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RESEARCH ARTICLE

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Transitions in Solvate Crystals of a Tetraaryladamantane

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Dedicated to the late *Jack D. Dunitz*

Obtaining high-resolution structures of liquid compounds can be difficult. Encapsulating them in the lattice of a larger organic molecule acting as crystallization chaperone is one option to overcome this difficulty. Tetraaryladamantane ethers can play the role of chaperones, accommodating a range of different guest molecules in their crystals. How well-ordered crystalline arrangements for molecules of different shape are achieved is not clear. Cases in which more than one structure is found may shed light on this phenomenon. Here, we report low-order cubic crystal structures of 1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane (TDA) encapsulating *ortho*-xylene or cyclohexane, together with better ordered structures obtained after warming the crystals to 60 °C. Evidence for cubic crystal systems was also found for limonene, hexachlorobutadiene and eucalyptol, with a transition to a triclinic system for the former two, but no transition up to 70 °C for the latter. These findings indicate that some solvate structures of TDA can readily undergo structural transitions to less solvated, better ordered systems. Crystals obtained by rapid thermal crystallization may be in kinetically trapped states, and the transition to a solvate-free crystal system appears to have a kinetic barrier that depends strongly on the structure of the liquid guest molecules encapsulated in the lattice.

Keywords: adamantane, crystallization, solvates, X-ray diffraction, organic solids.

Introduction

Scientifically, the term 'chaperone' is most frequently used for molecules that assist the folding of proteins in the cell.[1–3] But, chaperones are also used in crystallization, where they induce the (co)-crystallization of molecules that do not yield crystals by themselves. Perhaps best known are examples from structural biology,[4–6] but the concept of using a readily crystallizing, scaffold-forming compound to lure poorly crystallizing compounds into a crystalline lattice is also taking hold in the field of chemistry. One example are crystalline sponges, *i.e.* metal-organic frameworks that can be loaded with analyte molecules through soaking.[7–12] Other examples, where a chaperone-effect was found, are hydrogen-bonded frameworks co-crystallizing with medium-sized molecules[13] or tetraarylporphyrins.[14] Lastly, we have recently reported tetraaryladamantanes (TAAs) that can encapsulate liquid organic and inorganic compounds in their crystal lattices.[15–20]

Three tetraaryladamantane ethers have been shown to readily crystallize as solvates when a hot solution in the liquid of interest is allowed to cool to room temperature. Encapsulation has been observed for a broad range of organic liquids. The first TAA for which this promiscuity in solvate formation was found in our laboratories was 1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane (TDA).[16] Among other things, this TAA was shown to encapsulate reactive compounds that are liquids at room temperature, masking their hazardous properties, and liberating them again when dissolved in reaction mixtures.[15] The next compound exhibiting broad encapsulation behavior identified in our synthetic work was 1,3,5,7-tetrakis(2,4-dieth-

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oxyphenyl)adamantane (TEO), which also takes up compounds from the gas phase.[17] A third TAA with an unusually high propensity to crystallize as solvate from solutions of different liquids is 1,3,5,7-tetrakis(2-bromo-4-methoxyphenyl)adamantane (TBro), which was identified in our study on the determination of the absolute configuration of chiral analytes upon encapsulation.[18] In many cases, at least one guest molecule was found to be well ordered when encapsulated in TDA, TEO or TBro, so that the relative[19] or absolute stereochemistry can be revealed, qualifying the TAAs as a crystallization chaperone.[18] Still, for all TAA chaperones identified thus far, there is also a solvate-free form with similar crystallographic density as the solvates.[21]

The broad range of different solvates found for the TAA chaperones TDA, TEO and TBro poses an interesting problem. In order to form well-ordered crystal lattices, there must be tight packing between the molecules involved. The tetraaryladamantanes have a specific size and shape, and so do the different guest molecules encapsulated. How can one shape (the TAA) fit so many other shapes? Further, there is the question of why solvates are formed frequently, even though a tightly packed, solvate-free form exists for each of the TAA chaperones?[21] Solvates are commonly found when no such tightly packed form is accessible, and are often less favorable than the solvate-free form on entropic grounds, as the release of solvent molecules provides them with additional degrees of freedom.[22] Whether a solvate-free or solvate form is obtained as the predominant crystalline material is most probably the result of an intricate balance between compensating forces. It is not easy to come up with a general solution to the problem of obtaining a well-ordered, solvated crystalline system. Certainly, the initial temperature and the temperature gradient play an important role in thermal crystallization, and an optimization of these parameters may be required for new compounds.

