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A three-in-one crystal of mixed sized cucurbit[*n*] uril homologues†

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Crystallization-driven self-assembly of three macrocyclic members of the cucurbit[*n*]uril family is reported. The largest cucurbit[10]uril serves as a host for the smallest cucurbit[5]uril forming an inclusion complex of the macrocycle-within-macrocycle type. This supramolecular ensemble undergoes cocrystallization with cucurbit[7]uril. Such unusual cocrystallization is explained by the strong tendency of all cucurbit[*n*]urils to associate *via* multiple C–H···O hydrogen bonds.

Crystallization is a peculiar example of self-assembly.[1] The propensity of a given molecule to assemble on its own and/or with certain partners may result in one or different crystalline forms ranging from simple solvates, through salts, polymorphs, pseudopolymorphs, cocrystals, solid-state host–guest complexes, to advanced framework architectures.[2] Crystallization from multi-component mixtures often yields the resolution of the individual chemical entities due to differences in their solubility. This simple and powerful separation method is well-known as fractional crystallization. Failures of fractional crystallization[3] usually imply the formation of stoichiometric solid-state compounds (cocrystals)[4] or solid solutions.[5] Formation of cocrystals arise from non-covalent intermolecular interactions such as hydrogen bonds, halogen bonds, π–π interactions, *etc.* between two or more chemical species.[6] Crystal engineering uses knowledge on these non-covalent interactions of supramolecular synthons to design systems for which fractional crystallization will fail predictably, due to strong specific attraction between molecular components.[7]

Fractional crystallization is often used to isolate individual macrocyclic homologues from reaction mixtures. Indeed, cucurbit[*n*]uril (**CB***n*) synthesis yields a mixture of different homologues with *n* = 5–10, with **CB6** being the major component, with traces of **CB5**, **CB7**, **CB8**, **CB10** and other

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oligomers.[8] Isolation of each component is based on their solubility differences in water, water/methanol and hydrochloric acid solutions. Due to rather small differences in solubility, crystallization accompanied with careful examination of each fraction by NMR spectroscopy should be repeated multiple times (10–30) to achieve the separation of the individual **CB***n* homologues. Even then, some of the fractions are contaminated (contain mixture of **CB***n*) and may be further added to the next batch of mixed **CB***n* to be separated. We accidentally left one of such contaminated fractions to evaporate very slowly under ambient conditions for several months and as a result, we discovered a small amount of crystals in the forgotten vial. Single crystal X-ray analysis revealed surprising presence of three different **CB***n* macrocycles in the crystal lattice. The asymmetric unit consists of **CB5** included into the **CB10** macrocycle and **CB7** partnering them (Fig. 1). Although the formation of the ternary complex was not 'engineered', we decided to report it as it is a really unusual example of the failure of fractional crystallization. We explain the formation of a 'three-in-one'
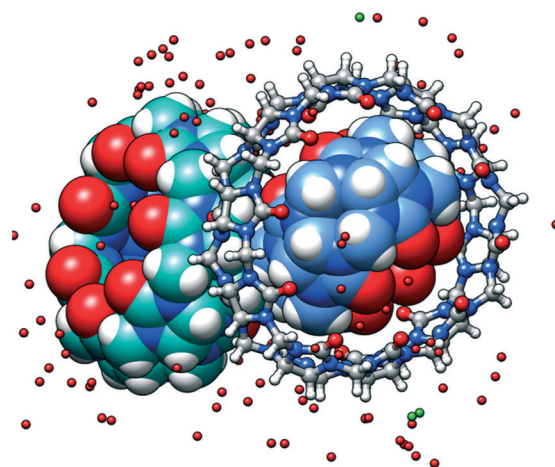

Fig. 1 The asymmetric unit of the multi-component crystal comprising **CB5** (in blue) included into the cavity of **CB10** and **CB7** (in sea green). The solid-state complex is highly hydrated.

cocrystal by strong tendency of all **CBn** to associate *via* multiple C–H⋯O hydrogen bonds.

There are several levels of the inclusion happening in the multi-component crystal. The cavity of the smallest **CB5** is filled with one water molecule disordered over two positions. Each of the **CB5** portals holds additional water molecules with O⋯O distances between carbonyl oxygen atoms and central water molecule typical for hydrogen bonding (Fig. 2a). The H$_2$O@CB5(H$_2$O)$_2$ assembly is surrounded by the cavity of large **CB10** (Fig. 2c and d). The centroids of the **CB10** and **CB5** are practically overlapped thus, the macrocycle-within-macrocycle assembly is concentric. The inclusion complex **CB5@CB10** was isolated and described for the first time by A. Day and co-workers.[9] This beautiful concentric fitting of a small macrocycle within a large one has been known in the supramolecular chemistry as a cucurbituril-based gyroscane. Structural studies on this supramolecular ensemble are quite

scarce, and besides the initial report, only two crystallographic works on the **CB5@CB10** complex have appeared concerning the rigidifying role of potassium[10] and neodymium[11] on this structure.

