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

Henrik F. Clausen,[a] Mads R. V. Jørgensen,[a] Simone Cenedese,[b, e] Mette S. Schmøkel,[a] Mogens Christensen,[a] Yu-Sheng Chen,[c] George Koutsantonis,[d] Jacob Overgaard,*[a] Mark A. Spackman,*[d] and Bo B. Iversen*[a]

Abstract: X-ray/neutron (X/N) diffraction data measured at very low temperature (15 K) in conjunction with ab initio theoretical calculations were used to model the crystal charge density (CD) of the host–guest complex of hydroquinone (HQ) and acetonitrile. Due to pseudosymmetry, 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 by using the brightest X-ray and neutron sources available, and the CD model of the guest molecule was ultimately based on theoretical calculations. On the other hand, the CD of the HQ host structure is well determined by the experimental data. The neutron diffraction data provide hydrogen anisotropic thermal parameters and positions, which are important 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 a $|\Delta U|$ value of 0.00058 Å^2 indicating outstanding data quality. The CD and especially the derived electrostatic properties clearly reveal increased polarization of the HQ molecules in the host–guest complex compared with the HQ molecules in the empty HQ apohost crystal structure. It was found that the origin of the increased polarization is 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 guest inclusion has a profound effect on the electrostatic potential suggests that nonpolarizable 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 noncovalent 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),[1–3] it is the origin of self-assembly processes in nanoscience,[4, 5] and it is the key driver of protein and drug interactions in biochemistry.[6] Since noncovalent interactions provide the basic control of a vast number of processes, they are of fundamental importance to quantitatively understanding 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, although chemists today can synthesize supramolecular structures with amazing complexity, often even a basic understanding of the interactions leading to such systems is lacking.[7] Information at the electron-density (ED) level is a potential way to provide understanding of noncovalent interactions, and molecular crystals are excellent supramolecular model entities facilitating their study.[8]

The porous host–guest systems obtained by crystallization of hydroquinone (HQ) from small-molecule solvents are simple supramolecular entities that have been known for many years.[9, 10] HQ exists in three polymorphs (α, β, and γ forms) under ambient conditions. In the β modification relatively rigid spherical cages of nearly 4 Å inner diameter are formed by six

[a] Dr. H. F. Clausen, Dr. M. R. V. Jørgensen, Dr. M. S. Schmøkel,
Dr. M. Christensen, Dr. J. Overgaard, Prof. Dr. B. B. Iversen
Center for Materials Crystallography
Department of Chemistry and iNANO, Aarhus University (Denmark)
E-mail: jacobo@chem.au.dk
bo@chem.au.dk

[b] Dr. S. Cenedese
Istituto di Scienze e Tecnologie Molecolari del CNR (CNR-ISTM) and
Dipartimento di Chimica Fisica ed Elettrochimica
Università di Milano (Italy)

[c] Dr. Y.-S. Chen
ChemMatCARS, Advanced Photon Source, University of Chicago (USA)

[d] G. Koutsantonis, Prof. M. A. Spackman
School of Chemistry and Biochemistry
University of Western Australia (Australia)
E-mail: mark.spackman@uwa.edu.au

[e] Dr. S. Cenedese
Current address: University of Toledo, Toledo, Ohio 43606 (USA)

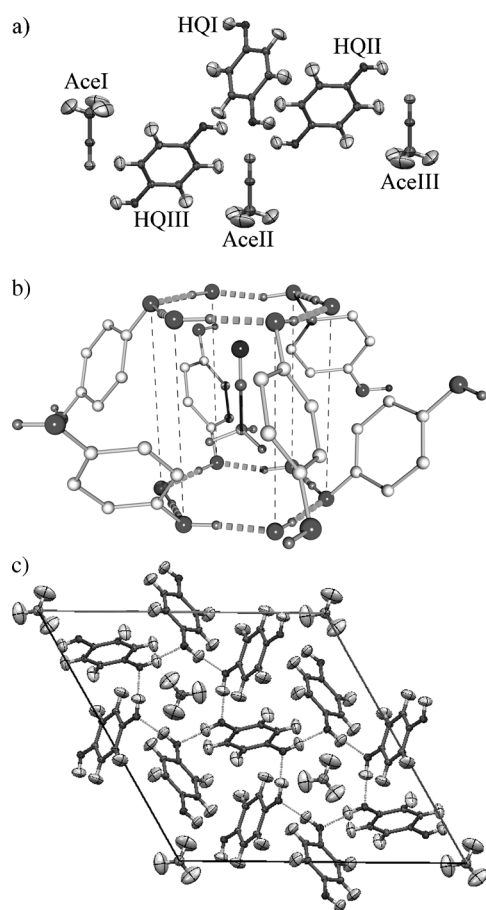🖳 Supporting information for this article is available on the WWW under
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Figure 1. a) The asymmetric unit of β-type hydroquinone clathrate with molecular labeling. b) The cavity generated by six HQ molecules enclathrating an acetonitrile molecule. c) 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% probability.