It seemed likely that many solvates are local energy minima in the structural landscape, making them what may be called 'metastable crystals'. Indeed, some TAA solvates were found to be labile towards a loss of solvent molecules, when the crystals were removed from the mother liquor. Among them are the solvates of TDA with dichloromethane or toluene.[16] Further, crystallization from a finely-powdered form of TDA occurred rapidly at room temperature when dispersed in a liquid like benzoyl chloride.[15] This rapid Ostwald ripening again indicated that transitions in some TAA solids can occur quite readily.

Beyond the anecdotal evidence mentioned above, it has been difficult to obtain experimental evidence for what processes occur when solvate crystals form and whether there are structural transitions from solvated to desolvated forms, as depicted in cartoon format in *Figure 1*. This prompted us to look for unusual crystal systems that may be transitional crystal forms. Further, we decided to look for phenomena that point to the (partial) desolvation of such crystal forms. As the result of this scrutiny, we present this brief report of five cubic crystals of TDA that are solvates of different organic liquids, as well as the results of studies on their transition to less solvated or desolvated forms. For two of the cubic crystals, low resolution structures were obtained that are interesting in the context of the chaperone effect.

Results

The most common crystals systems found for solvates of TDA are monoclinic or triclinic,[16] with a single published case of a hexagonal system.[15] During our crystallization runs, we noticed cubic crystals when samples from rapid thermal crystallization were inspected at room temperature. The liquid compounds that induced this highly symmetrical crystal system are shown in *Figure 2*, together with a three-dimensional drawing of TDA on the same scale. There is no obvious

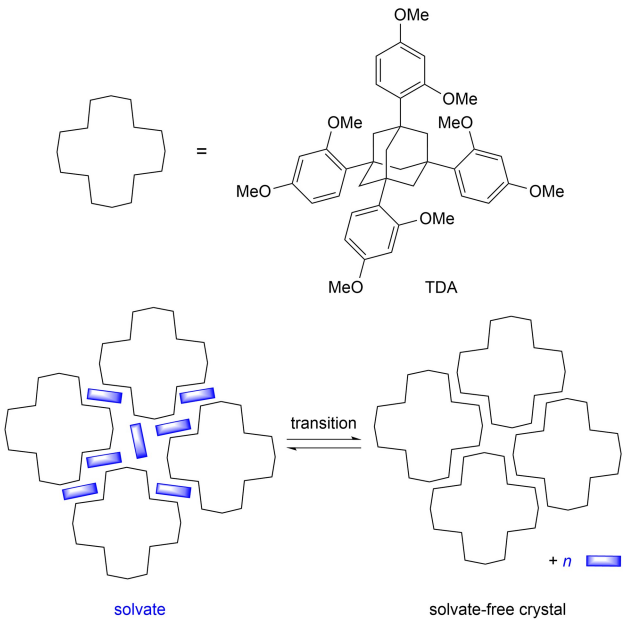

Figure 1. Cartoon of a putative transition from solvated to desolvated form in a crystal of TDA.

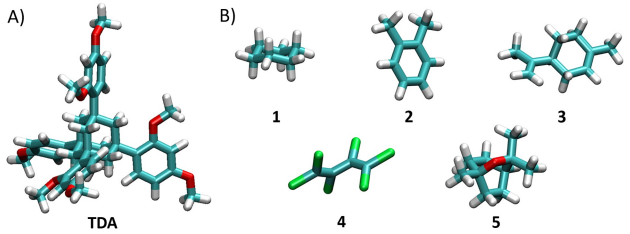

Figure 2. Three-dimensional representations of the molecules forming cubic solvate crystals, visualizing their size and shape. A) The crystallization chaperone (TDA), and B) liquids found as guests in the cubic solvate crystals, with **1** = cyclohexane, **2** = *ortho*-xylene, **3** = limonene, **4** = hexachlorobutadiene and **5** = eucalyptol. The structures of the liquids are force field minimized coordinates, obtained with the MacroModel module of Maestro 13.6. All structures were visualized in VMD 1.9.4.[23]

