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An Expandable Hydrogen-Bonded Organic Framework Characterized by Three-Dimensional Electron Diffraction

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ABSTRACT: A molecular crystal of a 2-D hydrogen-bonded organic framework (HOF) undergoes an unusual structural transformation after solvent removal from the crystal pores during activation. The conformationally flexible host molecule, **ABTPA**, adapts its molecular conformation during activation to initiate a framework expansion. The microcrystalline activated phase was characterized by threedimensional electron diffraction (3D ED), which revealed that **ABTPA** uses out-of-plane anthracene units as adaptive structural anchors. These units change orientation to generate an expanded, lower density framework material in the activated structure. The porous HOF, **ABTPA-2**, has robust dynamic porosity (SA_{BET} = 1183 m² g⁻¹) and exhibits negative area thermal expansion. We use crystal structure prediction (CSP) to understand the underlying energetics behind the structural transformation and discuss the challenges facing CSP for such flexible molecules.



■ INTRODUCTION

Porous organic molecular crystals are noncovalent materials that exhibit polymorph-specific physisorption properties.¹⁻⁴ The extended crystal packing and dynamic responsiveness of porous molecular crystals are important for a series of applications including selective gas sorption,^{3,5-8} molecular separations,^{1,9-12} sensing,¹³ catalysis,¹⁴ proton conduction,¹⁵ drug delivery,¹⁶ and enzyme encapsulation.¹⁷ Accurate crystal structure determination of the activated form underpins the design of functional porous molecular crystals for such applications.^{18,19} Understanding and, ultimately, predicting crystal packing is also the most important characterization step in the development of tunable porous organic molecular crystals for specific functions.^{20–22}

As a result of their noncovalent nature, it is common for nascent, solvated porous molecular crystals to undergo structural transformations during crystal activation. This often results in the loss of single crystallinity—and frequently the loss of porosity. Densification upon solvent removal is common. Such transformations are difficult to characterize, particularly for flexible systems, and it can become extremely difficult to obtain the structures of the activated systems. This characterization challenge spans different classes of porous molecular crystals. For example, we and others have reported porous organic cages whose structures transform during crystal activation. These transformations often result in the formation of microcrystals that are too small for single crystal measurements, preventing definitive X-ray structure determination of the activated form.^{23–26} Likewise, rapid crystallization techniques favor the formation of kinetic polymorphs, which often have significantly higher porosity than thermodynamic polymorphs, but such routes also tend to produce microcrystals.²⁷ HOFs often undergo structural transformations during activation, despite having extended network structures.^{1,28–30} For example, Chen et al. reported the tetrahedral diaminotriazine-based **HOF-1**^{1,31} transformed after activation into a selectively porous crystalline phase whose structure could not be determined. Stoddart et al. reported recently a series of porous triptycene-based 3-D HOFs with different interpenetration modes that transformed into undetermined structures after activation.^{28,29} Lastly, Hisaki et al. reported a layered 2-D HOF that transformed its structure during activation; in this case, crystal structure prediction was used to determine the structure of the activated HOF.³⁰

Porous HOFs are designed by appending hydrogen-bonding units to carbon-based scaffolds with rigid or awkward shapes.¹⁹ However, it remains difficult to predict how HOF precursors will crystallize in the lab and even more challenging to anticipate

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how their structures might transform during crystal activation or guest adsorption. To address these challenges, we have been developing computational tools that fuse crystal structure prediction with the computation of physical properties to screen for energetically stable porous molecular crystals with superior functions.³ This method relies on the prediction of stable crystal structures from an exploration of the lattice energy surface and encoding of these structures with a set of physical properties to generate energy–structure–function (ESF) maps.³ We have shown that this approach can direct the experimental discovery of porous HOFs with surface areas as high as 3425 m² g^{-1,3} the first molecular HOF with high photocatalytic activity,³² and new porous phases of well-studied molecules.³³

The use of ESF maps for the discovery of porous crystals of conformationally flexible molecules remains a challenge. This is due to the expanded configurational space made available by molecular flexibility combined with the need to locate all relevant structures in a wide energy range to allow for the energetic effects of solvent stabilization on crystallization outcome.^{3,34} Conformational flexibility can be comprehensively included in low throughput CSP, such as for flexible pharmaceuticals where only a few tens of crystal structures need to be calculated accurately.^{35,36} However, these methods typically rely on solid state density functional theory (DFT) and are not applicable for HOFs because of the steep cost of these methods and the need to treat very large numbers of potential crystal structures to allow for the energetic effects of solvent templating within porous structures. To make this problem computationally tractable, we have used the lower cost approach of using an ensemble of rigid gas phase conformers and a force field description of intermolecular interactions, without allowing for full molecular flexibility.^{3,33,37-40}

