronic parameters and ADPs for the guest molecules) the ADPs of the heavy atoms were compared with the values obtained from refinement against the neutron data. In general, the ADPs serve as a bin for uncorrected systematic errors in the experiments and hence inaccurate data will tend to show higher deviation between X-ray and neutron ADPs.³⁷ Comparing the ADPs of the 33 heavy atoms in **1** using the program UIJXN leads to a mean deviation ($\langle \Delta U \rangle$) of $0.00058 \text{ \AA}^2$,³⁸ which, for such a large system, is an excellent correspondence compared with other X-N studies.³⁹ The hydrogen nuclear positions and ADPs, which are important in accurate EDD modeling of hydrogen bonded systems such as **1**,⁴⁰ are therefore expected to be of excellent quality. Increasing the complexity of the multipole model of the host structure, e.g. removing the center of symmetry, removing constraints (electronic, positional and thermal) or adding additional radial expansion-contraction parameters did not result in a significant improvement of either the residual density or the agreement factors. Despite the imposed constraints, the refinement of the ED of the acetonitrile molecule still resulted in unrealistic polarization, i.e. a density of the acetonitrile which is very different from other acetonitrile molecules studied in the literature.^{40a}

Due to the problematic modeling of the acetonitrile ED another approach was chosen for the final refinements. Structure factors from a full theoretical calculation of **1** using the experimental geometry were used for multipole refinement in XD. Refinement details are

included in the supporting information. The resulting multipole parameters were used as starting values in the subsequent refinements against the experimental data. However, refinement of these parameters was still not successful for the guest molecules, probably due to the increased random noise along the symmetry axis, and they were therefore fixed to the theoretical values. The random noise that accumulates on the rotation axis and unfortunately coincides with the position of the acetonitrile molecule also hampers accurate determination of the scale factor. On the basis of these observations we conclude that the weak subgroup of reflections breaking the rhombohedral symmetry, $-h +k +l \neq 3n$, are not determined accurately enough despite the great care that was taken during the experiments ($\langle I/\sigma \rangle$ for these (1262) reflections is 4.4). It was not possible to generate a model for disorder on the acetonitrile sites that could lower the residuals.

In summary, the final multipole model used simultaneous refinement of the structural, thermal and electronic parameters of the host structure, whereas the electronic parameters of the acetonitrile molecules were fixed at the values obtained from the modeling of the theoretical structure factors. The geometries of all three acetonitrile guest molecules were fixed to be identical. The final model thus consisted of 192 parameters, which were refined against 4276 observations ($I > 2\sigma(I)$). The Hirshfeld rigid bond test was satisfactory fulfilled for the host ($\Delta_{A-B} \leq 8 \text{ pm}^2$, $\langle \Delta_{A-B} \rangle = 4.0 \text{ pm}^2$), however for the acetonitrile molecules the values are highly affected by noise, and this leads to values of 21 and 47 pm^2 .^{32,33} The residual density near the acetonitrile molecule showed peaks ranging from -0.66 to +0.71 $\text{e}\text{\AA}^{-3}$ situated on the three-fold rotation axis, whereas the residual density is less than $\pm 0.17 \text{ e}\text{\AA}^{-3}$ near the host HQ molecules. Residual density maps are provided in the supporting information.

Results and Discussion

Crystal structure

The host structure consists of two interconnecting hydrogen-bonded networks, which only have weak interactions between them. The crystal structure of **1** contains three unique HQ molecules and a total of 9 molecules in the unit cell, generating three cavities each occupied by one acetonitrile guest molecule (see Figure 1c). Three symmetry-independent acetonitrile molecules, which are situated on 3-fold axes, fit inside the voids of the rhombohedral hydroquinone framework with one guest molecule orientated in a direction opposite to that of the other two, see Figure 1a. The interactions between the HQ host framework and the acetonitrile guest molecules are expected to be weak. The position of the solvent in the cavity is mainly determined by two competing interactions, namely the guest-guest interaction and the host-guest interaction.⁴⁴ The guest-guest interaction of polar solvent molecules is of particular interest as the clathrates undergo a structural phase transition which, presumably, is driven by the interaction between the dipole moments of the guest molecules.⁴⁵ For **1**, the ordering occurs above room temperature and hence it crystallizes in the ordered phase. The ordering reduces the symmetry of the β -hydroquinone clathrates from R-3 to P3. The heat capacity of **1** was measured from 2 – 300 K (see the Supporting Information). There is no sharp structural transition due to the ordering of the solvent molecules. The transition temperature has been reported to be proportional to the squared dipole moment of the guest molecules and, due to the high dipole moment of acetonitrile, the transition is above room temperature.⁴⁶ In the range from 20 to 75 K the slope of the heat capacity changes smoothly due to the rotational ordering of the methyl groups, which has been investigated previously by Detken *et al.* using single crystal NMR and inelastic neutron scattering.⁴⁷ At the temperature of the present neutron and synchrotron experiments (~15 K) there should be no rotational disorder, as confirmed by the structural analysis.

