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Cyclobenzoin Esters as Hosts for Thin Guests

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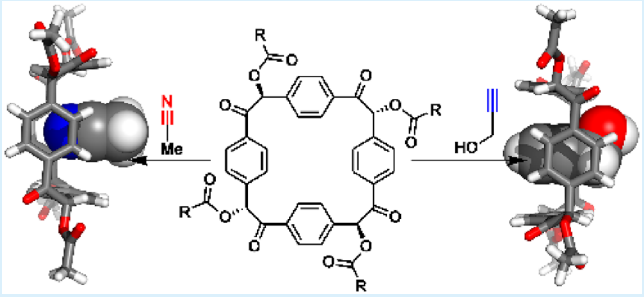
ABSTRACT: Cyclotetrabenzoin esters can host terminal triple bonds of alkynes and nitriles in their cavities, as revealed by cocrystal structures of four such complexes. Within cyclotetrabenzoin cavities, π-clouds of triple bonds establish favorable and virtually equidistant interactions with the four aromatic walls of the cyclotetrabenzoin skeleton. Binding is selective for aliphatic nitriles and terminal alkynes, with their aromatic counterparts residing outside of the cyclotetrabenzoin cavity.



Triple bonds of terminal alkynes and organic nitriles occupy a special place in organic chemistry. Their sp hybridization makes them linear, short, sterically undemanding, and acidic in the case of alkynes.[1] At the same time, the remaining p orbitals offer reactivity that ranges from electrophilic to nucleophilic in both uncatalyzed and metal-catalyzed reactions. Terminal alkynes have been undergoing a renaissance of interest as medicinal chemistry motifs,[2] synthons for the preparation of oligoyne rotaxanes[3] and mechanically interlocked molecules,[4] new allotropes of carbon,[5] and precursors in the Cu-catalyzed azide–alkyne cycloaddition (click reaction).[6] Nitriles remain hugely important as polymerization precursors[7] and as functional motifs in medicinal chemistry.[8]

Given the relevance of nitriles and terminal alkynes in these many contexts, their supramolecular chemistry had been surprisingly underexplored. Receptors developed for these two classes of molecules have relied chiefly on the coordination of the nitrogen's lone pair in nitriles[9] or the engagement of the terminal hydrogen in alkynes either via deprotonation[10] or [C–H···π] interactions;[11] however, the recognition of the triple bond itself as a motif for noncovalent interactions has little precedent. Nitriles have been included in the cavities of brominated calixarenes,[12] Klemperer's inorganic cavitand,[13] and a Mg-based metal–organic framework (MOF);[14] their recognition by pillarenes was utilized to construct supramolecular polymers.[15] Terminal alkynes were found to form complexes with urea as early as 1960,[16] and have been included in the cavities of Rebek's capsules[17] and V-shaped adamantane-based hosts.[18] In most cases, however, crystal structures were not obtained, nor was significant selectivity observed. In this Letter, we show that the readily synthesized cyclotetrabenzoin esters can serve as hosts for thin aliphatic nitrile and terminal alkyne guests, which engage their π-bonds through interactions with the four aromatic walls of the host cavity.

Cyclotetrabenzoin esters[19] **1a–c** (Figure 1) can be prepared on a gram scale by the acylation of cyclotetrabenzoin.[20] The

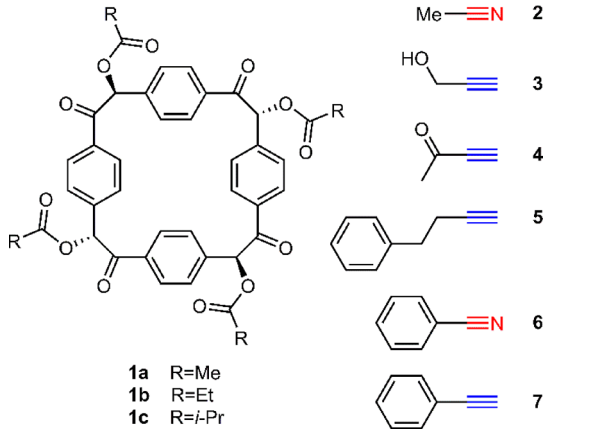


Figure 1. Cyclotetrabenzoin esters **1a–c** and nitrile (**2** and **6**) and terminal alkyne (**3–5** and **7**) guests used in this study.

crystal structures of **1a** and **1c** exhibited both intrinsic and extrinsic pores, whereas that of **1b** showed no discernible pores. Compound **1a** was found to be permanently porous upon solvent removal, with a Brunauer–Emmett–Teller (BET) surface area of 572 ± 16 $m^2\ g^{-1}$.