This combination of the limitations of classical diffraction methods for small, activated microcrystals and the difficulty of treating flexible molecules by using CSP makes direct structure solution for flexible porous molecular crystals extremely challenging. One potential experimental solution for submicrometer-sized crystalline solids is 3D electron diffraction (3D ED),^{41,42} which makes it possible to acquire three-dimensional reciprocal space data for crystals that are too small for conventional single-crystal X-ray diffraction (SC-XRD) methods.⁴³ Various techniques have been developed such as continuous rotation electron diffraction (cRED), $^{44-46}$ automated diffraction tomography (ADT),^{47–49} and microcrystal electron diffraction (MicroED).⁵⁰ Moreover, the collection of 3D ED data on crystals previously considered too beam sensitive has been made possible through advances in detector technology and software development,⁴³ as illustrated by studies on metal–organic frameworks (MOFs),^{51,52} proteins,^{50,53} and covalent organic frameworks.^{54–56} Here, we combine 3D ED with crystal structure prediction to understand the behavior of a flexible HOF; this is the first time that 3D ED has been used for such materials.

RESULTS AND DISCUSSION

We selected 5',5^{""}-(anthracene-9,10-diyl)bis(([1,1'3',1"-terphenyl]-4,4"-dicarboxylic acid)) (ABTPA) as a promising HOF building block (Figure 1a). ABTPA has four carboxylic acid groups with the geometry required, in principle, to direct the formation of a HOF net with the 2D square-lattice (sql) topology. Previous work using ABTPA as a MOF ligand confirmed the ability of the anthracene core to rotate out-of-



Figure 1. (a) Structure of **ABTPA**; the dihedral angles ϕ and ψ between the anthracene plane and adjacent phenyl group planes are indicated. (b) Overlay plot of the 63 unique low-energy conformations used in our initial CSP calculations. The conformers are aligned to minimize the total RMSD with the lowest energy conformer.

plane compared to the 9,10-substituted terphenyl groups,⁵⁷ and similar behavior has been reported in the solid state structures of related molecules (Supporting Information, Table S1).^{58,59} We performed a conformational search on the **ABTPA** molecule (see the Supporting Information, section 1.0, for details), finding 63 unique, low-energy conformers with similar energies (Figure 1b, Table S2, and Figure S2). Many of these conformers were within ~1 kJ/mol of the lowest energy conformer, that is, well within the error bounds of the computational methods used for energy evaluation.⁶⁰ This suggested that the anthracene unit would be dynamic in the solid state and might be used as an adaptive pivot to introduce responsive behavior, while the outof-plane orientation could stabilize the extended packing of **sql** HOF nets.

CSP was performed on the ensemble of 63 unique conformers to assess **ABTPA**'s ability to form porous frameworks. While the preliminary CSP results showed promising low-energy, porous structures, it was not immediately obvious which of these packing modes might be observed experimentally (Figure S3). The **sql** packing with fully satisfied hydrogen bonds is observed in some of the lower density predicted structures along the lowenergy leading edge of the CSP landscape (Figures S4 and S5), where most structures contain 1D pore networks and significant accessible surface area. While porous lower density structures have an energetic penalty in CSP, these phases can be formed experimentally because they are stabilized by solvent interactions.^{3,34}

Experiments showed that **ABTPA** could be crystallized from THF by adding 1,2-dimethoxybenzene and allowing the THF to evaporate at RT for 5 days. The solvated crystals were characterized by synchrotron SC-XRD (Supporting Information, section 3.1). In the solvated crystal structure, **ABTPA-1**, the carboxylic acid groups of **ABTPA** direct the structure of a HOF net with a **sql** topology. Four-membered hydrogenbonded rings are formed via cooperative $R_2^2(8)$ hydrogenbonding interactions at an O–H…O distance of 2.625(2) Å (Figure 2a). The angle between the plane of the 2-D hydrogen-