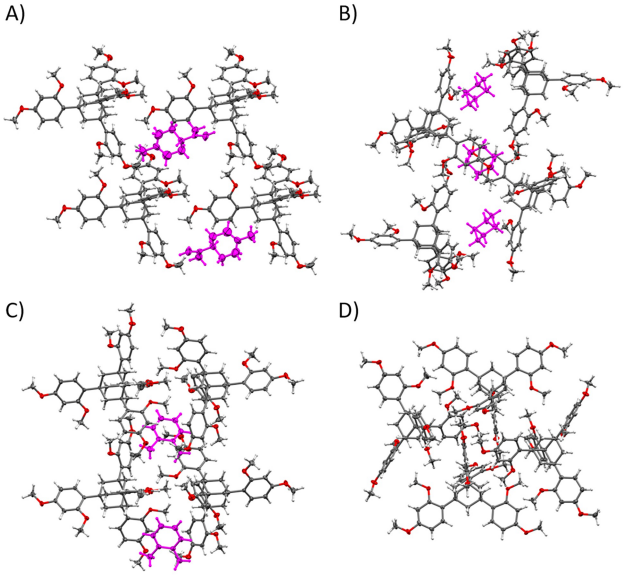

Figure 3. Crystal structures obtained after thermal treatment of cubic crystals, as listed in the last column of *Table 1*. Crystal packing is shown for crystals obtained from A) *rac*-limonene, B) cyclohexane, C) *ortho*-xylene, and D) hexachlorobutadiene. Thermal ellipsoids at 50% probability level are shown. Liquid guest molecules are colored in magenta. TDA molecules are colored by elements. Color code: white = hydrogen, grey = carbon, red = oxygen.

structural similarity between the liquids that led to the cubic solvates. Instead, the guest molecules being encapsulated in those crystals covered a range of sizes and shapes, functional groups and polarity. The smallest of them was cyclohexane (**1**), a saturated hydrocarbon with a molecular weight of 84 g/mol. The next liquid encapsulated was *ortho*-xylene (**2**), an aromatic compound with two aliphatic substituents and a mass of 106 g/mol. Also included in the group was the racemic mixture of the terpene limonene (**3**) at 136 g/mol, perhalogenated alkene hexachlorobutadiene (**2**) with a molecular weight 261 g/mol, and bicyclic ether eucalyptol (**5**), a natural product of M = 154 g/mol.

The initial analysis, performed after mounting of the crystals, gave a cubic system of space group P n-3 and Laue group m-3 with unusually large unit cells in all cases (*Table 1*). Neither of the crystals gave well resolved structures by conventional approaches. We then warmed the samples containing the cubic crystals in their mother liquor. For several of the samples, we noticed that the crystals undergo a thermally induced transition to a crystal system of lower symmetry. Further, whenever there was a transition, full or partial desolvation occurred and well resolved crystal structures with much smaller unit cells were obtained that could be readily solved by direct methods. *Table 1* lists the data of the cubic structures obtained, together with the conditions employed to induce a thermal transformation, and the crystal system thus obtained. The solvate undergoing a transition most readily was that with *rac*-limonene (**3**) as liquid. Here, a transition to a triclinic form with a unit cell volume of just 2′010 Å^3 was observed without heating, when the crystals were kept at room temperature for five days (third entry, *Table 1*).

The resulting structure is shown in *Figure 3A*. It contains only half as many guest molecules as the initial cubic crystals, with its stoichiometry of 2 : 1 (TDA:

Table 1. Cubic crystal structures initially obtained for TDA and the liquids shown in *Figure 2*, the conditions employed to induce a thermal transition, and data for crystals after thermal treatment.

Guest	Cubic unit cell $a = b = c$ [Å]	Cubic unit cell volume [Å^3]	Molar ratio [TDA : guest]	Thermal treatment	New crystal system, space group	New unit cell volume [Å^3]	New molar ratio [TDA:guest]
cyclohexane (**1**)	36.054	46′865	1 : 1	60 °C, 1 d	monoclinic, P21/c	7′656	2 : 1
o-xylene (**2**)	35.918	46′336	1 : 1	60 °C, 1 d	monoclinic, C2/c	16′380	2 : 1
limonene (**3**)	36.181	47′361	1 : 1	25 °C, 5 d	triclinic, P-1	2′010	2 : 1
hexachlorobutadiene (**4**)	36.290	47′793	4 : 3	70 °C, 4 d	triclinic, P-1	3′535	– (desolvated)
eucalyptol (**5**)	36.076	46′953	1 : 1	70 °C, 4 d	– (unchanged)	– (unchanged)	– (unchanged)