Taking into account the persistent nature of the **CB5@CB10** assembly, it was quite astonishing to find out that it is able to cocrystallize with another member of the **CBn** family. Indeed, individual **CB5@CB10** units are well separated in the crystal lattice by **CB7** molecules (Fig. 3a). A closer look at the **CB7** (Fig. 2b) reveals that it is filled with multiple water molecules, which were modelled as disordered over 16 positions. The water molecules reside in the inner cavity and in the proximity of the portals. The outer surface of the **CB7** is richly engaged in multiple C–H⋯O hydrogen bonds with the **CB5@CB10** entities acting both as a donor (Fig. 3b) and acceptor (Fig. 3c). As a result, each **CB5@CB10** complex is surrounded by four **CB7** molecules in the crystal lattice and *vice versa*. Such an alternating packing mode in the favorable 'cross' arrangement provides more **CB–CB** interaction possibilities than that in the native **CB5@CB10**
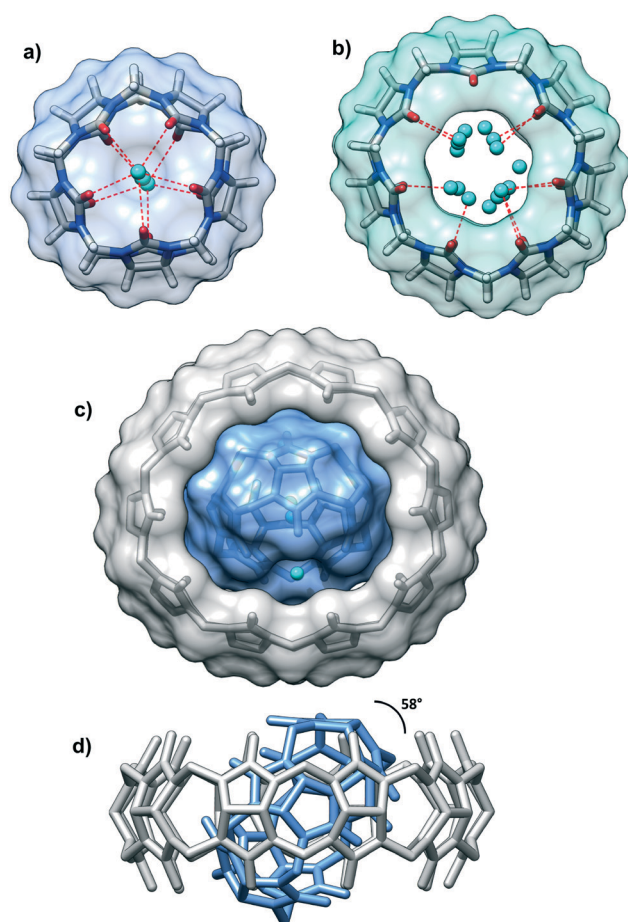

Fig. 2 (a) The **CB5** cavity contains disordered water molecules and is capped by two water molecules, and the O⋯O distances between carbonyl oxygen atoms and water molecules are in the range of 2.77–2.99 Å; (b) the **CB7** cavity contains disordered water molecules (over 16 positions), and the O⋯O distances between carbonyl oxygen atoms and water molecules are in the range of 2.59–2.96 Å; (c) the inclusion complex **CB5@CB10** (top view) and d) its side view. The dihedral angle between the mean planes of the **CB5** and **CB10** is 58°; two ring systems are concentric.
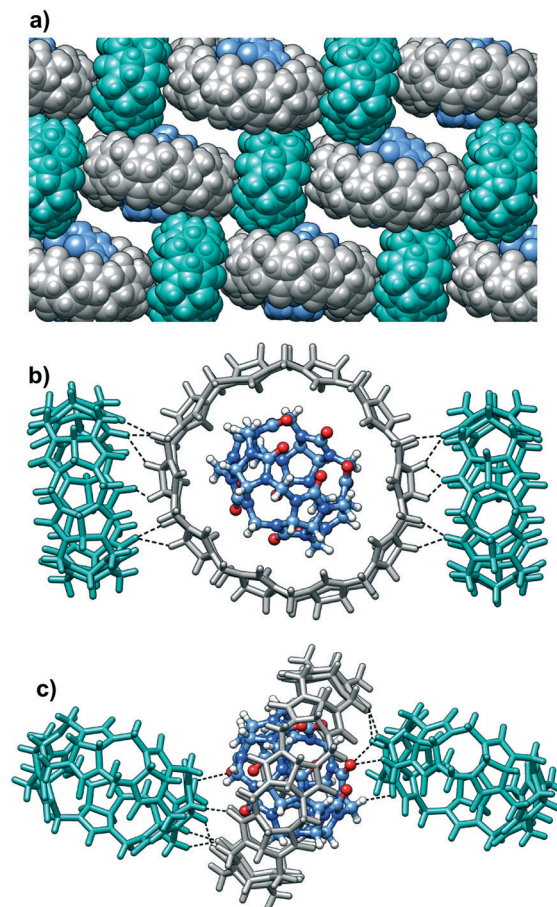