Figure 2. (a) In the **ABTPA-1** single crystal structure, the four-membered hydrogen-bonded rings generate a HOF net with a **sql** topology. (b) The **sql** HOF nets feature out-of-plane anthracene units. (c, d) In **ABTPA-1**, the **sql** HOF nets are stacked in an offset arrangement viewed along [103] (c); viewed along [010] (d), via offset $\pi - \pi$ interactions between the anthracene units, to generate a packing motif which repeats every seven layers. (e) This packing arrangement of **ABTPA** molecules in **ABTPA-1** generates 1-D solvent-filled pores viewed along [001]. (f, g, h, i) In the Rietveld refined **ABTPA-2** structure that used synchrotron PXRD data collected at 298 K, the **sql** HOF layers have a different geometry, and the anthracene units are packed in a herringbone arrangement viewed along [100] (i). (j) The alternating packing of **sql** HOF layers in **ABTPA-2** generates a 1-D pore viewed along [001].

bonded network and the plane of the anthracene unit in **ABTPA-1** is 76° (Figure 2b). Each four-membered hydrogenbonded ring has two out-of-plane anthracene units that prevent the interpenetration of the 2-D hydrogen-bonded layers. By contrast, a biphenyl analogue of **ABTPA** without these anthracene units was shown to crystallize as a 5-fold interpenetrated structure.⁶¹

In the extended crystal structure of **ABTPA-1**, the **sql** hydrogen-bonded layers are stacked along the [010] direction through the formation of offset, face-to-face, $\pi - \pi$ stacking interactions between the anthracene units in neighboring 2-D hydrogen-bonded layers, at a repeat distance of 5.0 Å (Figure 2d). This packing arrangement generates an open pore structure in **ABTPA-1** along the [001] direction, which is occupied by disordered solvent molecules (Figure 2e).

No good match for the experimental solvated structure, **ABTPA-1**, was found on the CSP landscape. We found that this was due to insufficient conformational sampling, rather than an inadequacy in the energy models used. Thus, the simplified approach of using an ensemble of rigid, gas phase conformers to reduce the expense of the CSP search has led to failure of the calculations. Further CSP calculations performed using constrained conformations of **ABTPA** based on the experimental conformer in **ABTPA-1** (see the Supporting Information for full details, section 1.2) correctly identified a structural match with

ABTPA-1. The predicted crystal structure that matches with **ABTPA-1** stands out as having low energy in the CSP map relative to other structures of similar density (Figure 3). The new conformer was missed in the initial conformer search due to its significant internal molecular strain (~ 26 kJ/mol relative to the gas phase conformers), highlighting the challenge of accounting for host—host and host—solvent interactions in the CSP of flexible molecules.

The solvated crystal structure, **ABTPA-1**, was prepared as a phase pure sample during scale-up crystallizations from THF/ 1,2-dimethoxybenzene (Supporting Information, section 3.1). The crystallization solvent was exchanged with acetone at RT for 5 days, and the acetone was then removed at RT under a dynamic vacuum for 2 h. PXRD showed that the acetone solvated **ABTPA-1** transformed into a new phase, **ABTPA-2**, during activation (Figures S7 and S8). The crystals of **ABTPA-1** also broke up during this transformation and became too small for analysis by SC-XRD, even using synchrotron radiation. SEM images of the activated crystals, **ABTPA-2**, revealed that they were shaped like regular cuboids and were 0.1–10 μ m in size (Figure S9).

ABTPA exhibits significant conformational flexibility in the gas phase (Table S2 and Figure S2): it is therefore unsurprising that the structure of **ABTPA-1** transforms during crystal activation. The structure solution of **ABTPA-2** using conven-



Figure 3. CSP map for initial **ABTPA** conformers (gray) and various gas-phase optimizations of the experimental conformations in **ABTPA-1** (orange) and the cRED **ABTPA-2** structure (blue). Angles ϕ and ψ refer to the arene-arene dihedral angles adjacent to the anthracene core. **ABTPA-1** fixed and **ABTPA-2** fixed refer to conformations in which all arene-arene and arene-carboxylic acid dihedrals were fixed from the conformations in the experimental crystal structures. Note that free optimization of the conformer from **ABTPA-1** resulted in one of the low-energy conformations from the initial CSP calculations, and hence this is not labeled.