limonene). Heating the crystalline samples to 60 °C for 24 h induced a transition for the solvates with cyclohexane and *ortho*-xylene (first and second entry in *Table 1*). The change in morphology from cubic to rectangular crystals is also shown photographically in *Figure 4* for the latter case. Again, there was a change in stoichiometry that accompanied the transition, with 50% of the solvent molecules being lost upon adopting the now monoclinic crystal system (*Figures 3B* and *3C*). Besides the transition to the space groups C2/c (**2**) and P21/c (**1**), the unit cells shrank to 16′380 Å^3 for xylene and 7′656 Å^3 for cyclohexane.

Among the remaining two cases, only hexachlorobutadiene (**4**) underwent a change in crystal structure when heated further, this time to 70 °C, for four days, the highest temperature employed in our study. For this solvate, the heating led to the release of all guest molecules, resulting in a known triclinic form of TDA alone,[16] as shown in *Figure 3D*. Only the cubic solvate of eucalyptol resisted the thermal treatment and remained in the same cubic form after being heated to 60 °C for one day and then to 70 °C for four days. No change in morphology or crystal structure was found for this, the only bicyclic guest molecule, in our group of liquids giving cubic solvates.

We then turned to elucidating the structure of two of the cubic crystals that gave weak, but detectable reflexes in the X-ray diffraction measurements, namely the one with *ortho*-xylene and the one with cyclohexane. Here, extensive computational work was required to obtain the structures of *Figure 5*. Disorder was the main challenge in solving the structures.

While usually the TAA frameworks are well defined in solvate crystals of TDA, partial disorder was found for both host and solvents guest molecules. Approximately two thirds of the TAAs were well ordered, but the remaining one third had one of its aryl arms in more than one orientation relative to the adamantane core. The rotational disorder in the TAA was correlated with the position of a guest molecule. Depending on whether the dimethoxyphenyl ring was in one of the three staggered conformation or the next, a solvent molecule occupied one resulting local cavity or the neighboring one.

Most probably, different partially solvated rotamers had been frozen out when incorporated in the crystalline lattice. Packing forces also led to a modest deviation from the ideal angle along the adamantane-aryl axis, again allowing the accommodation of the guest molecule in an arrangement that was not uniform throughout the lattice. The compensating displacements of the dimethoxyphenyl and solvent molecules when occupying one of the three different rotational isomers resulted in the poor overall order and required a special treatment of these pairs of ring molecules as 'domains' in the calculations. With this approach, the arrangement of the molecules in the cubic crystal system was achieved, albeit with substantial remaining unassigned electron density, as shown in gray ball-stick areas in *Figure 5*.

Overall, the analysis revealed the cubic space group P n-3 mentioned above in both cases (*ortho*-xylene and cyclohexane), with a unit cell volume of 46′336 Å^3 (TDA:**2**) and 46′865 Å^3 (TDA:**1**), respectively. Crystallographic axes of a length of 35.918 Å (TDA:**2**) and 36.054 Å (TDA:**1**) were found. Calculated densities of 1.121 Mg/m^3 (TDA:**2**) and 1.096 Mg/m^3 (TDA:**1**) were obtained mathematically, which is lower than the 1.277 Mg/m^3 (TDA:**2**) and 1.241 Mg/m^3 (TDA:**1**)[16] for the well-ordered counterparts. The unit cells contained unusually large numbers of TDA units, with 40 TDA molecules in both cases and a stoichiometric inclusion of the respective guest molecules. Despite the high symmetry of the cubic crystal system, the data were characterized by the disorder of both solvent and chaperone molecules, as noted above and discussed in more detail in the *Supporting Information*. Each spherical arrangement of approx. 20 TDA molecules shown in dark green in *Figure 5*, is surrounded by solvent molecules located in the center of the sphere and surrounding the TAAs. Independent of such details, it appeared that the flat *ortho*-xylene guests were less well ordered than the chair-shaped cyclohexanes.