HQ molecules, and potential guest molecules can fit inside the cavity (Figure 1). The general formula of these clathrates is $3 C_6H_4(OH)_2 \cdot x S$, where *x* is the fractional occupancy ($x = 0-1$) of the guest molecule S, such as CO_2, CH_3OH, and CH_3CN.[11–14] 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 supramolecular entities is that the apohost can be formed without any enclathrated guests, and we have previously carried out a CD study on this reference system.[15] On the basis of accurate low-temperature synchrotron X-ray diffraction data, the CD of the HQ apohost crystal structure was modeled by using the multipole method.[16] Analysis of the CD provided a detailed description of the chemical bonding and electrostatic properties of the cavity, which in turn determine the inclusion properties of the host system.[15] Due to its relatively limited complexity, the HQ apohost is well suited for fundamental studies on noncovalent 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.[17] 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),[18–23] and understanding the mechanism of 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 (Dianin's compound), it was found that the guest molecule significantly affects the energy landscape of hydrogen-bond reorientation.[17] 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 may 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.

There is a rich and varied crystal chemistry of the HQ clathrates and, depending on the ordering of the enclathrated solvent, the β-HQ clathrate is reported to crystallize in three different structure types.[24] 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, which has partially ordered solvent molecules. Type III clathrates are obtained by reduction of 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[11] 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 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 pseudorhombohedral structure of **1**. In the present study, we invested much effort into precisely measuring these weak reflections using an extremely intense synchrotron X-ray beam combined with a very low experimental temperature. To experimentally determine the very fine details of the ED, we combined the synchrotron X-ray diffraction data with

independent neutron diffraction data to obtain the unbiased hydrogen positional and thermal parameters. The combined X-ray/neutron (X/N) data provide an experimental CD that is not biased by the charge shift of the covalently bonded hydrogen atoms. However, we found that addition of theoretical calculations was necessary to complete the picture, since the noise in the very weak reflections limits the modeling of the ED of the solvent molecule.

Results and Discussion

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 nine molecules in the unit cell, generating three cavities, each occupied by one acetonitrile guest molecule (see Figure 1 c). Three symmetry-independent acetonitrile molecules, which are situated on threefold axes, fit inside the voids of the rhombohedral HQ framework with one guest molecule oriented in a direction opposite to that of the other two (Figure 1 a). The interactions between the HQ host framework and the acetonitrile guest molecules are expected to be weak, and the unit cell parameters increase as expected (ca. 66 Å³) on inclusion of the acetonitrile molecule in **1** ($a = 15.7807(5)$, $c = 6.1682(2)$ Å; $V = 1330.30(7)$ Å³) compared with the apohost **2** ($a = 16.5249(2)$, $c = 5.3430(1)$ Å; $V = 1263.55(4)$ Å³). The position of the solvent molecule in the cavity is mainly determined by two competing interactions, namely, the guest–guest interaction and the host–guest interaction.[25] The guest–guest interaction of polar solvent molecules is of particular interest, as the clathrates undergo a structural phase transition, which is presumably driven by the interaction between the dipole moments of the guest molecules.[26] For **1**, the ordering occurs above room temperature and hence it crystallizes in the ordered phase. The ordering reduces the symmetry of the β-HQ clathrate from $R\bar{3}$ to $P3$. The heat capacity of **1** was measured from 2–300 K (see Supporting Information). There is no sharp structural transition due to ordering of the solvent molecules. The transition temperature has been reported to be proportional to the square of the dipole moment of the guest molecules and, due to the high dipole moment of acetonitrile, the transition is above room temperature.[27] 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.[28] 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 an HQ molecule and of an acetonitrile molecule 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,
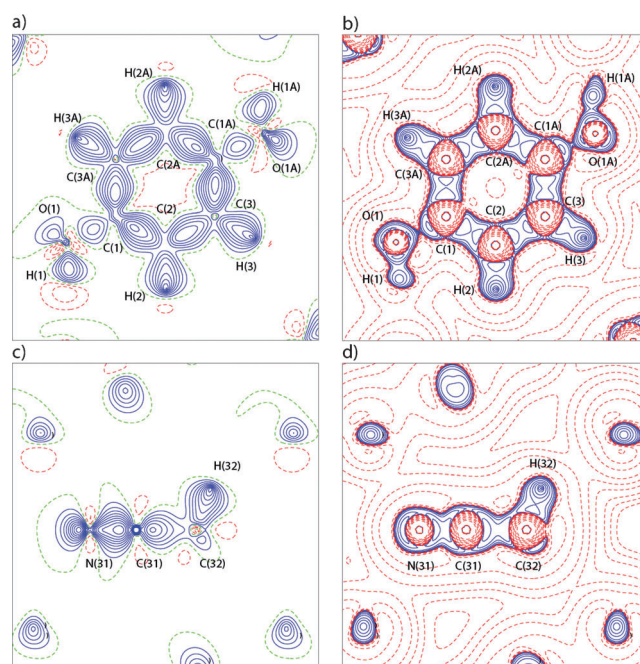

