JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

ARTICLE

pubs.acs.org/JACS

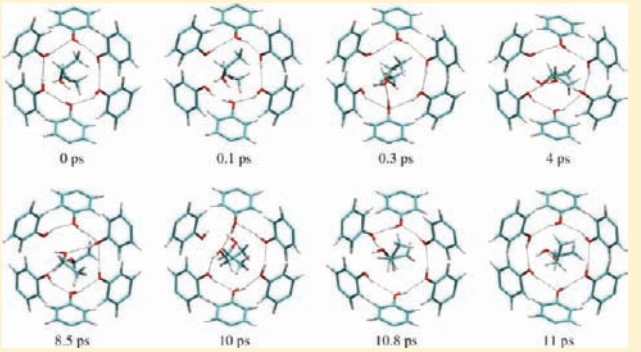
Mechanism of Concerted Hydrogen Bond Reorientation in Clathrates of Dianin's Compound and Hydroquinone

Alexandra Nemkevich, Mark A. Spackman, and Ben Corry*

School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, Perth, Australia

Web-Enhanced

ABSTRACT: Molecular dynamics provides a means to examine the mechanism of reorientation of hydrogen bond networks that are present in a range of biological and crystalline materials. Simulations of hydroxyl reorientation in the six-membered hydrogen bonded rings in crystalline clathrates of Dianin's compound (DC) and hydroquinone (HQ) reveal that in the clathrate of Dianin's compound with ethanol (DC:ethanol), hydroxyl groups perform single independent flips, and occasionally all six hydroxyls in a ring reorient following a sequential mechanism with participation of the guest ethanol molecule. The free energy estimated for this process agrees well with experimental results. The simulations suggest that hydroxyl reorientation occurs in the empty DC lattice as well, but at a higher energy cost, from which we conclude that it is the participation of ethanol that lowers the barrier of reorientation. Single independent flips of hydroxyl groups are observed to be more frequent in the hydroquinone clathrate with methanol (HQ:methanol) than in DC:ethanol, but reorientation of all six hydroxyls does not occur. This is attributed to the larger difference in energy between the original and reoriented positions of hydroxyl hydrogen atoms in HQ:methanol compared to DC:ethanol.



INTRODUCTION

Networks of hydrogen bonds are essential to the structure and function of biomolecules. They help, for example, to maintain the structure of α-helices in proteins and stitch together the double helix of DNA. A curious phenomenon dubbed flip-flop hydrogen bonding has been observed within rings and chains of hydrogen bonds made of hydroxyl groups, in which an individual hydrogen can alternate between hydrogen bonding to two acceptors, leading to a reversal of the direction of the entire network.[1] Such flip-flop hydrogen bonds are widely spread having been noted in hydrated saccharides,[1−3] suspected in some proteins[4] and nucleic acids,[5] crystals of small molecules of biological importance (resveratrol[6] and cholic acid[7]), as well as in nonbiological crystalline systems (calixarenes and resorcinarenes[8−10]), alcohols,[11−13] ice and ice clathrates.[14,15] Flip-flop hydrogen bonds generally stabilize the structure[2,16] and may be responsible for proton transfer in proteins.[17] The mechanism by which the reorientation of the hydrogen bonds occurs is not fully understood, but two possible mechanisms are hydrogen exchange and hydroxyl group rotation, and both are expected to happen in a concerted manner,[18,19] although a multistep hypothesis[20] or sequential breaking of hydrogen bonds[21] have also been suggested. Given the lack of knowledge in the area and the difficulty in studying the biological systems, much can be learned from a detailed study of hydrogen bond rearrangements in one of the simpler situations.

In this study we focus on the example of hydrogen bond reorientation reported in the six-membered hydrogen bonded rings of the deuterated clathrate of Dianin's compound (DC) with ethanol (DC:ethanol).[22] It was found that the six hydroxyl groups making up the ring perform rotations around the C−O bonds, thereby changing the direction of the hydrogen bonding in the ring. Careful analysis of the ^{2}H NMR data ruled out the possibility of deuterons jumping between the neighboring oxygens. Instead, all six hydroxyls reorient in what the authors referred to as a concerted manner, meaning that the time it takes the hydrogens to change sites is short compared with the time they spend in each of the sites. The authors recognized that rotational jumps of six hydroxyl groups in concert are a remarkable phenomenon, but they also refuted the possibility of totally independent jumps, because that would require two hydrogens to stay very close to each other for a considerable time, something that was not found in the experiment. Intra- or intermolecular hydrogen bonded rings are common structural motifs in organic and metal−organic host systems, and flip-flop hydrogen bonds have been observed in some of them (calixarenes, resorcinarenes), but not in the well-studied hydroquinone (HQ) clathrates, that have a structure similar to that of DC clathrates.

The flip-flop reorientation of hydrogen bonds in DC:ethanol is also an excellent example of the kind of dynamic process that can occur in crystals, materials that had long been thought of as nothing other than 'chemical cemeteries'.[23] The motion of atoms in crystals has begun to be appreciated through discoveries of the uptake of gases by seemingly nonporous materials[24−26] and their

Received: July 25, 2011
Published: October 12, 2011

release without destruction of the crystal lattice,[27−29] as well as porous materials with the ability to transport guest molecules larger than the size of interconnecting windows between cavities .[30,31] It is possible that the kind of hydrogen bond rearrangement described here could be important for enabling such transport behavior.

Our previous work employing molecular dynamics (MD) to study dynamics in a range of crystals formed from polar and nonpolar molecules[32] suggests that studying a reorientational process like this with MD simulations is feasible, given its femtosecond time resolution and the fact that individual atoms can be observed. Although several molecular dynamics studies have been reported of clathrates of DC[33,34] and HQ,[35−38] none of them has been concerned with hydroxyl reorientations. MD simulations of hydrogen-bond reorientation in β-cyclodextrin have been attempted in ref 39, where a good agreement with experiment was obtained for the number and location of the hydrogen bonds and even reorientations were observed, although little detail on the mechanism was given. In another molecular dynamics study of calixarenes, no evidence of flip-flop hydrogen bonds was found.[40] Attempts to model both possible mechanisms, proton exchange and hydroxyl rotation in calixarenes, have been reported in ref 41using ab initio methods. The proton exchange mechanism was found to have a lower barrier than hydroxyl rotation in vacuum and in a nonpolar solvent; however, a rotational mechanism could not be excluded in polar solvents. Here we apply MD to simulate the reorientation of hydroxyl groups in clathrates of DC and HQ with the aim of understanding more about the mechanism of hydroxyl reorientation in DC:ethanol and assessing the possibility of its happening in HQ clathrates. We also look into the role of the guest molecule in this rotational process by comparing simulations of the clathrates and the corresponding empty host lattices (apohosts).

SIMULATION DETAILS

In contrast with recent simulations reported for host−guest complexes of calix[4]arenes,[42,43] where isolated dimers or complexes were tethered, our simulations involve multiple crystallographic unit cells with periodic boundary conditions. The crystal structure of DC:ethanol at room temperature was taken from the literature ($R\bar{3}$, $a = b$ =26.969 Å, c = 10.990 Å).[44] The unit cell was replicated along the c direction making a supercell of 1 × 1 × 3 unit cells, 26.969 Å × 26.969 Å × 32.970 Å in size, 20767.3 Å^3 in volume. Such a simulated cell size should be enough to adequately describe the dynamics of the system.[32] Since in the crystal structure the coordinates of guest ethanol molecules were not determined, two ethanol molecules were arbitrarily placed per cage, and then the system was minimized and equilibrated for 25 ps at 300 K. As there is no structural information available for a HQ:ethanol clathrate, for comparison of the structure with that of DC:ethanol we chose the structure of HQ:methanol, which has been recently determined at 100 K by Clausen[45] ($R\bar{3}$, $a = b$ = 16.426 Å, c = 5.495 Å). The unit cell was replicated in three dimensions to form 2 × 2 × 6 unit cells, or a 32.852 Å × 32.852 Å × 32.970 Å supercell with a volume of 30815.8 Å^3 .