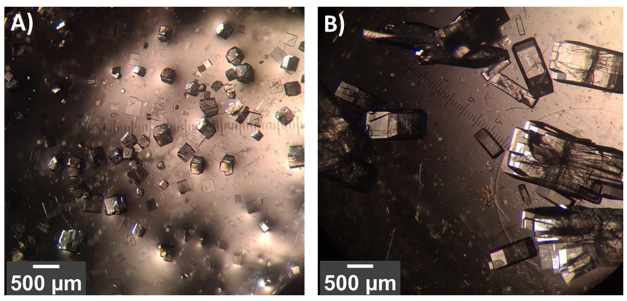

Figure 4. Photographs of samples of solvate crystals of TDA obtained from *ortho*-xylene, A) as initially obtained by thermal crystallization, and B) after heating to 60 °C for 24 h.

Discussion

The current study was motivated by a fundamental question. Why do so many solvent molecules fit into

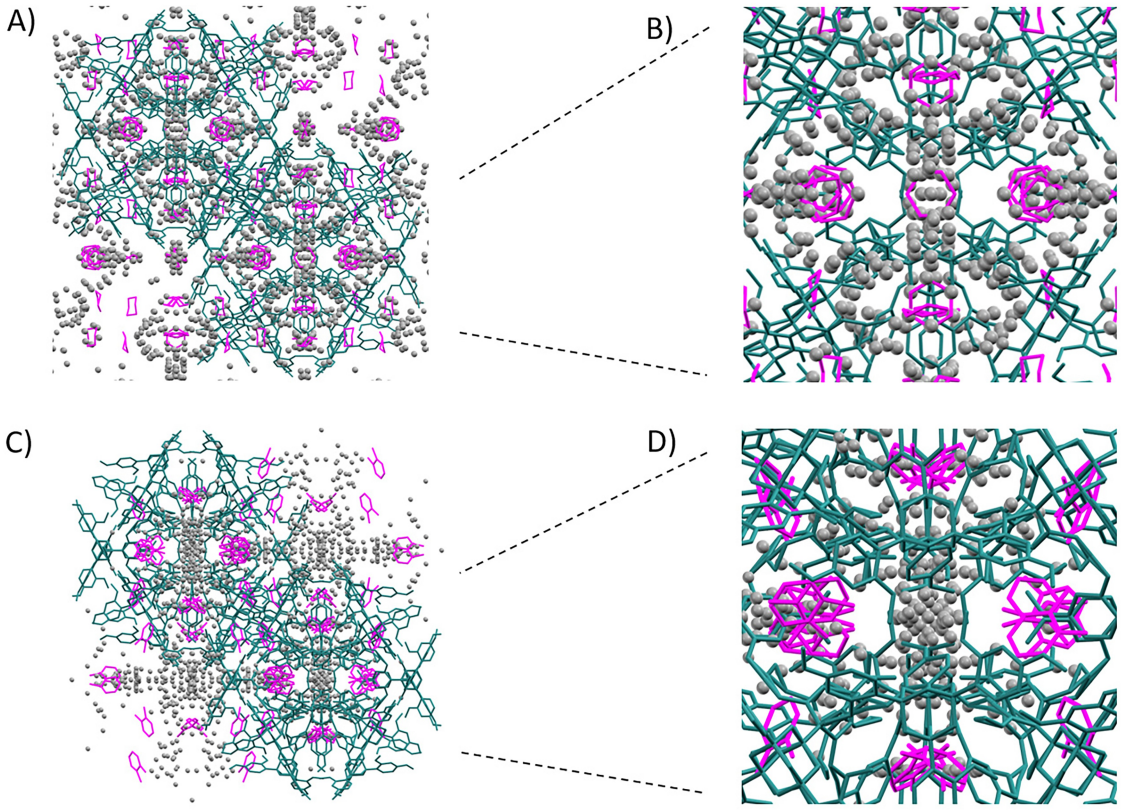

Figure 5. Crystal structures of the cubic solvate crystals of TDA with cyclohexane (**1**) or *ortho*-xylene (**2**) as guest molecules. A) View of the structure of the cyclohexane solvate along the *a*-axis. B) Core of the spherical agglomerate solvated by partially disordered cyclohexane molecules. C) Packing arrangement in crystals of TDA and *ortho*-xylene (**2**), and D) view of the center of a spherical agglomerate. Color code: well resolved TDA molecules are shown in dark green, resolved guest molecules are show in capped stick models in magenta with a line width of 0.12 Å, and residual electron density is in ball and stick style in gray, with Van der Waal radii set to 20 %. Hydrogens were omitted for clarity.

crystalline lattices of TAA chaperones? The majority of crystals of organic molecules are solvent-free forms of a pure compound. For tetraphenyladamantane ethers, solvent-free forms exist, but they are the exception. What is the basis of this effect? How can such a broad range of smaller molecule be accommodated in well-ordered lattices? Packing requires structural complementarity, and one chaperone cannot fit all sizes and shapes.