Electron density

Static deformation electron densities and Laplacian distributions in the plane of a HQ molecule and of an acetonitrile molecule, respectively, are shown in Figure 2. The bonding regions of the aromatic system show single peak maxima, which is an indication of the accuracy of the derived density. We emphasize that, while the ED of the acetonitrile molecules is mainly determined from the theoretical data, that of the host structure is based solely on experimental data, and this is used in the analysis of the chemical bonding and electrostatic properties.

Figure 2. a) Static deformation ED and b) Laplacian distribution of one unique hydroquinone host-molecule (experimental refinement) of **1**. c) Static deformation density and d) Laplacian distribution of a guest-acetonitrile molecule of **1** (fixed at theoretical multipole values). For the deformation density the contour interval is $0.1 \text{ e}\text{\AA}^{-3}$ with solid contours being positive and

dashed negative. For the Laplacian the contour level is 2×10^y ($x = 0, 1, 2, 3$ and $y = -2, -1, 0, 1, 2, 3$) with the red dashed lines being positive values and solid blue lines negative.

The chemical bonding of the host structure can be analyzed using the quantum theory of atoms in molecules,⁴⁸ and topological properties at the bond critical points (BCPs) of selected bonds are summarized in Table 2. The perturbation of the HQ host due to inclusion of acetonitrile is not reflected in the covalent intramolecular interactions. On the other hand, the hydrogen bonds are significantly affected. The intermolecular hydrogen bonds of the HQ molecules of **1** are all fairly similar with a BCP ED in the range $0.23\text{--}0.27 \text{ e}\text{\AA}^{-3}$. These values are significantly smaller than observed for the hydrogen bond in the empty β -HQ, **2**.¹³ The intermolecular hydrogen bonds of the HQ molecules are primarily closed shell type interactions with positive Laplacian values. However, the slightly negative total energy density indicates that there are covalent contributions to these hydrogen bonds. A crude estimation of the energy of the hydrogen bond based on the energy density was suggested by Espinosa *et al.*, and for **1** this results in $E(\text{HB}) = 0.5 \cdot V = -41 \text{ kJ/mol}$,⁵¹ while the value found for the empty HQ clathrate, **2**, was 50% higher.¹³

Bader atom charges are additive and a summation of the host-structure charges derived from the experimental ED results in an overall neutral network with zero charge. Given that the multipole parameters of the acetonitrile guest atoms are fixed to the values obtained from modeling the theoretical data the observation of charge neutrality of the host-framework is expected, but it is still an important observation illustrating the reliability of the integration of charge. The Bader charges obtained for **1** are listed in Figure 4, together with charges for **2** for comparison.¹³ The aromatic hydrogen atoms of the HQ molecules of **1** are more positively charged compared with those of the empty host structure, and the transferred electrons are primarily moved into the hydroxyl-bonded carbon of the aromatic ring. This indicates that

upon inclusion of the acetonitrile guest molecule, the ED of the host structure is significantly perturbed. To ensure that this conspicuous result is not due to the use of neutron parameters an X-ray only model of **1** was produced in a similar manner to our previous study of **2**.¹³ The obtained atomic Bader charges (shown in green in Figure 4) deviate only slightly from the values obtained for the combined X-N model of **1**, thus adding confidence to the conclusion that the electron redistribution of HQ occurs as a consequence of the inclusion of the acetonitrile molecules in the cavities. Whether this is a result of an electrostatic interaction between the host and the guest, or simply a result of the increased distance between HQ molecules as evidenced by the increased hydrogen bonding distances in Table 2, is examined below in the analysis of the electrostatic potential.