All simulations were performed at 300 K with periodic boundary conditions and a constant pressure of 1 bar using the General Amber Force Field (GAFF),[46] MD code NAMD,[47] and the PLUMED plugin for free energy calculations.[48] GAFF was chosen because it has previously been shown by us to satisfactorily model thermal motion in organic crystals and those involving hydrogen bonds,[32] and it is easy to use with complex molecules such as DC. Some previous modeling studies of HQ have also used Amber force fields.[36,38] The input files for the structures were obtained using Antechamber package,[49] with the AM1BCC method[50,51] used to obtain atomic charges. No modification of the force field parameters was done. The collective variable biased in the free energy simulations was a CCOH dihedral angle or a set of six CCOH dihedral angles belonging to the molecules in one ring. These angles are described in more detail in the following section. The parameters of the simulations for different systems were kept as similar as possible. Parameters used in metadynamics simulations were the following: Gaussian height 2.0 kcal mol^{-1} (gradually increased for systems other than DC:ethanol), Gaussian width 8.6°, Gaussians were deposited every 1 ps, values of dihedrals recorded every 50 fs. In umbrella sampling simulations we used the spring constant of the restraining potential of 30 kcal mol^{-1} rad^{-2} for DC:ethanol and DC, and 40 kcal mol^{-1} rad^{-2} for HQ:methanol and HQ, window width of 10°, and the system was run for 100 ps in each window.

STRUCTURE

In clathrates of both DC and HQ six molecules are linked by hydrogen bonds between their hydroxyl groups, forming a ring with alternate molecules pointing up or down. These complexes are stacked on top of each other, forming continuous pores of joined cages with spaces between the hydrogen-bonded rings. In clathrates of DC these cages are of approximately hourglass shape, ∼11 Å long, and are occupied by two guest molecules, whereas in clathrates of HQ they are roughly spherical in shape, ∼4 Å in diameter, and occupied by a single guest (Figure 1).

Throughout this work, to describe reorientations of the hydroxyl moieties in these molecules, we use CCOH dihedral angles chosen in such a way that they are close to 0° when oriented as in the crystal structure and close to 180° after reorientation. As discussed in detail in ref 22, the equilibrium positions of hydroxyl groups in the crystal structure represent a balance between (1) achieving coplanarity with the phenyl ring of the molecule they belong to, (2) establishing a linear hydrogen bond with the next oxygen in the ring, and (3) maintaining an optimal COH angle. Because not all of these conditions can be fully satisfied simultaneously, the CCOH dihedrals in the ring are not zero but alternate between ∼12.5° and −12.5° for DC:ethanol and 12° and −12° in HQ:methanol in the known crystal structures. In our simulations these dihedral angles average to ∼6.5° or −6.5° and 12.7° or −12.7° respectively, and they fluctuate with a standard deviation of ∼12.5°. Unlike hydroquinone, where the position of the phenyl ring is determined by the two hydroxyl groups being involved in hydrogen bonding in different hydrogen-bonded rings, the large molecule of DC can allow a better alignment of its hydroxyl group with the phenyl ring in the simulation.

In this peculiar arrangement of molecules, two directions of hydroxyl rotation are possible, into a cavity and out of a cavity (Figure 2). Only rotation into a cavity permits the reorienting hydroxyl to form a hydrogen bond with the oxygen of the guest molecule (ethanol or methanol). Due to the alternating orientations of hydroxyls in the ring, this bond can be formed with the guest molecule in the cavity on either side of the ring. The value of the CCOH dihedral for the hydroxyl reorienting into a cavity can be positive or negative; thus, to distinguish between the two directions of hydroxyl reorientation without confusing the

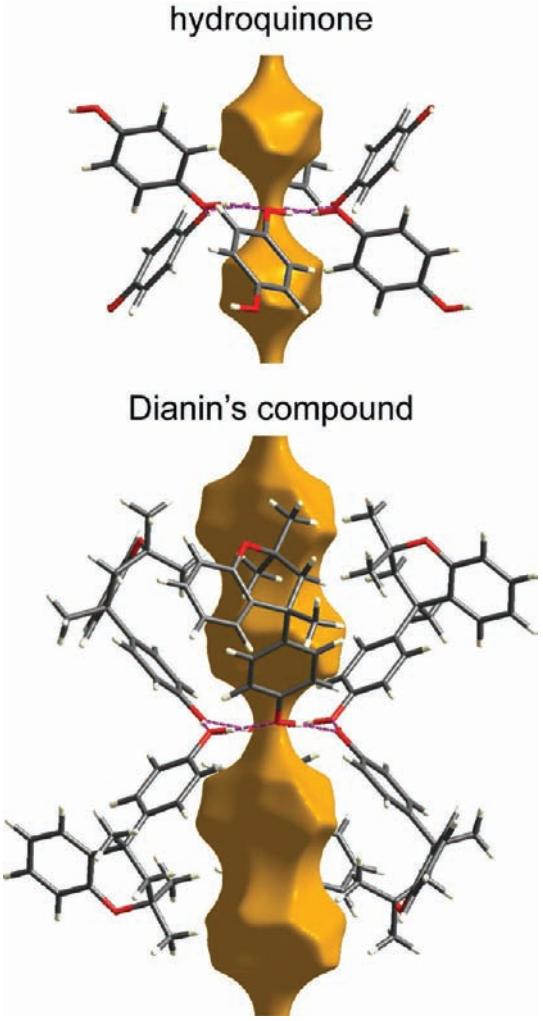


Figure 1. Visualization of the cavities formed by six molecules in guest-free HQ and DC. Hydrogen bonds in the six-membered ring are shown as magenta dashed lines, and the yellow surface is the 0.0003 au isosurface of the procrystal electron density.[52]