tional X-ray diffraction techniques proved challenging: the crystallite sizes were too small, even for synchrotron single crystal measurements. In addition, we again could not find a close structural match between the experimental PXRD pattern of ABTPA-2 and any of the predicted structures on the CSP landscape. To determine the structure of ABTPA-2, cRED data were collected by continuously tilting a 0.5 μ m crystal cooled to 97 K (Figure S10). Data were collected by using the software Instamatic,⁶² and the acquired frames were then processed using XDS.⁶³ Reflection conditions were examined using the RED software package.45 The structure was solved by using SHELXT⁶⁴ and refined by full-matrix least-squares on $|F|^2$ by using SHELXL,⁶⁵ interfaced through the program OLEX2.⁶⁶ All the non-hydrogen atoms were located in the initial structure solution (see the Supporting Information for full refinement details, section 3.2, and Figure S10). To further validate our cRED model, a Rietveld refinement was performed on the ABTPA-2 structure by using synchrotron radiation PXRD data collected at 298 K (Figure S14). After performing this refinement, we observed a close structural match between the cRED and Rietveld refined ABTPA-2 structures (Figure S15), with the latter refining to a smaller cell volume (Table S3), which is likely to be due to the overestimation of cell parameters by using the cRED data.

The crystal packing in the Rietveld refined **ABTPA-2** structure is distinct to that in **ABTPA-1** (Figure 2, $e \rightarrow j$). In **ABTPA-2**, the 2-D hydrogen-bonded nets have the same underlying **sql** topology, but the geometry of the HOF layers is different (Figure 2, $b \rightarrow g$), with the carboxylic acid groups rotated out of plane to their adjacent ring to better satisfy the H-bonding network. In **ABTPA-2** the 2-D HOF layers are packed

in an A–B stacking arrangement, with the anthracene units packed in a herringbone-type arrangement when viewed along the [100] direction (Figure 2, d \rightarrow i).

As with ABTPA-1, gas-phase optimization of the ABTPA conformation found in the cRED structure of ABTPA-2 was performed with and without restricting the torsional angles. Free optimization of the experimental conformer in ABTPA-2 found an additional gas-phase minimum that was not sampled in the original CSP set. This freely optimized conformer was just ~0.7 kJ/mol above the minimum-energy conformation. Fixing only the two dihedral angles ϕ and ψ adjacent to the anthracene core (Figure 1a) resulted in a molecular energy \sim 2.6 kJ/mol above the minimum-energy conformer, while optimization restricting all the arene-arene and arene-carboxylic acid dihedrals resulted in a higher molecular strain of ~11.9 kJ/mol. In contrast with our findings for ABTPA-1, all the optimized conformer variations of ABTPA-2 result in CSP predicted structures with the same packing as the experimental structure, albeit with significant strain to the hydrogen bonding for the less constrained conformations. Despite the increasing molecular energy, the total crystal energy is lowered successively as more constraints are applied to intramolecular dihedrals (Figure 3).

These results again demonstrate the importance of incorporating molecular flexibility into the CSP procedure: by using the rigid molecule CSP based on gas-phase conformers, the observed packing barely stands out from the overall landscape (ABTPA, opt.), while small deviations facilitate significantly improved hydrogen bonding, more than compensating for the intramolecular strain associated with the conformational change. It should be noted, however, that even performing rigid molecule CSP on the ensemble of conformations is computationally demanding, particularly when the crystal structure landscape needs to be sampled up to relatively high energies, which is required when searching for porous crystal structures. The incorporation of accurate intramolecular flexibility models for systems with 6+ internal degrees of freedom with sub-kJ/mol accuracy is an immense challenge due to the higher dimensionality of the search space and greater demands on the energy model, illustrating the current limitations of these a priori predictive methods. The results of this study add to our knowledge of the extent of molecular strain that can be adopted in molecular crystals, which will guide the development of constraints that can be applied to focus crystal structure search methods, while minimizing the risk of missing important structures.

Remarkably, the reorientation of 2-D HOF layers in ABTPA-2 results in the crystal structure undergoing a framework expansion during crystal activation, decreasing the density of the HOF from 0.78 g/cm³ in ABTPA-1 to 0.66 g/cm³ in the Rietveld refined ABTPA-2 structure (Table S3). While both of these crystal structures appear to have similar lattice energies (ABTPA-1 is ~1 kJ/mol lower in energy than ABTPA-2 when adjusted for intramolecular energy), this transformation can be explained by considering the relative internal molecular strain of ABTPA in each of the crystal structures: ~26 kJ/mol in ABTPA-1 vs ~12 kJ/mol in ABTPA-2. We, therefore believe that the framework expansion may be triggered by the release of strain in the ABTPA conformer.