Table 2. Topological analysis of the hydrogen bonding in the host structure of **1**. The second line gives the values obtained for the HQ apohost in reference 13. R (Å) is the bond distance, R_{ij} (Å) is the sum of the distance from the first atom through the BCP to the other atom, d_l (Å) is the distance from the O-atom to the BCP, ρ is the electron density ($\text{e}\text{\AA}^{-3}$), $\nabla^2\rho$ is the Laplacian ($\text{e}\text{\AA}^{-5}$), and ε is the ellipticity of the bond. G , V and H are the local kinetic, potential and total energy densities estimated using the Abramov functional.⁴⁹ The random errors on the values derived from the electron density obtained from the least squares multipole model are known to be much too small, and therefore only two significant digits are listed.

	R	R_{ij}	d_l	ρ	$\nabla^2\rho$	ε	G	V	H
O(1)···H(11A)	1.7512(5)	1.7774	1.1797	0.24	2.4	0.58	0.19	-0.21	0.0
	1.6899(2)	1.6916	1.1217	0.34	2.2	0.03	0.2	-0.3	-0.1
X1_H(11)-X1_O(1A)		1.7647	1.1361	0.27	1.9	0.33	0.18	-0.23	-0.05
O(11)-X3_H(1A)		1.7776	1.1800	0.26	2.1	0.57	0.18	-0.22	-0.04
X1_O(14)-X2_H(14A)		1.7700	1.1423	0.27	1.9	0.36	0.18	-0.22	-0.04
O(11A) -X3_H(1)		1.7800	1.1508	0.25	1.9	0.41	0.17	-0.21	-0.04
O(14A) -X2_H(14)		1.7763	1.1797	0.25	2.3	0.60	0.19	-0.21	-0.03

Figure 4. Topological charges of the Bader atoms of **1** (blue), the β -HQ apohost, **2** (red), and **1** based on X-ray refinement only, without including the neutron parameters (green). The arrows show the movements of electrons due to the inclusion of the acetonitrile molecules.

Electrostatic properties

The ED and the overall charge state of the host system are important since the inclusion properties of the host are directly determined by these. As is evident from the above discussion, the atomic charges are affected by the inclusion of acetonitrile in the HQ host. However, to assess the effect of these changes on the electrostatics, which strongly influences the interaction energies, the electrostatic potential (EP) on the molecular surfaces of the HQ molecules has been calculated, Figure 5. Five different isosurfaces are shown originating from a) the experimental ED of **1** ($\mathbf{1}^{\text{exp}}$), b) the theoretical ED of **1** ($\mathbf{1}^{\text{theo}}$), c) the experimental ED of **2** ($\mathbf{2}^{\text{exp}}$), d) the theoretical ED of **2** ($\mathbf{2}^{\text{theo}}$), and e) the theoretical ED from a modification of **1** ($\mathbf{1}^{\text{theo,mod}}$) in which the HQ molecules were in the same geometry as **1**, but the acetonitrile solvent molecules were omitted. The theoretical models in b), d), and e) are based on multipole refinement using the program XD against theoretical structure factors.

Three main conclusions come from this comparison: Firstly, it is clear that the experimental and theoretical EP on the molecular surfaces are similar for both **1** (Figure 5a,

b) and for **2** (Figure 5c, d), except for the electropositive (red) area on top of the OH group in **1**^{theo} (Figure 5b) which is not seen for **1**^{exp}. This indicates that the polarization of the HQ molecules in the crystal structure is indeed accessible from experiment using a multipole model. Secondly, the differences observed in the ED between **1** and **2** are clearly expressed in the EP since for **1** the aromatic hydrogen atoms are significantly more positive (electrophilic; yellow-red), whereas the aromatic rings and the carbonyl groups are more nucleophilic (blue) compared to **2**, as also inferred from the atomic charges. However, the most important point remains the origin of the polarization of the host molecules. There are at least two viable alternative explanations for the polarization,; (i) that the electrostatic moments of the acetonitrile directly polarize the HQ molecules; or (ii) that the larger separation between HQ molecules has changed the intermolecular contacts to an extent that influences the HQ electrostatics. In Figure 5e, the EP from an artificially expanded empty HQ crystal structure (HQ geometry as in **1** but without acetonitrile inclusion) is shown, and from its remarkable similarity with Figure 5d it is immediately clear that the enlargement of the cavity has virtually no influence on the EP evaluated at the HQ isosurface. On the other hand, the inclusion of the acetonitrile, which may be regarded as the difference between Figure 5b and 5e, has a profound effect on the EP on the molecular surface. We are fully aware of the existing negative results on experimental and theoretical descriptions of interaction densities,⁷⁴ but recognize that the differences between the two compounds studied here, **1** and **2**, are based on two different crystal structures.