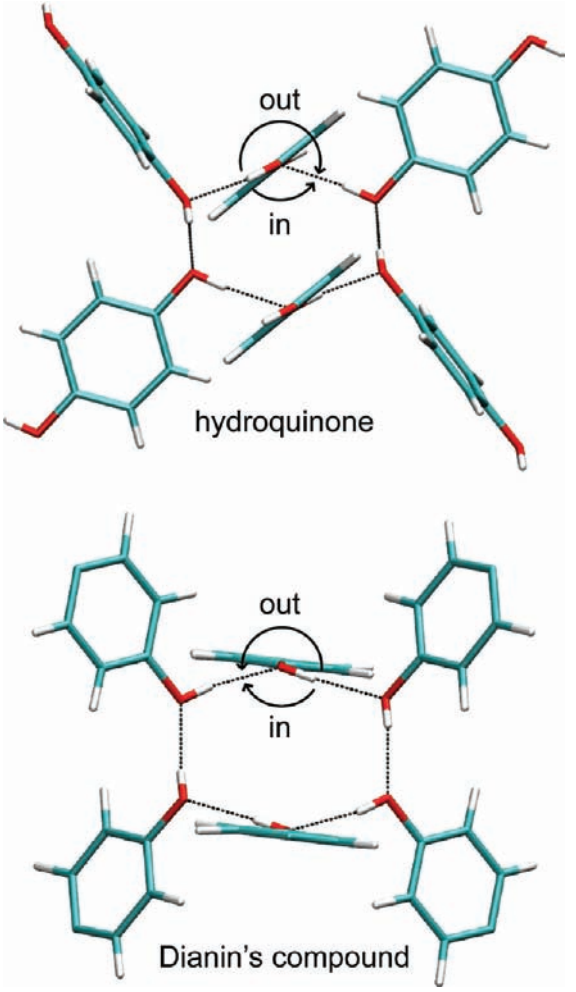


Figure 2. Views of the six-membered hydrogen-bonded rings in the crystal structures of HQ and DC projected down the planes of two of the phenyl rings in each case; only the phenyl rings of DC are shown for clarity. It can be seen that the equilibrium CCOH dihedral angles are not zero and two pathways of reorientation are possible. One can also imagine approximate reoriented positions of hydrogens and note that the two hydroxyl orientations are similar for DC, but distinctly different for HQ.

reader, further in this work we adjusted the figures in such a way that a reorientation into a cavity always has a positive sign.

Crystal structures were reproduced well in the simulations, giving unit cell parameters $a = b = 27.065(42)$ Å and $c = 11.029(17)$ Å for DC:ethanol, which is 0.35% larger than experimental values, and $a = b = 16.591(19)$ Å, $c = 5.550(6)$ Å for HQ:methanol, which is some 1% larger than experimental values at 100 K and includes thermal expansion. As described in ref 32, there is no obvious correlation between the direction of change of the unit cell lengths and the chemical contents of the unit cell.

Thermal motion, assessed using isotropic atomic displacement parameters (ADPs) following a method described previously,[32] was underestimated by about a third in the case of DC:ethanol, and no comparison could be made for HQ:methanol due to different temperatures of the crystal data and the simulation.

RESULTS AND DISCUSSION

Dianin's Compound. Given the experimental enthalpy of activation of 33.1 ± 1 kJ mol^{-1},[22] the reorientation of hydroxyls is expected to be a rare event, and we only observed one random flip of a single hydroxyl in 80 ns of equilibrium simulation. To speed up the process we performed a metadynamics simulation where the positions of all six dihedrals were biased. In metadynamics one or more coordinates (collective variables) are forced to explore their free energy landscape by a history-dependent potential made up of a sum of Gaussians, a procedure that speeds up rare events.[53] Biasing all six dihedrals at the same time excludes the possibility that the bias will favor a specific mechanism of reorientation. In this simulation the hydroxyls perform frequent, independent 180° flips, and occasionally (about 50 times in total within 80 ns) all six of them reorient (Figure 3a) following a sequential mechanism that also involves the guest molecule. In this mechanism one reoriented hydroxyl prompts the neighboring hydroxyl to reorient to avoid close contact through establishing a hydrogen bond with the guest ethanol molecule and so on along the ring until all six hydroxyls have rotated.

To demonstrate that reorientations occur in a sequential manner, we plot one of the six CCOH dihedrals against that of

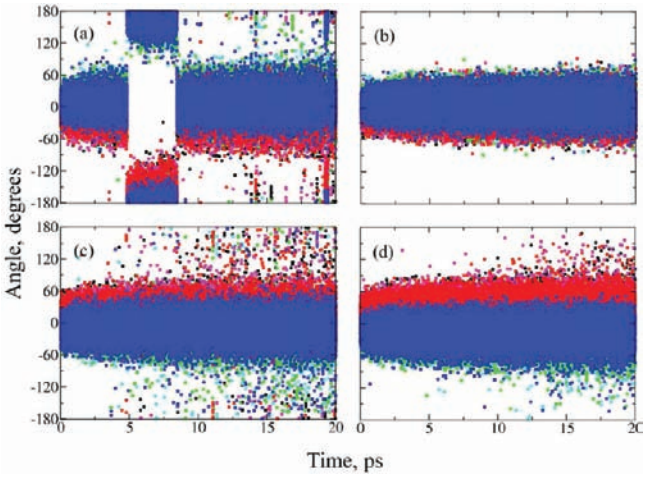


Figure 3. CCOH dihedral angles of a hydrogen-bonded ring of (a) DC:ethanol, (b) DC, (c) HQ:methanol, and (d) HQ in the first 20 ns of a simulation where metadynamics is performed on all six dihedrals. The same metadynamics parameters were used for all four systems: Gaussian height, 2.0 kcal mol^{-1}; Gaussian width, 8.6°; Gaussians are deposited every 1 ps; and the values of dihedral angles are plotted here with the same frequency. The coloring of atoms starts from an arbitrarily chosen first (black) and runs consecutively along the ring (cyan, magenta, green, red, blue).

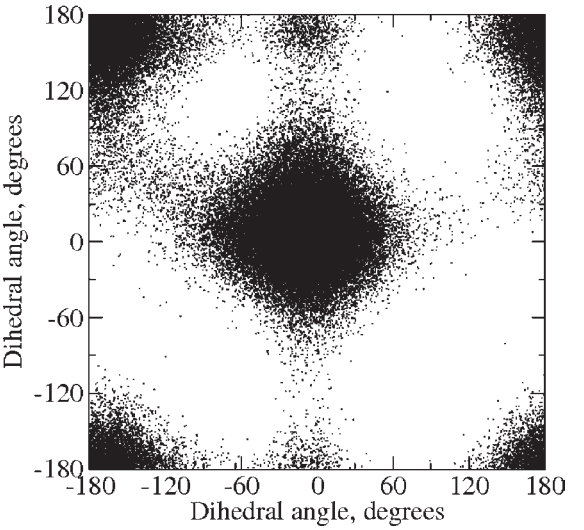


Figure 4. Plot of CCOH dihedral angles of molecules number 1 (x axis) and 2 (y axis) in the ring. One can see that, while the first hydroxyl is in its initial position around 0, the second hydroxyl can perform random flips. However, when the first hydroxyl reorients in a random jump, the second hydroxyl is forced to lean away and reorient. Similar plots are obtained for any pair of neighboring molecules, demonstrating the sequential mechanism of reorientation.

a neighboring molecule (Figure 4). This plot shows two commonly frequented states: both dihedrals near zero as in the crystal structure (center of plot) and both reoriented near 180° (corners of plot), as well as a less commonly sampled state in which only one hydroxyl reorients. If the hydroxyls reoriented in a concerted manner, the pathway linking the two most probable regions would be a straight line from the center to the top left corner of the plot. If they reoriented totally independently it would be L-shaped with only horizontal and vertical pathways taken on this figure. However, the presence of the curved trajectories in Figure 4 shows that the most common reorientation mechanism is neither perfectly concerted nor perfectly independent.

Since in this simulation the reorientation starts with a random flip of one hydroxyl group, to study this process in a more controlled manner we set up a simulation where one hydroxyl in the ring is rotated and kept in this position using a harmonic potential until other hydroxyls in the ring follow. Figure 5 depicts a number of stages in this simulation. The forcefully rotated hydroxyl makes the next hydroxyl in the ring (second hydroxyl) avoid close contact by reorienting toward the ethanol in the cavity above the ring and forming a hydrogen bond with its oxygen (0.3 ps). This is a dynamic equilibrium of multiple hydrogen bonds and, given the large thermal vibrations of atoms and especially hydrogens at room temperature and the fact that ethanol molecules can rotate freely in the large cavities of the clathrate, a moment comes when the second hydroxyl loses the hydrogen bond with the ethanol and rotates toward the third hydroxyl in the ring. The third hydroxyl group then reorients into the cavity below the ring and establishes a hydrogen bond with its ethanol molecule (4 ps). This process repeats until all hydroxyls reorient (11 ps).