Figure 2. a) Static deformation ED and b) Laplacian distribution of one unique hydroquinone host molecule (experimental refinement) of **1**. c) Static deformation density and d) Laplacian distribution of a guest acetonitrile molecule of **1** (fixed at theoretical multipole values). For the deformation density the contour interval is 0.1 e Å⁻³ with solid contours being positive and dashed negative. For the Laplacian the contour level is $2^x \times 10^y$ ($x = 0, 1, 2, 3$; $y = -2, -1, 0, 1, 2, 3$), the red dashed lines indicate positive values, and the solid blue lines negative values.

whereas the ED of the acetonitrile molecules was mainly determined from the theoretical data, that of the host structure was based solely on experimental data, and this was used in the analysis of the chemical bonding and electrostatic properties.

The chemical bonding of the host structure can be analyzed by using the quantum theory of atoms in molecules,[29] and topological properties at the bond critical points (BCPs) of selected hydrogen bonds are summarized in Table 1. 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 0.24–0.27 e Å⁻³. These values are significantly smaller than those observed for the hydrogen bond in empty β-HQ.[15] The intermolecular hydrogen bonds of the HQ molecules are primarily closed-shell interactions with positive Laplacian values. However, the slightly negative total energy density is indicative of covalent contributions to these hydrogen bonds. A crude estimation of the energy of the hydrogen bonds based on the energy density was suggested by Espinosa et al., and for **1** this resulted in $E(HB) = 0.5 V = -41$ kJ mol⁻¹,[30] while the value found for the empty HQ clathrate **2** was 50 % higher.[15]

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

Table 1. Topological analysis of the hydrogen bonding in the host structure of **1**. The second row gives the values obtained for the HQ apohost in ref. [13]. R [Å] is the bond length, R_{ij} [Å] the sum of the distance from the first atom through the BCP to the other atom, d_1 [Å] the distance from the O atom to the BCP, ρ is the electron density [eÅ^{-3}], $\nabla^2\rho$ is the Laplacian [eÅ^{-5}], and ε the ellipticity of the bond. G, V, and H are repectively the local kinetic, potential, and total energy densities estimated by using the Abramov functional.[31] The random least-squares errors in the values derived from the electron density are smaller than systematic errors between different models, and therefore only two significant digits are listed.

Bond[a]	R	R_{ij}	d_1	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
O(1A)···H(11)iv	1.7512(5)	1.7647	1.1361	0.27	1.9	0.33	0.18	−0.23	−0.05
O(11)···H(1A)i	1.7607(5)	1.7776	1.1800	0.26	2.1	0.57	0.18	−0.22	−0.04
O(14)···H(14A)iii	1.7543(5)	1.7700	1.1423	0.27	1.9	0.36	0.18	−0.22	−0.04
O(11A)···H(1)i	1.7606(5)	1.7800	1.1508	0.25	1.9	0.41	0.17	−0.21	−0.04
O(14A)···H(14)ii	1.7544(5)	1.7763	1.1797	0.25	2.3	0.60	0.19	−0.21	−0.03

[a] i: $-x+y+1$, $-x-1$, $z+1$; ii: $-y-1$, $x-y$, $z+1$; iii: $-y-1$, $x-y-1$, $z-1$; iv: x, y, $z-1$.