Figure 5. The electrostatic potential mapped from -0.10 (blue) to $0.10 \text{ e}\text{\AA}^{-1}$ (red) on the electron density isosurface of $0.01 \text{ e}\text{\AA}^{-3}$ visualized using MoleCoolQt.^{13,57} The surfaces are calculated from multipole models based on structure factors from: a) experiment, HQ-acetonitrile ($\mathbf{1}^{\text{exp}}$); b) theory, HQ-acetonitrile ($\mathbf{1}^{\text{theo}}$); c) experiment, empty HQ ($\mathbf{2}^{\text{exp}}$); d) theory, empty HQ ($\mathbf{2}^{\text{theo}}$); e) a theoretical modified version of $\mathbf{1}$ in which the acetonitrile molecules are omitted but the geometry of the HQ molecules in HQ-acetonitrile is unchanged ($\mathbf{1}^{\text{theo,mod}}$).

The electrostatic effects of incorporating guest molecules into the HQ apohost structure can be further examined by plotting the EP in planes parallel to the *a*- and *c*-axes along the 3-fold axis, Figure 6. These plots clearly show the electro-positive nature of the cavity.

Figure 6. a) The plane used in the EP plots, which is parallel to the *a*- and *c*-axes of the unit cell of one cavity generated by six HQ molecules. The EP of b) AceI, c) AceII and d) AceIII in the cavities plotted in a $6.1 \times 6.1 \text{ \AA}^2$ plane. The contour level is $0.01 \text{ e \AA}^{-1}$ in steps ranging from $0.40 \text{ e \AA}^{-1}$ (near atom centres) to $0.15 \text{ e \AA}^{-1}$. Red contours are drawn for every $0.05 \text{ e \AA}^{-1}$.

Theoretical modeling of hydrogen storage in metal organic frameworks (MOF) has revealed that the host-guest interactions are promoted by the local polarity of the host network, which induces a dipole in the otherwise non-polar H_2 guest molecules.⁵⁸ This shows that the electrostatic properties of the host are of great importance in prediction of the properties of host-guest systems.⁵⁹ In the chromium-wheel host complex $[\text{Cr}_8\text{F}_8(\text{tBuCO}_2)_{16}]$ the EP was funnel-shaped with a three-dimensional saddle point located at the center that was found to be

highly electronegative with an electrostatic potential of $-1.24 \text{ e}\text{\AA}^{-1}$.⁴¹ In **1** and in the empty β -HQ, **2**, a saddle point is also observed, however, in this case the EP is positive. In **1** the EP goes from $\sim 0.30 \text{ e}\text{\AA}^{-1}$ near the hydrogen bonded hexagon of the host structure to $\sim 0.21 \text{ e}\text{\AA}^{-1}$ at the center of the cavity. Hence, the electrostatic interaction energy with the acetonitrile molecules is considerably weaker in **1** compared with e.g. the chromium-wheel compound. The polarization of the host structure upon inclusion of acetonitrile changes the electrostatic potential in the center of the cavity from $0.014 \text{ e}\text{\AA}^{-1}$ to $0.13 \text{ e}\text{\AA}^{-1}$, and this directly demonstrates that host structure polarization has important energetic consequences. The difference between the EP in the cavities of HQ and the chromium wheel compound results in different affinity towards molecular groups. In the chromium wheel the electronegative cavity attracts the electropositive groups of the molecular guests, and hence the electronegative group is expected to point out of the cavity. This preferential alignment was indeed experimentally observed for a number of chromium wheel host-guest complexes. Thus, acetonitrile orients the positively polarized carbon into the electronegative center of the cavity of the chromium wheel, whereas the negatively polarized nitrogen points towards the more electropositive surface of the host.⁴¹