Two factors facilitate this process: the weakness of the hydrogen bonds in the ring (with distances between the oxygens and hydrogens of around 2 Å) and the absence of competition for the same guest molecule. The hydroxyl groups in the six-membered ring are directed alternately to different sides of the average plane passing through the six oxygens, and the ethanol molecules on both sides of the oxygen ring are, in turn, involved in establishing hydrogen bonds with the reorienting hydroxyl groups of DC.

Figure 6a plots distances between the hydrogens of the reorienting hydroxyl groups and the oxygens of the ethanol molecules during reorientation. There is a clear line at around 2 Å occupied by each molecule in the ring in turn, corresponding to the hydrogen bond distance. Figure 6b plots on the same time scale the six CCOH dihedral angles. The sequence of reorientation is clearly seen. By comparing a and b of Figure 6 it is easy to see that while the hydroxyl groups rotate they are hydrogen bonded to the ethanols. For example, during reorientation of the second dihedral (colored cyan) between 0 and 4 ps, the angle oscillates around 90°, and at the same time the distance between the hydroxyl and the oxygen of the ethanol molecule is in the hydrogen-bonding range. Once the second dihedral has reached 180°, it forces the third dihedral, colored magenta, to move out of its place and oscillate around 90° until ~8.5 ps. During this time the distance between its hydrogen and the oxygen of a second ethanol molecule is in the hydrogen-bonding range.

From the start of the simulation it only takes less than 11 ps for full reorientation to occur. Thus, the proposed mechanism does not contradict the experimental findings of ref 22 that the reorientations happen very quickly and that hydrogens (deuterons) do not spend any considerable time close to each other. These findings led the authors of ref 22 to conclude that reorientations happen in a concerted manner, but they can also be rationalized with the more complicated sequential mechanism suggested by molecular dynamics.

We have estimated the free energy barriers to sequential reorientation of hydroxyls in DC:ethanol. First we estimated the barrier for a single random flip of a hydrogen. To this end we performed umbrella sampling on one hydroxyl group of the ring with other hydroxyls not constrained (labeled barrier 1 in Figure 7).

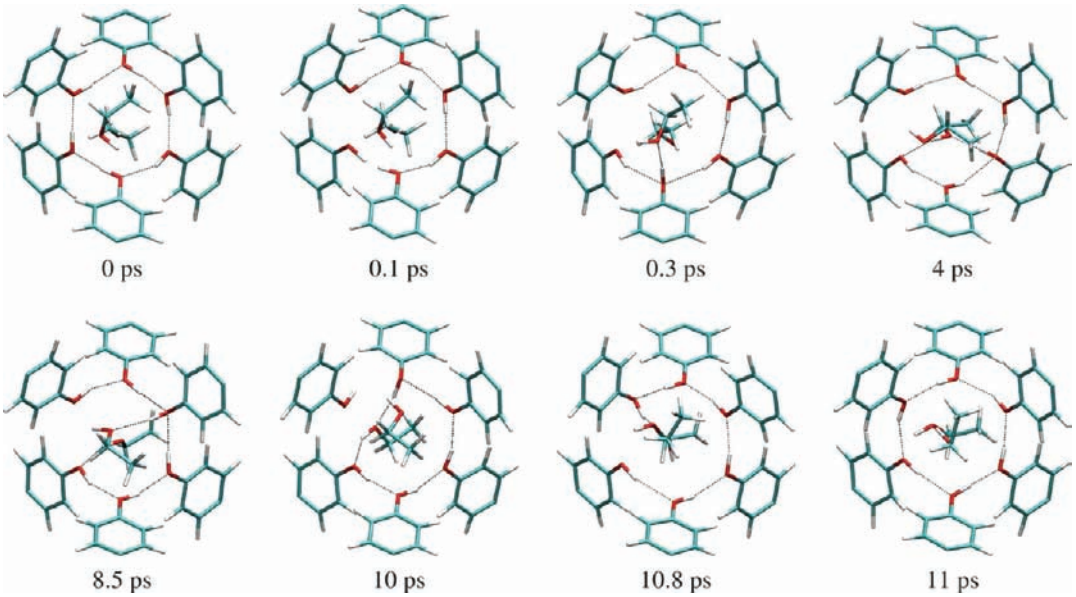


Figure 5. Ⓦ Snapshots of a simulation showing different stages of the reorientation process. Hydroxyls reorient following a sequential mechanism that involves the guest ethanol molecules. Only the phenyl groups of DC are shown for clarity. It is possible to see that the two ethanol molecules are coordinated in turn. Movie 1 of this simulation is included as a web enhanced object that can be viewed in the HTML.

We excluded the frames where the neighboring hydroxyl has a dihedral angle greater than 90°. With one hydroxyl rotated, how hard is it for the second one to rotate? To answer this question, we kept the first hydroxyl rotated and determined the free energy for the second hydroxyl to reorient using umbrella sampling. Again we excluded frames where the third hydroxyl in the ring rotates beyond 90°; this is barrier 2. Analogously, to assess barrier 3, we kept the first two hydroxyls rotated and biased the position of the third one using umbrella sampling. Only the frames where the dihedral angle with the fourth hydroxyl in the ring does not exceed 90° were used. Figure 7 shows all three barriers.

For the first hydroxyl to reorient, it has to overcome a barrier of 37.2 kJ mol^{-1}, and the minimum it reaches is only 2.6 kJ mol^{-1} deep. So a hydroxyl can every now and then flip to the other side, but it is not likely to stay there for long. However, with one hydroxyl reoriented, the energy it takes for the next one to flip decreases dramatically and is only 4.1 kJ mol^{-1}! Thus the flipping of the second hydroxyl becomes almost as likely as the return of the first hydroxyl back to its starting orientation. With two hydroxyls rotated the third one faces a "barrier" of 1.9 kJ mol^{-1}. A similar value of 1.8 kJ mol^{-1} is also the difference between the two hydroxyl orientations in our simulations (described later): the configuration seen in the crystal structure is favored by ~1.8 kJ mol^{-1}. The preference arises because the three geometric factors for CCOH dihedrals to deviate from 0° (listed in the Structure section) can be satisfied better for one position of hydroxyls (majority site, lower minimum) than for the other (minority site, higher minimum). The experimental value for the difference in enthalpy between the two sites is 2.9 kJ mol^{-1}.[22]

We also see a clear preference for hydroxyls to reorient via the inside of a cavity, where hydrogen bonding to the guest ethanol molecule is possible. For the first barrier the difference in reorienting via two directions is 5.9 kJ mol^{-1}, which still does not exclude reorientations via the outside of the cavity, but makes them less likely. This can be seen in the metadynamics simulations represented in Figure 4, where the majority of reorientations happen via the inside (shown by the high density of points on the left of the plot linking the two main states), but some happen via the outside of a cavity (lower density of points on the right of the plot). The difference in free energy for the two directions of reorientation is much greater for the second and third hydroxyls (see barriers 2 and 3 in Figure 7), which makes the pathway via the inside of a cavity a lot more probable. Thus, the reorientation of the first hydroxyl is the limiting stage of the full reorientation, and we can compare the value of its lower free energy barrier (37.2 ± 0.1 kJ mol^{-1}) to the enthalpy of activation found in the solid-state NMR experiment (33.1 ± 1 kJ mol^{-1}).[22]

We have also estimated the free energy barrier for all six hydroxyls to reorient together in perfect concert. It is 52.3 kJ mol^{-1} and was obtained as a sum of results of two calculations: an umbrella sampling where all six dihedral angles reorient, having the same value (22.6 kJ mol^{-1}), and a free energy perturbation to estimate the free energy cost of all dihedrals having the same value (29.7 kJ mol^{-1}). The difference between the minima in the umbrella sampling is 1.8 kJ mol^{-1}, as noted earlier, 52.3 kJ mol^{-1} is significantly higher than 37.2 kJ mol^{-1}, which supports the idea that the probability of this concerted reorientation occurring is extremely low.