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 shown in Figure 3, together with charges for **2** for comparison.[15] The aromatic hydrogen atoms of the HQ molecules of **1** are more positively charged than those of the empty host structure, and the transferred electrons are primarily moved onto the hydroxyl-bonded carbon atom of the aromatic ring. This indicates that, on 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 on **2**.[15] The obtained atomic Bader charges (shown in green in Figure 3) deviate only slightly from the values obtained for the combined X/N model of **1**, and thus add 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 electro-
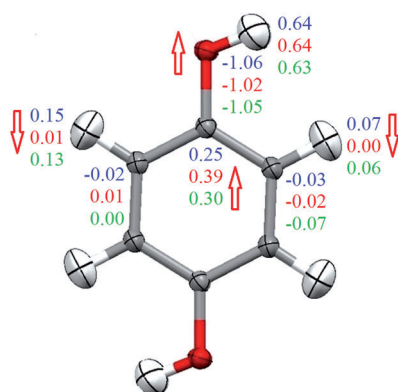

Figure 3. Topological charges of the Bader atoms of **1** (blue), the β-HQ apohost **2** (red), and **1** based on X-ray refinement only, without including the neutron parameters (green). The arrows show the movements of electrons due to the inclusion of the acetonitrile molecules.

static interaction between the host and the guest, or simply a result of the increased distance between HQ molecules, as evidenced by the increased unit-cell and hydrogen-bonding distances, is examined below in the analysis of the electrostatic potential.

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 was calculated (Figure 4). The five different isosurfaces originate from 1) the experimental ED of **1** (**1**^{exp}), 2) the theoretical ED of **1** (**1**^{theo}), 3) the experimental ED of **2** (**2**^{exp}), 4) the theoretical ED of **2** (**2**^{theo}), and 5) the theoretical ED from a modification of **1** (**1**^{theo,mod}) in which the HQ molecules were in the same geometry as **1**, but the acetonitrile solvent molecules were omitted.

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 4a, b) and **2** (Figure 4c, d), except for the electropositive (red) area on top of the OH group in **1**^{theo} (Figure 4b), which is not seen for **1**^{exp} (Figure 4a). This indicates that polarization of the HQ molecules in the crystal structure is indeed accessible from experiment by 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 with **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: 1) that the electrostatic moments of the acetonitrile molecule directly polarize the HQ molecules; 2) that the larger separation between HQ molecules changes the intermolecular contacts to such an extent that the electrostatics of HQ are influenced. Figure 4e shows the EP of an artificially expanded empty HQ crystal structure (HQ geometry as in **1** but without acetonitrile inclusion), and from its remarkable similarity with Figure 4d it is immediately clear that enlargement of the cavity has virtually no influence on the EP evaluated at the HQ isosurface. On the other hand, the inclusion of acetonitrile, which may be regarded as the difference between Figure 4b and e, 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,[32,33] but recognize that the differences between the two compounds studied here, **1** and **2**, are based on two different crystal structures. The electrostatic effects of incorporating
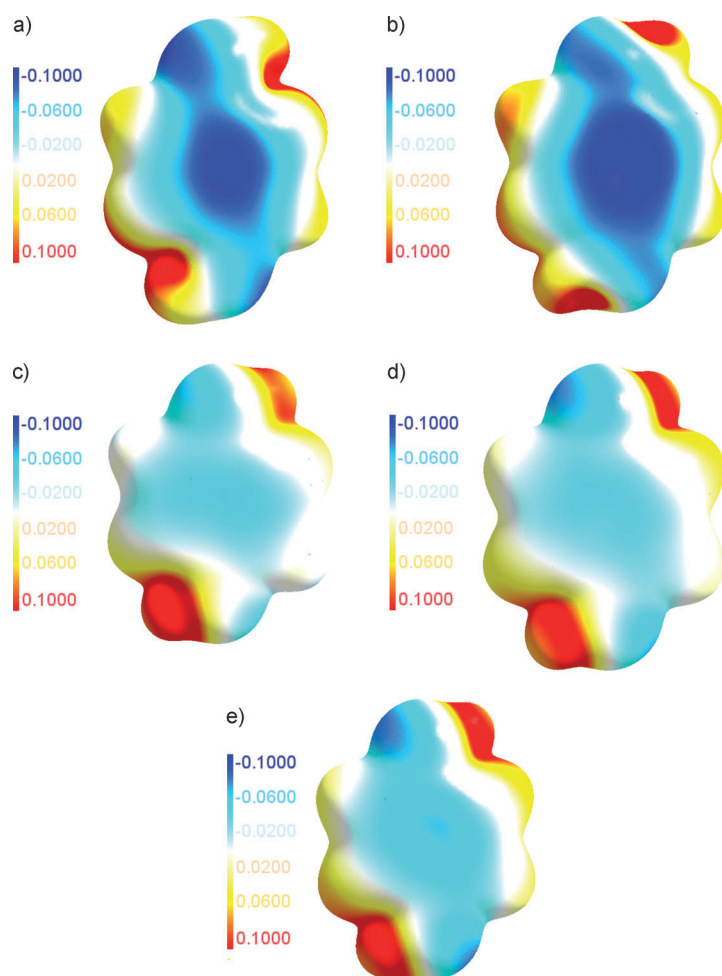
Figure 4. The electrostatic potential mapped from −0.10 (blue) to 0.10 e Å^{-1} (red) on the electron-density isosurface of 0.01 e Å^{-3} visualized by using MoleCoolQt.[62] The surfaces were calculated from multipole models based on structure factors from a) experiment, HQ–acetonitrile (**1**[exp]); b) theory, HQ–acetonitrile (**1**[theo]); c) experiment, empty HQ (**2**[exp]); d) theory, empty HQ (**2**[theo]); e) a theoretical modified version of **1** in which the acetonitrile molecules are omitted but the geometry of the HQ molecules is as in HQ–acetonitrile (**1**[theo,mod]).