In **1** the center is electropositive, and moving along the cavity in the direction of the 3-fold axis the potential increases, which suggests that molecules situated in the cavity would point the electronegative regions towards these directions, e.g. towards the hexagon of hydrogen bonded HQ molecules. This is in fact the case for the nitrogen atom of the cyano-group in one end of the acetonitrile molecule. In the perpendicular direction away from the center of the cavity the electrostatic potential drops further, but due to steric hindrance the guest molecules in **1** cannot point in that direction. Therefore, the inclusion of acetonitrile must be associated with an electrostatic penalty since it cannot obtain electrostatic complementarity at both ends as tilting of the molecule is hindered. If tilting was feasible the

positively charged atom could be placed away from the 3-fold axis to reduce the electrostatic energy penalty, since the EP falls off when moving perpendicular to the 3-fold axis. Remembering that acetonitrile is the largest molecule that can be accommodated and form a stable HQ host-guest compound, it is expected to be sterically hindered. In the case of the smaller methanol guest a tilt of $\sim 31^\circ$ is observed in the host HQ,⁶⁰ and this presumably is due to the electrostatically more favorable tilted position. It should be noted, though, that HCN is aligned along the rotation axis, and, hence, other contributions to the combined energy may play significant roles in this particular case. Overall, the inclusion and orientation of guest molecules in the HQ cavities most probably depend on several factors and are a combination of steric, electrostatic and covalent contributions.

The electric field (EF) of the host structure in **1** was calculated, excluding the contribution from the guest molecules (i.e. due solely to the host molecules), and it is seen to be fairly symmetric, Figure 7. The field is close to zero near the center of the cavity (by symmetry it is exactly zero at the inversion center), and in general, when moving along the 3-fold axis away from the center the field increases. The EF along the *c*-axis of the unit cell 1 Å from the center of the three cavities ranges from 0.027 to 0.036 e/Å², depending on the cavity, and the fields point toward the center of the cavity. The numerical values are significantly higher than observed in the empty β-HQ structure (0.0185 e/Å²). When moving perpendicular to the 3-fold axis the EF also increases, but it now points away from the center of the cavity. The EF values 1 Å away from the cavity center in this direction range from 0.013 to 0.019 e/Å², whereas the EF of the empty β-HQ was previously found to be 0.0105 e/Å². In both directions, parallel and perpendicular to the 3-fold axis, the EF of **1** is up to twice as high as the EF reported for the empty β-HQ reference structure.

Figure 7. The electric field due to just the host molecules in **1**, plotted in a $2 \times 2 \text{ \AA}^2$ plane parallel to the a - and c -axes of the unit cell and through the center of the cavities of a) AceI, b) AceII and c) AceIII. The center of the cavities are denoted by the green dots. Arrows indicate the direction of the EF and their length its magnitude.

The observed differences between **1** and the empty host, **2**, show that the inclusion of the acetonitrile guest molecules is accompanied by a polarization of the host structure that involves movement of electrons from the aromatic hydrogen atoms onto the benzene ring carbon atoms. This leads to almost a doubling of the electric field and the EP in **1** at a distance of $1 \text{ \AA}$ from the center of the cavity compared with **2**. The change in the ED of the host structure has general implications for theoretical calculations, such as molecular dynamics (MD) calculations that implement force field calculations to obtain the potential energy of a given system. Force fields are the foundation e.g. for many investigations of the protein–ligand interactions in drug design.⁶¹ The molecules in such calculations are composed of atom types, which depend on the atomic number and the type of chemical bonding.⁶² The molecules are described by a “ball and spring” model, where atoms in a non-polarizable force field are considered as static and thereby unable to be perturbed by nearby ions or molecules. The observed perturbation of the host molecule in **1** compared with the empty HQ structure

of **2** would not be accounted for in typical MD calculations with non-polarizable force fields, and this must lead to errors in the electrostatic energy, which contributes to the non-covalent part of the potential energy being minimized. For non-polar systems, such as hydrocarbons, the electrostatic energy term is not crucial, but for polar systems the long-range electrostatic interaction is often the dominating term.⁶² Typical examples of non-polarizable force fields are MM2, MM3 and OPLS.⁶³⁻⁶⁵ Another commonly used force field is the General Amber Force Field (GAFF), which provides parameters for small organic molecules for simulations of drugs and small molecule ligands. As explained in the introduction, Nemkevich *et al.* recently used GAFF in a study of flip-flop hydrogen bonding in clathrates such as Dianin's compounds and HQ.¹⁵ The barrier of reorientation of a single hydroxyl group in the two host molecules was found to be lowest for the β -HQ, and hence the reorientation of the hydrogen bonding is more frequent. A non-polarizable force field was used for the study; however, the energy estimations of the barriers must be influenced by the polar guest molecules, as indicated in the present study which shows that they have the ability to polarize the host structure of β -HQ.