At the outset, we wondered whether TAA chaperones form a lattice first, into which the guest molecules diffuse, or whether crystallization occurs with incomplete desolvation. The structures from the less ordered cubic systems, which may be early forms of crystallization, were expected to shed at least some light on our questions. To obtain them was challenging, as conventional approaches for X-ray diffraction-based structure elucidation are designed for well-ordered lattices. Still, while we are far from having definite answers to the fundamental questions, the evidence obtained helps to get a better picture of the phenomena underlying the TAA chaperone effect.

What appears likely, based on the available data, is that TAAs crystallize readily, due to their high symmetry and rigidity. Many molecular contacts between the growing nuclei and incoming TAAs lead to incorporation into growing crystallites. Further, the TAAs appear to represent a good compromise between structural preorganization and the ability to adapt to local packing requirements through changes in conformation. Rotation about the aryl-adamantane bonds, combined with conformational changes in the ether substituents and relative positioning of TAA units in the overall lattice produces a flexible landscape of crystal systems that fit many (but not all) guest molecules.

Additionally, the partially ordered structures presented in *Figure 5* now suggest the following. Probably, as crystallization sets in rapidly, even without full desolvation, the partially solvated TAAs form an initial

three-dimensional array with some long-range order, but with substantial disorder in the unit cells. The initial low order assemblies then transition into crystal lattices of higher order with greater ease than is typical for organic crystals. The transition to higher order is made possible by a significant level of mobility of the solvent molecules that either move within the partially ordered TAA lattices or leave them entirely in (partial) desolvation processes.

To what extent the structural changes occur depends on the structure of the solvent, *i.e.*, on shape complementarity and intermolecular forces. When structural rearrangements occur, as in the transitions from the cubic to the monoclinic forms of *ortho*-xylene and cyclohexane solvates, there is probably a concerted change in position for dimethoxyphenyl/solvent domain units that are roughly isosteric. Highly mobile, near spherical, guest molecules, like dichloromethane, leave the initial loosely ordered well solvated assemblies readily, resulting in crystals that disintegrate with solvent release even at room temperature.[15,16] Other guest molecules of larger size and flatter shape like *ortho*-xylene undergo the transition to the more highly ordered, partially desolvated form upon gentle heating. Yet more complex molecules of more intricate shape, like eucalyptol, do not move within or out of the crystalline lattice at all, even when heated to 70 °C for several days. For some that are sufficiently mobile, four-state equilibria like the one indicated in *Figure 6* exist.

This indicates that kinetic barriers depending on size, shape, shape complementarity to the chaperone and intermolecular forces decide whether transitions from the readily formed, initial lattices to the desolvated, conventional organic crystals occur. In the latter, the TAA chaperones are packed without any solvent molecules trapped in their unit cells. For many liquids, the ability to stay in the crystals at room temperature has been demonstrated.[16,18,19] It will be interesting to see where the limits of the chaperone effect are and how they can be pushed to ever larger and more complex guest molecules.