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 threefold axis (Figure 5). These plots clearly show the electropositive nature of the cavity.

Theoretical modeling of hydrogen storage in metal–organic frameworks (MOFs) has revealed that the host–guest interactions are promoted by the local polarity of the host network, which induces a dipole in the otherwise nonpolar H_2 guest molecules.[34] This shows that the electrostatic properties of the host are of great importance in predicting the properties of host–guest systems.[35] In the chromium-wheel host complex [$Cr_8F_8(tBuCO_2)_{16}$] the EP was funnel-shaped with a three-dimensional saddle point located at the center, which was found to be highly electronegative with an electrostatic potential of −1.24 e Å^{-1}.[36] In **1** and in empty β-HQ (**2**), a saddle point is also observed, but in this case the EP is positive. In **1** the EP goes from about 0.30 e Å^{-1} near the hydrogen-bonded hexagon of the host structure to about 0.13 e Å^{-1} at the center of the cavity. Hence, the electrostatic interaction energy with the

acetonitrile molecules is considerably weaker in **1** than in, for example, the chromium-wheel compound. The polarization of the host structure on inclusion of acetonitrile changes the electrostatic potential in the center of the cavity an order of magnitude from 0.014 e Å^{-1} in **2** to 0.13 e Å^{-1} in **1**, and this directly demonstrates that host-structure polarization has important energetic consequences. The difference between the EP in the cavities of HQ and in 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 atom into the electronegative center of the cavity of the chromium wheel, whereas the negatively polarized nitrogen atom points towards the more electropositive surface of the host.

In **1** the center of the cavity is electropositive, and the potential increases along the cavity in the direction of the threefold axis, which suggests that electronegative regions of molecules situated in the cavity would point in these directions, for example, towards the hexagon of hydrogen-bonded HQ molecules. This is in fact the case for the nitrogen atom of the cyano group at one end of the acetonitrile molecule, and this placement of electronegative groups was also suggested by Zubkus et al.[37] 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 attain electrostatic complementarity at both ends, because tilting of the molecule is hindered. If tilting were feasible the positively charged atom could be placed away from the threefold axis to reduce the electrostatic energy penalty, since the EP decreases on moving perpendicular to the threefold axis. Since acetonitrile is among the largest molecules 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 about 31° is observed in the HQ host,[38] and this presumably is due to the electrostatically more favorable tilted position. However, 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 with all host molecules residing inside a box of 2×2×3 unit cells excluding the contribution from the guest molecules (i.e.,
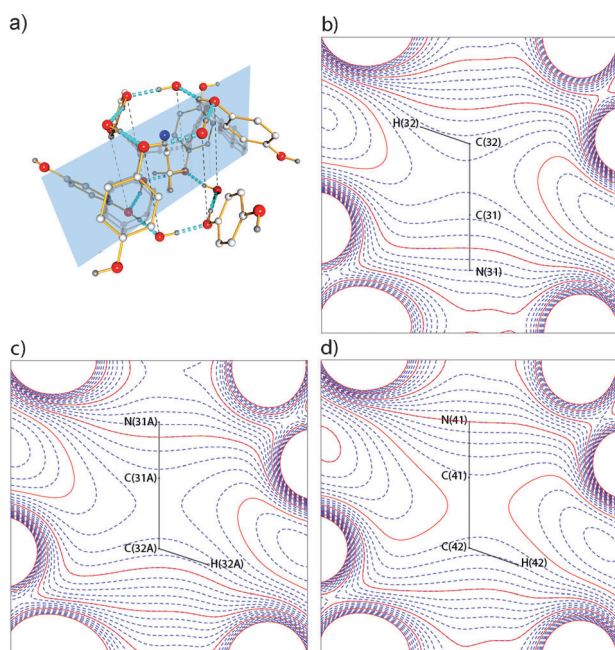
Figure 5. a) Schematic showing the plane used for the EP maps. It is parallel to the *a* and *c* axes of the unit cell. b)–d) show the EP of the cavities holding acetonitrile molecules AceI, AceII, and AceIII, respectively, plotted in a 6.1×6.1 Å^2 section. The contour interval is in 0.01 e Å^{-1} steps with EP ranging from 0.40 e Å^{-1} (near atom centers) to 0.15 e Å^{-1}. Red contours are drawn for every 0.05 e Å^{-1}.