Another important implication of the present results concerns so-called pseudoatom databases, such as ELMAM,⁶⁶ ELMAM2,⁶⁷ Invariom^{68,69} and UBDB,⁷⁰⁻⁷² which are used for experimental structure refinement using aspherical scattering factors as an alternative to the standard independent atom model. Bak *et al.* recently compared the effectiveness of the different databases, and found that the estimation of molecular electrostatic potential is limited to purely qualitative information due to low precision of the obtained EPs,⁷³ and this suggested that also the electrostatic interaction energies will be poorly determined. One of the principal ideas behind these databases is that the ED and the derived properties of an atom should be transferable to another molecule if the local environment is similar (i.e. the neighboring atoms are identical). This transferability provides a tool for using the fragments

as building blocks for the additive generation of the ED of larger systems or to obtain EDs from low-resolution data. However, the perturbation of the charge observed in **1** compared with the apohost, **2**, indicates that such transferability may not be strictly valid, and, therefore, derived properties such as EPs may be in significant error. One approach to remedy this situation would be to include longer-ranging interactions when categorizing atom types for the ED databases. This is, however, not an option when building force fields in e.g. protein docking studies where the small molecules are free to roam around looking for potentially energy rich places to interact. In studies of this kind, the energies that separate one site from another typically are small, and hence the host polarization revealed in the present study, although small, may be a very important contribution to the total energy. It should be noted that Bak *et al.* and Dittrich *et al.*,⁷⁴ recently concluded, based on theoretical studies of amino acids, that the multipole model is not able to quantitatively describe effects of the crystal field on electrostatic properties. In particular, they showed that multipole refinements of unperturbed and perturbed densities cannot differentiate electrostatic energies of up to 60 kJ/mol. However, Bak *et al.* were operating with identical geometries while the HQ distribution and the hydrogen bonding network in **1** is significantly different from that in the apohost. It is thus not immediately obvious that the conclusions made by Bak *et al.* have validity in this study. Using the electrostatic potential as the probe it is clear that the effect of the guest inclusion is at least an order of magnitude larger than the geometry change, and accessible using a multipole refinement in contrast to the results by Bak *et al.* Changes in atomic charges of the order of 0.15 e constitute a significant contribution to the electrostatic energies of the system.

Conclusions

State-of-the-art synchrotron X-ray diffraction data combined with single crystal neutron diffraction data measured at very low temperature have been used to obtain an experimental charge density model of the HQ:acetonitrile clathrate, **1**. Significant efforts were devoted to obtain accurate Bragg intensities for the weak reflections containing information about ED of the acetonitrile guest molecules, but these weak data currently remain out of reach for experimentalists at the level of precision required to perform a successful ED modeling. Instead, an ED model was obtained through use of theoretical calculations on the guest molecule and constraints on the symmetry of the host structure. The HQ:acetonitrile crystal structure features three independent molecules of acetonitrile of which two point in a direction opposite to that of the third.

The ED of the HQ host molecule in **1** is observed to be significantly different than that of the HQ apohost, **2**, and there is an intramolecular transfer of electrons from the hydrogen atoms to the carbon atoms. This induces a change in electrostatic potential on the periphery of the HQ molecules. The observed change in EP is shown to follow not from the geometrical change that happens upon inclusion, but from the polarizing interaction between host and guest. The fact that the HQ molecule is polarized in **1** compared with the apohost structure of **2** due to incorporation of a guest molecule may have a significant implication for molecular simulations with non-polarizable force fields since the interaction energies possibly contain significant errors.

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Supporting Information. Synthesis description, topological analysis of the chemical bonding, atomic properties, specific heat data, crystallographic and refinement details, residual maps, and a bond length table. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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