Hydroquinone. In all of our simulations of HQ:methanol (whether equilibrium, performing metadynamics on all six hydroxyl groups (Figure 3c), or holding one hydrogen reoriented) the reorientation of all six hydroxyl groups was not observed to occur. The effect of holding one hydroxyl group reoriented is shown in Figure 8. The hydrogen next to the reoriented hydroxyl tries to avoid close contact and establishes a hydrogen bond with a methanol molecule (Figure 8a). Occasionally it flips, forcing the next hydroxyl to start reorienting (Figure 8b); however, such a conformation does not last long, and the system reverts to the previous conformation (Figure 8a).

We have estimated the free energy barriers to reorientation of hydroxyls in HQ:methanol following the same methodology described for barriers of DC:ethanol (Figure 9). Surprisingly, the

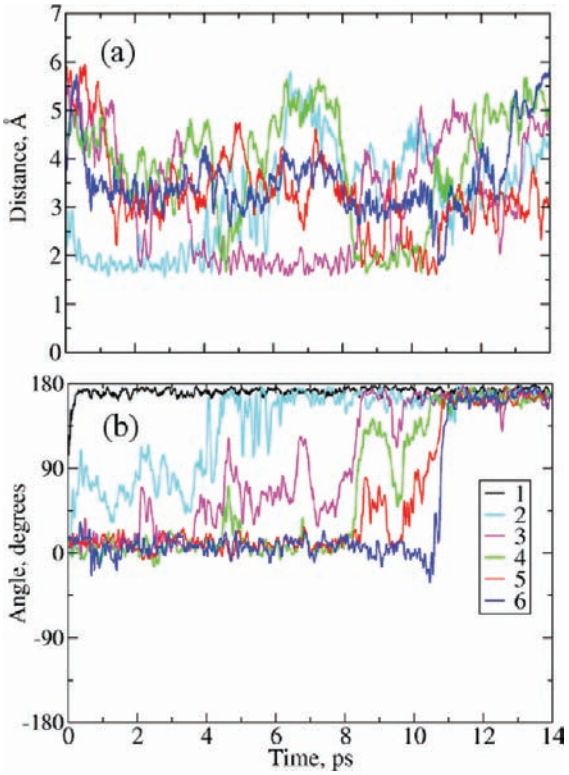


Figure 6. Distance between the hydrogens of the reorienting hydroxyl groups and the oxygens of the ethanol molecules (a) and dihedral angles involving the hydroxyl groups (b) over the course of simulation for DC:ethanol. In (b) angles are adjusted in such a way that a reorientation into a cavity is always positive. In this case all reorientations happen into a cavity. The coloring of dihedrals in the ring starts from the one that is being reoriented forcefully (black) and continues along the ring in the direction of reorientation (cyan, magenta, green, red, blue). Comparison of a and b shows that while the hydroxyl groups rotate they are hydrogen bonded to the ethanols.

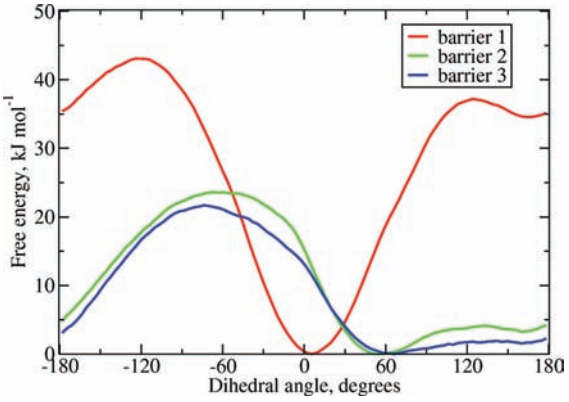


Figure 7. Sequential barriers to reorientation of hydroxyls in DC:ethanol. The graphs are adjusted so that the reorientation into the cavity (and via the guest) is in the positive half of the $[-180,180]°$ range. The first barrier corresponds to a single flip of a hydroxyl and is quite high, but the second and the third are very low. There is a clear preference for hydroxyls to reorient via the guest ethanol molecule.

barrier to reorientation of a single hydroxyl group in HQ:methanol is slightly lower than that in DC:ethanol, which suggests that

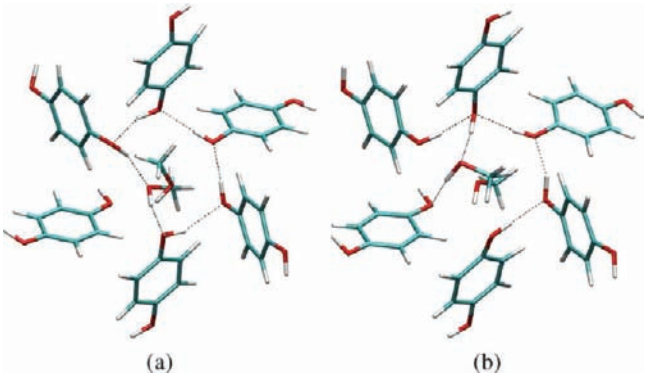


Figure 8. Ⓦ Snapshots of a simulation showing the effect that forceful reorientation of one hydroxyl group in the six-membered hydrogen-bonded ring of HQ:methanol has on the overall ring structure. Reorientation of all six hydroxyls in the ring does not occur. Movie 2 of this simulation is included as a web enhanced object that can be viewed in the HTML.