due solely to the host molecules), and it is as expected fairly symmetrical (Figure 6). 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, on moving along the threefold 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 Å^{-2}, depending on the cavity, and the fields point toward the center of the cavity. The numerical values are significantly higher than those observed in the empty β-HQ structure (0.0185 e Å^{-2}). On moving perpendicular to the threefold 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 Å^{-2}, whereas the EF of the empty β-HQ was previously found to be 0.0105 e Å^{-2}. In both directions, parallel and perpendicular to the threefold axis, the EF of **1** is up to twice as high as that reported for the empty β-HQ reference structure **2**.

The observed differences between **1** and the empty host **2** show that 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 carbon atoms of the benzene ring. This leads to almost a doubling of the electric field and the EP in **1** at a distance of 1 Å 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 MD calculations that implement force-field methods to obtain the potential energy of a given system. Force fields are the foundation, for
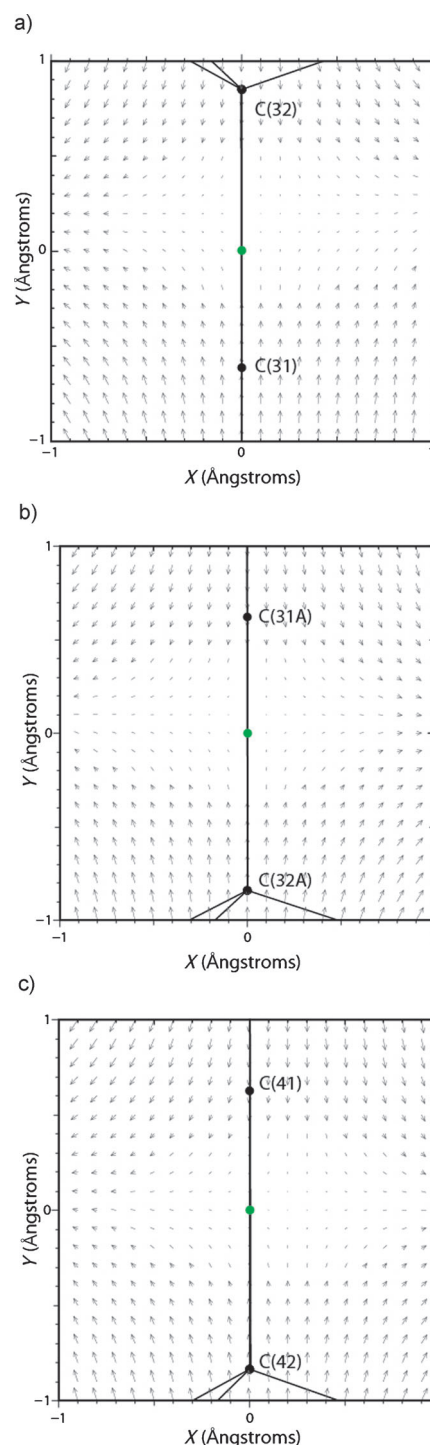

Figure 6. The electric field due to just the host molecules in **1**, plotted in a 2×2 Å plane parallel to the *a* and *c* axes of the unit cell and through the center of the cavities of a) AceI, b) AceII, and c) AceIII. The centers of the cavities are denoted by the green dots. Arrows indicate the direction of the EF and their length its magnitude.

example, of many investigations of protein–ligand interactions in drug design.[39] The molecules in such calculations are composed of atom types that depend on the atomic number and the type of chemical bonding.[40] The molecules are described by a ball-and-spring model, in which atoms in a nonpolarizable

force field are considered to be 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 nonpolarizable force fields, and this must lead to errors in the electrostatic energy, which contributes to the noncovalent part of the potential energy being minimized. For nonpolar systems, such as hydrocarbons, the electrostatic energy term is not crucial, but for polar systems the long-range electrostatic interaction is often the dominant term.[40] Typical examples of nonpolarizable force fields are MM2, MM3, and OPLS.[41, 42] 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. Nemkevich et al. recently used GAFF in a study of flip-flop hydrogen bonding in clathrates such as Dianin's compounds and HQ.[17] The barrier of reorientation of a single hydroxyl group in the two host molecules was found to be lowest for β-HQ, and hence the reorientation of the hydrogen bonding is more frequent. A nonpolarizable 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.