The simulated PXRD pattern of **ABTPA-2** determined by using the cRED model matches the experimental PXRD pattern of the activated material (Figure S8). Activated **ABTPA-2** has a BET surface area of 1183 m² g⁻¹ and a pore size of 1.8 nm, which agree with the crystal structure (Figure S16a). **ABTPA-2**

adsorbs 12.68 mmol g⁻¹ of CH₄ at saturation at 115 K (Figure S16b). The stability of ABTPA-2 was investigated by variable temperature (VT) PXRD, thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC). The VT-PXRD data, collected between RT and 175 °C, revealed that ABTPA-2 undergoes a negative area thermal expansion, with the 2-D sql HOF layers contracting along the *b*-axis (Figures S17–S19). At the same time, it undergoes an interlayer expansion along c_i indicating a rippling of the 2-D HOF layers upon heating. DSC and PXRD data collected after heating ABTPA-2 to 300 °C indicated that the structure remains crystalline, and the same phase is preserved over this temperature range (Figures S20 and S21). TGA showed an onset of weight loss at 350 °C (Figure S22). After immersion of ABTPA-2 in o-xylene, m-xylene, pxylene, mesitylene, 1,2-dimethoxybenzene, 1,3-dimethoxybenzene, n-butylbenzene, and toluene for 1 day, the PXRD patterns indicated that ABTPA-2 is dynamic and can adapt its structure to accommodate these guests in the crystal pore while retaining the extended packing of molecules in ABTPA-2 (Figures S23 and S24).

CONCLUSION

In summary, **ABTPA-2** is a dynamic 2-D HOF material built from anthracene units that can adapt their conformation, both to stabilize porous crystal packings and to respond to external stimuli, such as guest absorption and changes in sample temperature. The combination of very high conformational flexibility and the influence of stabilizing solvent in pores represents a veritable nightmare scenario for CSP. Thus, a commonly used simplification of using rigid molecular conformers from isolated molecule calculations, rather than a more rigorous sampling of conformational flexibility, meant that the searches failed to identify the observed crystal structures and point to this as a crucial area for methodological development.

Our results indicate that the ABTPA HOF material adapts its conformation to drive a structural change and in the process undergoing a highly unusual structural expansion after desolvation of the crystal pores. It has been shown previously that flexible porous solids can adapt their pore structures to generate additional functionalities, for example, to initiate a gate-opening type response during guest adsorption^{1,67-74} or induce negative gas adsorption transformations.^{75,76} Our study, by contrast, demonstrates that the molecular structure of a HOF adapts during activation to initiate a structural expansion, and chemical analogues of ABTPA might also exhibit similar behavior as HOF materials. Importantly, this study demonstrates that such behavior can be computationally screened for such as by calculating the effect of crystal packing on conformational strain in predicted HOF materials and identifying structural pairs on the crystal structure landscape that represent routes for the relaxation of high intramolecular strain via a structural transformation to a less strained structure.

ABTPA-2 is the first example of a porous HOF structure that was solved by 3D ED. More broadly, these results show that 3D ED is an accurate method for rapidly determining the functional structure of porous organic crystalline solids, particularly those that undergo structural transformations during crystal activation, and we believe that 3D ED will become an important new tool for materials of this type in the future.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c04885.

Figures S1–S24, Tables S1–S3, computational methodology, powder and single crystal X-ray diffraction, electron diffraction, SEM, DSC, TGA, and gas sorption (PDF) X-ray crystallographic data of **ABTPA-1** (CIF) X-ray crystallographic data of **ABTPA-2** (CIF) X-ray crystallographic data of **ABTPA-2** (CIF)

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Notes

The authors declare no competing financial interest.

CIF files for **ABTPA-1** (deposition number: 1977891) and **ABTPA-2** (1998745) are deposited at the Cambridge Crystallographic Data Centre.

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ABBREVIATIONS

ABTPA, 5',5^{*m*}-(anthracene-9,10-diyl)bis(([1,1'3',1"-terphen-yl]-4,4"-dicarboxylic acid)); CSP, crystal structure prediction; 3D ED, three-dimensional electron diffraction.

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