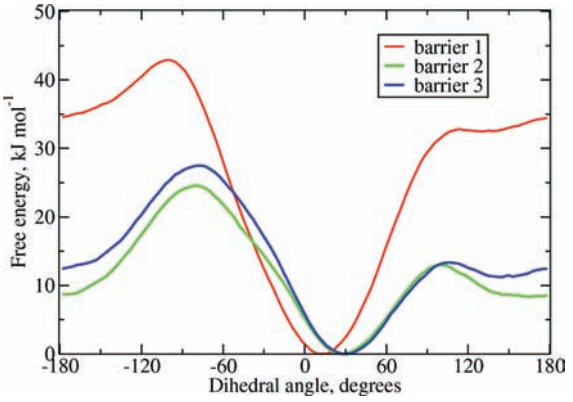


Figure 9. Sequential barriers to reorientation of hydroxyl groups of HQ:methanol in sequence. The angles are adjusted so that the reorientation via the inside of a cavity is always positive.

single random flips are more likely in the case of HQ:methanol than in the case of DC:ethanol. This can be confirmed by comparing a and c of Figure 3, where a higher frequency of single flips is seen for HQ:methanol than for DC:ethanol. The smaller first barrier seen here compared to DC:ethanol occurs as the reorientation of the first hydroxyl does not disrupt the neighboring hydrogen bond as much as in the case of DC:ethanol. But the second and the third barriers in HQ:methanol are higher than those in DC:ethanol and do not show the decreasing trend observed in that case, in fact the third is even slightly higher than the second. Unlike DC:ethanol, the barrier for the first hydroxyl to return to the original position (0.4 kJ mol^{-1}) is much smaller than the barrier for the second to reorient (13 kJ mol^{-1}). The difference between minima, representing all of the hydroxyls oriented in each direction, is greater as well: 8.4 kJ mol^{-1} compared to 1.8 kJ mol^{-1} in DC:ethanol. This suggests that the reorientation of all six hydroxyls in HQ:methanol does not occur because the reoriented conformation is far less favorable. Indeed, as seen from Figure 2 the three factors determining the positions of hydroxyls—coplanarity with the phenyl ring, ability to form a hydrogen bond with another oxygen in the ring, and maintaining an optimal COH angle—cannot be

dx.doi.org/10.1021/ja206962f |J. Am. Chem. Soc. 2011, 133, 18880–18888

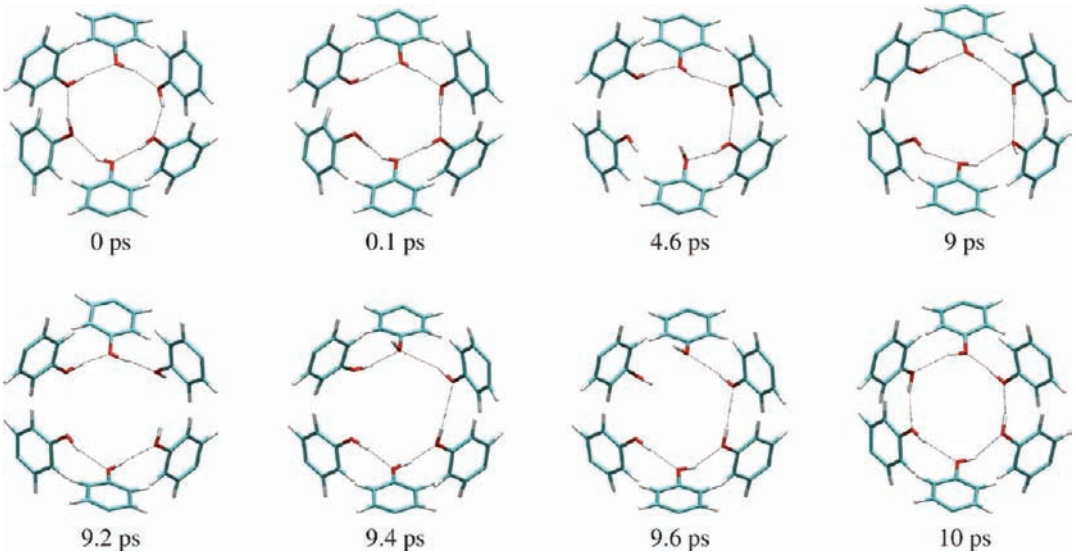


Figure 10. Ⓦ Snapshots of a simulation showing hydroxyls reorienting following a sequential mechanism similar to the one in DC:ethanol, without ethanol as a guest. Only the phenyl groups of DC are shown for clarity. Movie 3 of this simulation is included as a web enhanced object that can be viewed in the HTML.

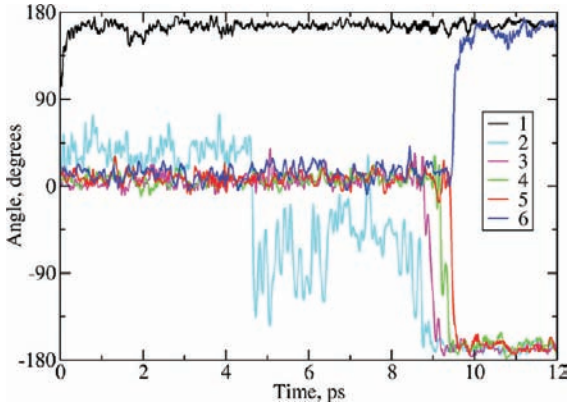


Figure 11. Dihedral angles of six molecules of DC in a ring during reorientation without ethanol as a guest. The graphs are adjusted so that the reorientation via the inside of a cavity is always positive. Unlike in Figure 6 both directions of reorientation are seen here. The coloring of atoms in the ring starts from the one that is being reoriented forcefully (black) and continues along the ring in the direction of reorientation (cyan, magenta, green, red, blue).

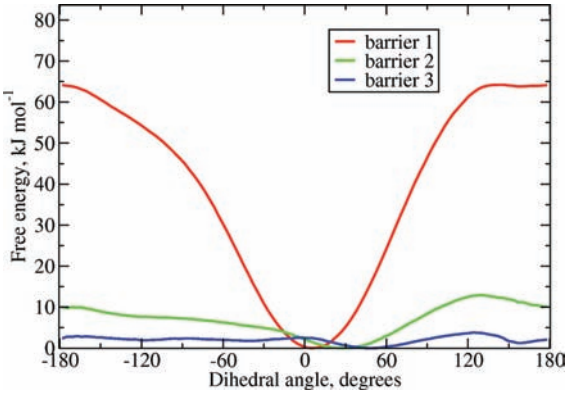


Figure 12. Sequential barriers to reorientation in DC without ethanol as a guest.The angles are adjusted so that the reorientation via the inside of a cavity is always positive.

optimized satisfactorily in the reoriented position. The rotation of each hydroxyl group involves the replacement of an "optimal" hydrogen-bonding planar geometry with a less ideal configuration, yielding higher barriers than for DC:ethanol.

Role of the Guest. To explore the importance of ethanol in the reorientation of hydroxyls we performed metadynamics on six hydroxyls of empty DC to see if the reorientation will occur without ethanol as a guest. The value of Gaussian height had to be increased from 2 kcal mol^{-1} used for DC:ethanol to 5 kcal mol^{-1} to observe a reorientation within the first 35 ns of the simulation. The reorientation occurred following a similar sequential mechanism: one hydroxyl flips and prompts the neighboring one to flip to avoid close contact, and so on. As with DC:ethanol, to study the process in more detail, we performed a simulation where one hydrogen was rotated and held rotated. Figure 10 gives snapshots from that simulation, and Figure 11 shows the six dihedral angles during reorientation. The reorientation takes ~10 ps.

The sequential barriers to reorientation of hydroxyls in sequence in DC (Figure 12) are higher than those in DC:ethanol but show the same trend. The first barrier is quite high, 64.2 kJ mol^{-1} (compared to 37.2 kJ mol^{-1} in DC:ethanol), and its second minimum is extremely shallow, 0.4 kJ mol^{-1} (compared to 2.6 kJ mol^{-1} in DC:ethanol). Single random flips in DC are therefore likely to be less frequent than in DC:ethanol, and the hydroxyl group is likely to spend even less time in the reoriented position. However, the second and the third barriers are only about 10 and 3 kJ mol^{-1}, respectively, which means that the reorientations of the second and the third hydroxyls are possible and the remaining three hydroxyls are likely to follow. As for the direction of reorientation, in the absence of ethanol the barrier heights for reorientations via the inside and the outside of a cavity are the

same; therefore, the hydroxyls can reorient either way, as can be seen in Figure 11.