The present results also have important implications for the so-called pseudoatom databases, such as ELMAM,[43] ELMAM2,[44] Invariom,[45, 46] UBDB,[47–49] and MOF building blocks,[50, 51] which are used for experimental structure refinement with 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 the low precision of the obtained EPs,[32] and this suggested that the electrostatic interaction energies will also 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 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, including intermolecular interactions, when categorizing atom types for the ED databases. This is, however, not an option when building force fields in, for example, 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 are typically small, and hence the host polarization revealed in the present study, albeit small, may be an important contribution to the total energy. Bak et al. and Dittrich et al.[33] recently concluded, on the basis of theoretical studies on amino acids, that the multipole model is not able to

quantitatively describe the 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^{-1}. However, Bak et al were operating with identical geometries, and the HQ distribution and the hydrogen-bonding network in **1** are significantly different from those 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 reveals that the effect of guest inclusion is at least an order of magnitude larger than the geometry change and is accessible by using a multipole refinement, in contrast to the results of Bak et al. Changes in atomic charges on the order of 0.15 e make a significant contribution to the electrostatic energies of the system.

Conclusion

State-of-the-art single-crystal synchrotron X-ray diffraction data in combination with single-crystal neutron diffraction data measured at very low temperature have been used to obtain an experimental CD model of the HQ:acetonitrile clathrate **1**. Significant efforts were devoted to obtaining accurate Bragg intensities for the weak reflections containing information about the 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 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** was found to be significantly different from that of the HQ apohost **2**, and intramolecular transfer of electrons from the hydrogen atoms to the carbon atoms takes place. This induces a change in electrostatic potential at the periphery of the HQ molecules. The observed change in EP was shown to follow not from the geometrical change that happens on 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 nonpolarizable force fields, since the interaction energies possibly contain significant errors.

Experimental Section

Synthesis

β-HQ clathrates $3 C_6H_4(OH)_2 \cdot x S$ are simply prepared by evaporation of the solvent from HQ solutions. For the synthesis of **1**, several batches were prepared to accommodate the different crystal sizes needed for 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) by using pellets pressed from finely ground powder. The data are shown in the Supporting Information.

Neutron diffraction data collection

Single-crystal neutron diffraction data of **1** were collected at the D19 instrument at the Institute Laue-Langevin, France, by using monochromatic thermal neutrons with a wavelength of 0.9458 Å. A hexagonal prism-shaped crystal with dimensions of $1.5 \times 1.5 \times 2.5$ mm was wrapped in Al 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 43 696 reflections were collected to a maximum resolution of 0.929 Å^{-1}. The crystal faces were indexed as {100}, {$-$120} and {101}, and the data were integrated and corrected for absorption by using locally developed programs and a calculated absorption coefficient of 1.8 cm^{-1}.[52] Outlier rejection and merging with the program SORTAV gave a total of 5699 unique reflections with an internal agreement factor of $R_{int} = 3.26\%$ and an overall completeness of 94.9%.[53] Further experimental details are listed in Table 2.

Table 2. Crystallographic details and refinement residuals.

	Neutron	Synchrotron X-ray
empirical formula	$(C_6H_6O_2)_3CH_3CN$	$(C_6H_6O_2)_3CH_3CN$
T [K]	15(2)	15(2)
a [Å]	15.7845(2)	15.7807(5)
c [Å]	6.1736(1)	6.1683(2)
V [Å^3]	1332.08(3)	1330.30(7)
λ [Å]	0.9458	0.41328
μ [mm^{-1}]	0.18	0.011
T_{min}/T_{max}	0.6783/0.8028	0.89/1.00
$N_{measured}/N_{unique}$	43 696/5699	144 185/21 872
R_{int}	0.0326	0.044
$(\sin\theta/\lambda)_{max}$ [Å-1]	0.93	1.20
		X/N multipole model
space group	$P3$	$P3$
N_{obs}	5699	4276 (2σ level)
$N_{par}/N_{restraints}$	157/12	192
$R_{all}(F)$, $R2\sigma(F)$	0.0892/0.0511	0.1134/0.0221
$wR(F^2)$	0.0825	0.0610
residuals	$-1.44/+2.12$	$-0.66/+0.71$ (acetonitrile), <0.17 (HQ)
GoF	1.541	0.7510