Fig. 3 (a) Part of the supramolecular assembly of **CB5@CB10** and **CB7**. Note that each **CB5@CB10** ensemble is surrounded by four **CB7** molecules in the 'cross' arrangement and *vice versa*; (b) the methine and methylene groups of **CB10** donate multiple C⋯H⋯O hydrogen bonds to the carbonyl oxygen atoms of **CB7**; (c) the methine and methylene groups of **CB7** form C–H⋯O hydrogen bonds toward **CB5** and **CB10** portals.
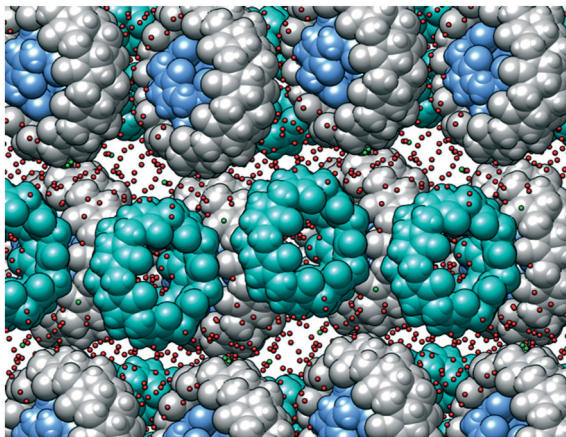
Fig. 4 The crystal packing viewed along the *a* direction. The **CB** layers are separated by rich aqueous regions. **CB7** is colored sea green, **CB10** is grey and **CB5** is cornflower blue. There are no **CB**–**CB** interactions between the layers.

assembly.[9] It is well known in the cucurbit[*n*]uril solid state chemistry that multiple C–H⋯O hydrogen bonds are responsible for the peculiar properties of the homologues, such as solubility, thermal stability, self-assembly and crystal-to-crystal transformations.[12] We postulate that also the unusual cocrystallization of three different homologues can be explained by the cumulative effect of multiple C–H⋯O hydrogen bonds that are effectively realized between **CB5@CB10** and **CB7**. Surprisingly, despite the intensive **CB**–**CB** interactions, the complex is highly hydrated in the solid state, and we have been able to identify at least 79 water molecules per three **CB** molecules. For comparison, there are only 25 water molecules per **CB5@CB10** solid state supramolecular assembly.[9] The careful examination of the crystal packing reveals that the efficient **CB**–**CB** interactions are achieved only in two dimensions within the tightly associated layers composed of **CB5@CB10** and **CB7** (Fig. 4). There are no **CB**–**CB** interactions between the layers. The spaces between the layers are richly loaded with water molecules that render the crystals vulnerable when out from the mother solution due to rapid solvent loss. Besides multiple water molecules, the aqueous layers contain disordered molecules of hydrochloric acid. The hydrochloric acid solution was used upon fractional crystallization in the attempt to separate individual **CB***n* homologues.

In conclusion, crystallization driven self-assembly between cucurbit[5]uril, cucurbit[7]uril and cucurbit[10]uril is described. The cocrystal comprises the **CB5@CB10** inclusion complex interacting with **CB7** *via* outer surface interactions. The small differences in solubility of the cucurbit[*n*]uril homologues, the rigid geometry of the macrocycles and the cumulative effect of the multiple C–H⋯O hydrogen bonds contribute to this peculiar 'failure' of fractional crystallization. The example demonstrates that besides the significant advances in the understanding, prediction and control of molecular solids,[13] the crystallization outcome is sometimes rather unpredictable. The cocrystallization of

different cucurbit[*n*]uril homologues is not a mere crystallographic curiosity.[14] We believe that this phenomenon can shed some light on the nucleation/crystallization from multi-component mixtures[15] and supramolecular alignment of different macrocycles in space without the help of a linker.[16] Since **CB7** and **CB5@CB10** interact with each other in the specific direction ('cross' geometry) and the overlap between them is partial, such an assembly mode potentially enables future utilization of the cavity features of the heteromacrocyclic system towards even more complex geometries.

Experimental

Cucurbit[*n*]urils were synthesized according to the literature procedure.[8b] The cocrystals of mixed sized cucurbit[*n*]urils were obtained serendipitously upon very slow evaporation of the 'contaminated' fraction containing differently sized cucurbit[*n*]urils upon fractional crystallization from the reaction mixture.

Crystal data: $(C_{30}H_{30}N_{20}O_{10})@(C_{60}H_{60}N_{40}O_{20})$ $\cdot(C_{42}H_{42}N_{28}O_{14})\cdot2HCl\cdot79(H_2O)$, M_r = 5169.6, colourless, monoclinic, space group $P2_1/c$, a = 20.3464(1), b = 37.9267(3), c = 30.4684(2) Å, β = 97.040(1)°, V = 23334.3(3) Å³, Z = 4, ρ_{calc} = 1.47 g cm⁻³, SuperNova Agilent diffractometer, Cu-Kα radiation, T = 100.0(1) K, μ(CuKα) = 1.38 mm⁻¹, θ_{max} = 65.1°, 94 788 reflections measured, 39 678 unique, 3495 parameters, R = 0.102, wR = 0.291 (R = 0.119, wR = 0.314 for all data), GooF = 1.08. CCDC 1986639.

Conflicts of interest

There are no conflicts to declare.

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