Because the barrier heights to hydroxyl reorientation are the same in both directions in DC, we ascribe the difference between barriers in two directions for DC:ethanol to the influence of the guest. In DC:ethanol the barrier heights for reorientation via the inside of a cavity compared with those for reorientation via the outside of a cavity are lower by 5.9 kJ mol^{-1} for barrier 1 and by 19.5 and 19.8 kJ mol^{-1} for barriers 2 and 3, respectively.

We also observe that the heights of the first barrier for reorientation in the direction outside a cavity are not the same in DC and DC:ethanol (Figure 7 and Figure 12). The barrier in DC:ethanol is 21.1 kJ mol^{-1} lower, even though the DC lattice is unchanged. We conclude that in DC:ethanol even reorientations via the outside of a cavity are affected by the guest ethanol molecule.

In DC:ethanol two new hydrogen bonds can be formed when a hydroxyl reorients via either pathway. One of these hydrogen bonds is between the reorienting hydroxyl and the guest ethanol molecule in the cavity on one side of the ring. When a hydroxyl reorients into a cavity, its hydrogen acts as a donor and the ethanol oxygen acts as an acceptor, but when reorientation proceeds out of a cavity the roles are reversed. Steric restrictions imposed by the closeness of the cavity walls make the hydrogen bond slightly longer (2.15 Å compared to 1.85 Å) and hence weaker when the ethanol guest acts as a donor (i.e., for reorientation via the outside of a cavity). For both pathways, the second hydrogen bond that can be formed is between the ethanol molecule in the cavity on the opposite side of the ring and the ring hydroxyl that lost a hydrogen bond as reorientation occurred. Formation of these two hydrogen bonds lowers the barrier to hydroxyl reorientation in DC:ethanol compared with that in the empty DC lattice; however, for a reorientation into a cavity, the barrier lowering is greater than for reorientation out of a cavity due to the difference in strengths of hydrogen bonds between the reorienting hydroxyl and a guest ethanol molecule in the two cases.

Thus, ethanol lowers the barrier to hydroxyl reorientation in DC:ethanol. This effect can be easily seen by comparing a and b of Figure 3 where the frequency of single flips is higher in the presence of ethanol. The same is true for methanol in HQ:methanol as well; compare c and d of Figure 3.

CONCLUSIONS

Our simulations of crystalline DC:ethanol suggest a reasonable model for the dynamics of hydroxyl groups in its six-membered hydrogen-bonded rings. In this model hydroxyls perform single, random independent flips and occasionally reorient following a mechanism that is neither totally independent nor totally concerted but is sequential and involves the guest ethanol molecule: one rotated hydroxyl prompts the neighboring one to avoid close contact and reorient through hydrogen bonding to the guest ethanol molecule, and so on, along the ring. The limiting stage of the full reorientation is a random hydroxyl flip, and from our simulations the value of the free energy needed for it to occur (37.2 kJ mol^{-1}) compares well with the experimental value for the enthalpy of activation of the full reorientation (33.1 $\pm$ 1 kJ mol^{-1})[22].

We also confirm that analogous hydrogen reorientation is not likely to occur in hydrogen-bonded rings of HQ clathrates due to the reoriented conformation being much less energetically favorable. However, single flips are likely to be more frequent than in DC:ethanol.

We find that both ethanol in DC:ethanol and methanol in HQ:methanol lower the activation energy of hydrogen reorientation by stabilizing the intermediate state. Formation of hydrogen bonds between host and guest molecules has been reported and studied for both DC[54,55] and HQ,[56] as well as clathrate hydrates[57,58] before, but it has not previously been shown to participate in the reorientation of hydroxyl groups in the six-membered hydrogen-bonded ring. In a similar way a small molecule with a capacity for hydrogen bonding could be lowering the barrier of structural rearrangements in a protein. An interesting finding is that a similar reorientational process is likely to occur in empty DC as well, but at a lower rate. We expect that it could also be occurring in other clathrates of DC with small hydrogen-bonding guests, and in other host−guest systems where the difference in energy between different positions of hydroxyl hydrogens is small. In those cases the existence of two orientations will also increase the entropy of the system.

It is likely that the mechanism described here for hydrogen-bond reorientation in DC:ethanol and empty DC could also explain the concerted reorientations of hydrogen bonds in some systems mentioned in the Introduction. Although the guest can be seen to assist reorientation in DC:ethanol, the fact that reorientation also occurs in a sequential manner even in the absence of a guest shows that this mechanism may apply in a large number of cases including those in which the participation of a guest is not possible. This study is a good example of how molecular dynamics can be used to understand the mechanism of reorganization of hydrogen-bond networks and can complement experiments on dynamic phenomena in organic molecular crystals. It should not be overlooked as a means to rationalize ambiguous experimental data, and we anticipate its increased uptake in coming years.

ASSOCIATED CONTENT

Web Enhanced Feature. Three movies of simulations, where one hydroxyl in the rings of DC:ethanol (Figure 5), HQ:methanol (Figure 8), and DC (Figure 10) was held reoriented. In the movies only one hydrogen-bonded ring is shown from the unit cell, where umbrella sampling is used to bias the position of the hydroxyl. Hydrogen bonds are depicted using standard VMD settings of a distance cutoff of 3.0 Å and an angle cutoff of 20°.

AUTHOR INFORMATION

Corresponding Author
ben.corry@uwa.edu.au

ACKNOWLEDGMENT

We thank Associate Professor Dylan Jayatilaka for fruitful discussions and Australian Research Council for financial support. A.N. acknowledges the Australian Government for the International Postgraduate Research Scholarship and the University of Western Australia for the University Postgraduate Award. Computer time was allocated under the merit allocation scheme of the National Computational Infrastructure (Australia).

REFERENCES

(1) Saenger, W.; Betzel, C.; Hingerty, B.; Brown, G. M. *Nature* **1982**, *296*, 581–583.

(2) Betzel, C.; Saenger, W.; Hingerty, B. E.; Brown, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7545–7557.