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 ($0.040 \times 0.040 \times 0.050$ mm) was cooled to 15(2) K by using an open-flow liquid-helium cryostat. The data were collected at a wavelength of 0.41328 Å with a maximum resolution of 1.20 Å^{-1}. A combination of exposure times of 0.5, 1, and 3 s was chosen 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 144 185 reflections were collected and integrated with SAINT+.[54] Subsequently the data were cor-

rected for the imperfect detection by the CCD phosphor by using a transmission factor of 0.6041 in the program SADABS.[54,55] 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 were 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 3 s runs to avoid poorly determined intensities from the measurements with shorter exposure times. The remaining 131 229 reflections were averaged and outliers were rejected with the program SORTAV to give a total of 21 872 unique reflections with $R_{int} = 4.40\%$.[53] Only reflections measured three times or more were used in the subsequent multipole refinements. Selected experimental details are listed in Table 2.

Theoretical calculations

A wave function was calculated by using ab initio periodic DFT with the B3LYP exchange and correlation functional[56,57] implemented in the program CRYSTAL06.[58] A standard Pople 6-311G** all-electron basis set was used in the calculations. The calculations were performed with the present experimental geometry and the geometry of the apohost from Clausen et al.[15] The SCF (self-consistent field) energy convergence threshold was set to $\Delta E < 10^{-6}$ hartree. The topology of the density was analyzed with the program TOPOND08.[59]

Refinement of neutron data

The guest molecules in **1** are ordered with two acetonitrile molecules pointing up and one pointing down (Figure 1a). The model that was used for describing the molecular structure included an inversion center for the host atoms (adhering to $P\bar{3}$), while the individual guest molecules were allowed to differ ($P3$ symmetry). The geometry and ADPs of the three unique acetonitrile molecules were constrained to be identical. Details of this constrained refinement are listed in Table 2.

A Hirshfeld rigid-bond test was satisfactorily fulfilled for the structure[60,61] with a mean value of the difference of mean-square displacement amplitudes (DMSDA) of $\Delta A - B = 5.9$ pm^2. The maximum $\Delta A - B$ value of the host was 10 pm^2, whereas in the cyano group of the solvent molecule the DMSDA value rose to 21 pm^2.[62] The positions and (scaled) ADPs of the hydrogen atoms were used in the X/N 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,[63] and non-H atom parameters were refined against the high-order part of the synchrotron data with $\sin\theta/\lambda > 0.8$ Å^{-1}. The constraints used for the neutron model, for example, center of symmetry 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 lengths from the heavy atoms to the hydrogen atoms were fixed to the values obtained in the refinement of the neutron data. To optimize the starting model, nonzero multipole populations were retrieved from Invariom atoms by using the InvariomTool.[64] After initial refinement of these parameters, a full multipole model was introduced with gradually increasing complexity while maintaining the symmetry restrictions. The imposed constraints reduced the number of refin-

able 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 possible that forcing identical electronic distributions on the two different orientations of the acetonitrile molecules (up and down) is inappropriate; 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 were fixed to the Invariom values. Experimental noise tends to accumulate on the high-symmetry axis,[65] which in this structure coincides with the threefold 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 tend to show higher deviation between X-ray and neutron ADPs.[66] Comparing the ADPs of the 33 heavy atoms in **1** by using the program UIJXN leads to a mean deviation $\langle \Delta U \rangle$ of 0.00058 Å^2,[67] which, for such a large system, is an excellent correspondence compared with other X/N studies.[68] The hydrogen nuclear positions and ADPs, which are important in accurate ED modeling of hydrogen-bonded systems such as **1**,[69] were therefore expected to be of excellent quality. Increasing the complexity of the multipole model of the host structure, for example, by 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 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, that is, a density of acetonitrile that is very different from other acetonitrile molecules studied in the literature.[70]

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 ($I/\sigma = 4.4$ for these (1262) reflections). 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 model-ing 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 ($\Delta A - B \leq 8$ pm^2, $\langle \Delta A - B \rangle = 4.0$ pm^2), but for the acetonitrile molecules the values are highly affected by noise, and this led to values of 21 and 47 pm^2, respectively. The residual density near the acetonitrile molecule showed peaks ranging from -0.66 to $+0.71$ e Å^{-3} situated on the threefold rotation axis, whereas the residual density is less than ± 0.17 e Å^{-3} near the host HQ molecules. Residual density maps are provided in the Supporting Information.

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