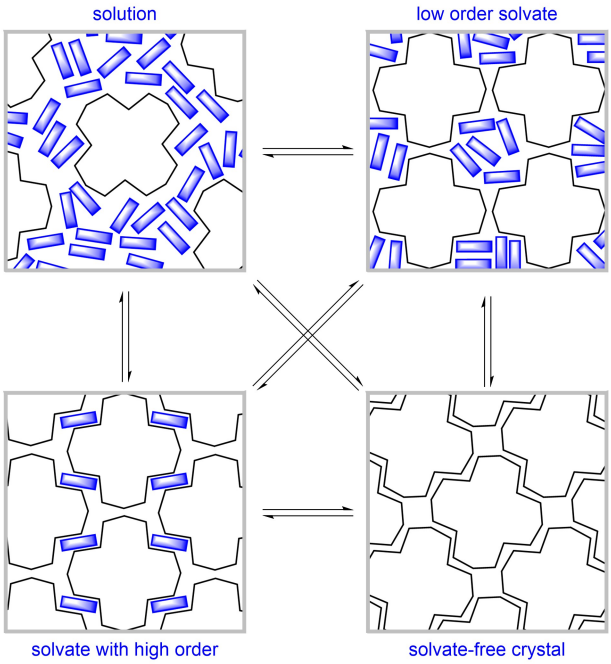

Figure 6. Cartoon depiction of transitions between four states of solvated or unsolvated TDA, with solvent molecules shown in blue.

Conclusions

The structural arrangements in the less well ordered, cubic crystal of the *ortho*-xylene and cyclohexane solvates of TDA provide an interesting glimpse of how tight packing and long-range order are achieved in TAA crystals. The initial semi-ordered states observed show disorder in both TAAs and solvents. These partially ordered states then transition into well-ordered solvates when gently warmed. During the transition, the dimethoxyphenyl arms fall into the better-packed, lattice-wide conformation, and the solvent molecules move to the remaining cavities. The early state is somewhat reminiscent of the molten globule state of protein folding,[24,25] where secondary elements with high local order exist, but their relative position of a well-folded tertiary structure has not been established yet. Although the current structural insights are only a glimpse of what occurs when solvate crystals of TAA form, and more research is needed to understand the chaperone effect, they help to explain a phenomenon that has remained enigmatic thus far.

Experimental Section

General

All chemicals were purchased from Sigma–Aldrich (Darmstadt, Germany) and were used without purification. The chaperone TDA was synthesized according to published protocols.[16] For the crystallographic analysis, a KAPPA APEXII DUO diffractometer from Bruker

AXS (Karlsruhe, Germany) was used. Data was collected at 140 K using MoKα (λ = 0.71073 Å) or CuKα (λ = 1.54178 Å). Cell refinement and data reduction were performed with the SAINT program package and absorption correction with SADBAS3. Structures were solved by using SHELXL97 (directs methods). Least-squares methods were used for isotropic refinement. Rigid models were used to calculate geometrically the positions of the hydrogens. The visualizations of the crystallographic data were generated with Mercury v3.8.0. Photographs of the crystals were taken with a Samsung Galaxy S20+ (SM-G985F) smartphone in pro mode (ISO 80, 1/80s–1/60 shutter speed, auto focus, 2′500–3′500 K white balance) through a microscope from Carl Zeiss (Oberkochen, Germany). Scale bars were generated using ImageJ with external calibration.

The following deposition numbers have been assigned for the X-ray crystal structures in the Cambridge Crystallographic Data Centre (CCDC, https://www.ccdc.cam.ac.uk) 2280112 for cubic crystals of TDA:**1**, 2280109 for cubic crystals of TDA:**2**, 2280108 for crystal structure of TDA:**2** after thermal treatment, 2280110 for TDA:**3**. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe at http://www.ccdc.cam.ac.uk/structures.

Crystallization and Thermal Treatment

The following protocol is for the crystallization and thermal treatment of TDA and *ortho*-xylene and is representative. A cylindrical glass vial ($d = 15$ mm, $h = 40$ mm) was charged with TDA (120 mg, 176 μmol) and *ortho*-xylene (1 mL). The vial was allowed to sit on a preheated hotplate set to 150 °C until a homogenous solution formed. The hotplate was then switched off, and the sample was allowed to cool to room temperature within approx. 30 min. Cubic crystals became visible after approximately 1 h. The mixture was kept at room temperature overnight (14 h) to complete crystallization. A suitable crystal was then harvested and analyzed by X-ray diffraction. To induce transitions, the same sample was placed in a preheated oven, set to 60 °C. After 24 h, no more cubic crystals were observed. Instead, rectangular crystals were found, as depicted in *Figure 4B*, of which one was picked and analyzed by X-ray diffraction.

Supporting Information

Additional data on the X-ray crystal structures reported can be found in the *Supporting Information*.

Acknowledgements

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Author Contribution Statement

A. S. and T. B. synthesized chaperone samples and performed the crystallization experiments, W. F. solved the crystal structures. C. R. conceived the study, and all authors wrote the manuscript.

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