(3) Mossine, V. V.; Barnes, C. L.; Mawhinney, T. P. *Carbohydr. Res.* **2009**, *344*, 948–951.
(4) Teeter, M. M. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 6014–6018.
(5) Kennard, O. *Pure Appl. Chem.* **1984**, *56*, 989–1004.
(6) Caruso, F.; Tanski, J.; Villegas-Estrada, A.; Rossi, M. *J. Agr. Food Chem.* **2004**, *52*, 7279–7285.
(7) Lessinger, L.; Low, B. W. *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 85–99.
(8) Dieleman, C. B.; Marsol, C.; Matt, D.; Kyritsakas, N.; Harriman, A.; Kintzinger, J. P. *J. Chem. Soc., Dalton Trans.* **1999**, 4139–4148.
(9) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305–1312.
(10) Hibbs, D.; Hursthouse, M.; Malik, K.; Adams, H.; Stirling, C.; Davis, F. *Acta Crystallogr., Sect. C* **1998**, *54*, 987–992.
(11) Aliev, A. E.; Harris, K. D. M.; Shannon, I. J.; Glidewell, C.; Zakaria, C. M.; Schofield, P. A. *J. Phys. Chem.* **1995**, *99*, 12008–12015.
(12) Aliev, A. E.; MacLean, E. J.; Harris, K. D. M.; Kariuki, B. M.; Glidewell, C. *J. Phys. Chem B* **1998**, *102*, 2165–2175.
(13) Aliev, A. E.; Atkinson, C. E.; Harris, K. D. M. *J. Phys. Chem B* **2002**, *106*, 9013–9018.
(14) Pauling, L. *J. Am. Chem. Soc.* **1935**, *57*, 2680–2684.
(15) Hollander, F.; Jeffrey, G. A. *J. Chem. Phys.* **1977**, *66*, 4699–4705.
(16) van Hoorn, W. P.; Briels, W. J.; van Duynhoven, J. P. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1998**, *63*, 1299–1308.
(17) Meyer, E. *Protein Sci.* **1992**, *1*, 1543–1562.
(18) Saenger, W.; Betzel, C.; Zabel, V.; Brown, G. M.; Hingerty, B. E.; Lesyng, B.; Mason, S. A. *J. Biosci.* **1985**, *8*, 437–450.
(19) Molins, M. A.; Nieto, P. M.; Sanchez, C.; Prados, P.; Demendoza, J.; Pons, M. *J. Org. Chem.* **1992**, *57*, 6924–6931.
(20) Lang, J.; Vagnerova, K.; Czernek, J.; Lhotak, P. *Supramol. Chem.* **2006**, *18*, 371–381.
(21) Rudkevich, D. M. *Chem.—Eur. J.* **2000**, *6*, 2679–2686.
(22) Bernhard, T.; Zimmermann, H.; Haeberlen, U. *J. Chem. Phys.* **1990**, *92*, 2178–2186.
(23) Heilbronner, E.; Dunitz, J. D. *Reflections on Symmetry: In Chemistry ... and Elsewhere*; Verlag Helvetica Chimica Acta: Basel, 1993; p 105.
(24) Atwood, J. L.; Barbour, L. J.; Thallapally, P. K.; Wirsig, T. B. *Chem. Commun.* **2005**, 51–53.
(25) Tsue, H.; Ono, K.; Tokita, S.; Ishibashi, K.; Matsui, K.; Takahashi, H.; Miyata, K.; Takahashi, D.; Tamura, R. *Org. Lett.* **2011**, *13*, 490–493.
(26) Dobrzanska, L.; Lloyd, G. O.; Raubenheimer, H. G.; Barbour, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 698–699.
(27) Tian, J.; Thallapally, P. K.; Dalgarno, S. J.; Atwood, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13216–13217.
(28) Riddle, A. A.; Bollinger, J. C.; Lee, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6689–6693.
(29) Deak, A.; Tunyogi, T.; Karoly, Z.; Klebert, S.; Palinkas, G. *J. Am. Chem. Soc.* **2010**, *132*, 13627–13629.
(30) Fletcher, A. J.; Cussen, E. J.; Prior, T. J.; Rosseinsky, M. J.; Kepert, C. J.; Thomas, K. M. *J. Am. Chem. Soc.* **2001**, *123*, 10001–10011.
(31) Cussen, E. J.; Claridge, J. B.; Rosseinsky, M. J.; Kepert, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 9574–9581.
(32) Nemkevich, A.; Buergi, H. B.; Spackman, M. A.; Corry, B. *Phys. Chem. Chem. Phys.* **2010**, *12*, 14916–14929.
(33) Zaborowski, E.; Zimmermann, H.; Vega, S. *J. Am. Chem. Soc.* **1998**, *120*, 8113–8123.
(34) Brouwer, D. H.; Alavi, S.; Ripmeester, J. A. *Phys. Chem. Chem. Phys.* **2007**, *9*, 1093–1098.
(35) Santikary, P.; Yashonath, S.; Rao, C. N. R. *Chem. Phys. Lett.* **1992**, *192*, 390–394.
(36) Zubkus, V. E.; Shamovsky, I. L.; Tornau, E. E. *J. Chem. Phys.* **1992**, *97*, 8617–8627.
(37) Vonszentpaly, L.; Shamovsky, I. L.; Ghosh, R.; Zubkus, V. E.; Tornau, E. E. *J. Chem. Phys.* **1994**, *101*, 683–692.
(38) Daschbach, J. L.; Chang, T.-M.; Corrales, L. R.; Dang, L. X.; McGrail, P. *J. Phys. Chem B* **2006**, *110*, 17291–17295.
(39) Koehler, J. E. H.; Saenger, W.; van Gunsteren, W. F. *Eur. Biophys. J.* **1988**, *16*, 153–168.
(40) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165–4176.
(41) Matousek, J.; Cajan, M.; Kulhanek, P.; Koca, J. *J. Phys. Chem. A* **2008**, *112*, 1076–1084.
(42) Breite, M. D.; Cox, J. R.; Adams, J. E. *J. Am. Chem. Soc.* **2010**, *132*, 10996–10997.
(43) Adams, J. E.; Cox, J. R.; Christiano, A. J.; Deakyne, C. A. *J. Phys. Chem A* **2008**, *112*, 6829–6839.
(44) Flippen, J. L.; Karle, J.; Karle, I. L. *J. Am. Chem. Soc.* **1970**, *92*, 3749–3755.
(45) Clausen, H. F. Private communication. 2011.
(46) Wang, J. M.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. *J. Comput. Chem.* **2004**, *25*, 1157–1174.
(47) Phillips, J. C.; Braun, R.; Wang, W.; Gumbart, J.; Tajkhorshid, E.; Villa, E.; Chipot, C.; Skeel, R. D.; Kale, L.; Schulten, K. *J. Comput. Chem.* **2005**, *26*, 1781–1802.
(48) Bonomi, M.; Branduardi, D.; Bussi, G.; Camilloni, C.; Provasi, D.; Raiteri, P.; Donadio, D.; Marinelli, F.; Pietrucci, F.; Broglia, R. A.; Parrinello, M. *Comput. Phys. Commun.* **2009**, *180*, 1961–1972.
(49) Wang, J.; Wang, W.; Kollman, P. A.; Case, D. A. *J. Mol. Graphics Modell.* **2006**, *25*, 247–260.
(50) Jakalian, A.; Bush, B. L.; Jack, D. B.; Bayly, C. I. *J. Comput. Chem.* **2000**, *21*, 132–146.
(51) Jakalian, A.; Jack, D. B.; Bayly, C. I. *J. Comput. Chem.* **2002**, *23*, 1623–1641.
(52) Turner, M. J.; McKinnon, J. J.; Jayatilaka, D.; Spackman, M. A. *CrystEngComm* **2011**, *13*, 1804–1813.
(53) Laio, A.; Parrinello, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 12562–12566.
(54) Lee, J. J.; Fuller, R. O.; Sobolev, A. N.; Clausen, H. F.; Overgaard, J.; Koutsantonis, G. A.; Iversen, B. B.; Spackman, M. A. *Chem. Commun.* **2011**, *47*, 2029–2031.
(55) Selbo, J. G.; Desper, J. M.; Eckhardt, C. J. *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *45*, 73–78.
(56) Boeyens, J. C. A.; Pretorius, J. A. *Acta Crystallogr., Sect. B* **1977**, *33*, 2120–2124.
(57) Alavi, S.; Susilo, R.; Ripmeester, J. A. *J. Chem. Phys.* **2009**, *130*, 174501.
(58) Buch, V.; Devlin, J. P.; Monreal, I. A.; Jagoda-Cwiklik, B.; Uras-Aytemiz, N.; Cwiklik, L. *Phys. Chem. Chem. Phys.* **2009**, *11*, 10245–10265.