During the crystallization of **1c** from CS_2, we found that this linear solvent molecule was included in the central cavity of the

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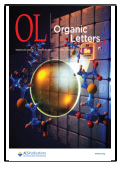

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cyclotetrabenzoin host in an arrangement that resembled an insulated wire. This finding suggested that **1a**−**c** could act as supramolecular hosts for other guests that are thin enough to fit into their cavities or for linear components of more complex molecules. To test this hypothesis, we crystallized **1a** from acetonitrile (**2**) as the solvent. To our delight, the single crystal structure of complex **1a**·**2** (Figure 2, left) showed the triple

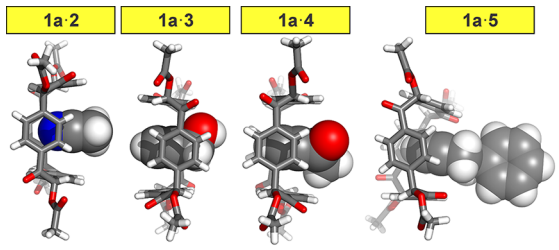

Figure 2. Crystal structures of complexes **1a**·**2**, **1a**·**3**, **1a**·**4**, and **1a**·**5** show the inclusion of their triple bonds in the central pore of **1a**. The guest is disordered over four (**2**, **3**, and **4**) or two (**5**) orientations; only one of these orientations is shown. Element colors: C, gray; O, red; N, blue; H, white.

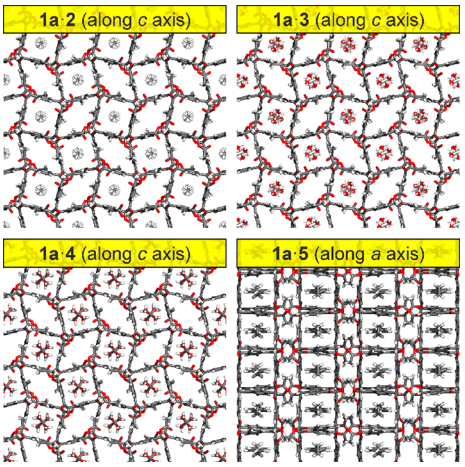

Figure 3. Crystal packing diagrams of **1a**·**2**, **1a**·**3**, and **1a**·**4**, all shown along the crystallographic *c* axis, highlight the virtually identical framework of host molecules **1a** filled with different guests. The packing diagram of **1a**·**5** is quite different and is shown along the crystallographic *a* axis. Element colors: C, gray; O, red; N, blue; H, white.

bond of **2** included in the cavity of **1a**. Molecules of **2** are disordered over four orientations: One pair of positions has the C≡N bond inserted in the cavity of **1a** from the "left", and the other one has it inserted from the "right". (Only one of these orientations is shown in Figure 2.) Within each pair, two different orientations of the Me group are observed, rotated by 60° relative to each other around the axis of the C≡N bond. The centroid of each C≡N bond is positioned 3.60 Å away from the averaged planes of two aromatic rings on the opposite sides of **1a** and 3.28 Å away from the averaged planes of the other two aromatic rings of **1a**. These pairs of distances are very close to the idealized 3.40 Å [$\pi\cdots\pi$] stacking distance between aromatic rings.[21] To evaluate how deeply the C≡N bond is included in the cavity of **1a**, we measured the distance of its centroid from the average horizontal plane of **1a**, defined by the four Ph—C═O and four Ph−CHOAc bonds. The triple bond's centroid resides 1.20 Å above this averaged plane.

Several notable short contacts were observed in the extended packing diagram of **1a**·**2**. Two hydrogen atoms of the Me group of **2** establish short (2.49 and 2.61 Å) contacts with the ester carbonyl oxygen atoms of the two neighboring molecules of **1a**. Short (2.79 Å) contacts are also established between the hydrogen atoms of the methyl group of one molecule of **1a** and the ester carbonyl oxygen atoms on another molecule of **1a**. These contacts repeat themselves on each of the four corners of **1a**, organizing the molecules into a square grid with molecules of **2** included in every other pore (Figure 3, top left). Neighboring sheets are rotated by ±27.8° (measured as the angle between planes of benzene rings in molecules of **1a** in neighboring sheets) with respect to each other. The vertical alignment of these sheets involves no strong directional interactions. Only [C−H···O] contacts between (a) the ketone oxygen in one molecule and hydrogen atoms on two aromatic rings in its neighbor (2.72 and 2.85 Å), (b) the ester carbonyl oxygen in one molecule and hydrogen atoms on two aromatic rings in its neighbor (2.78 and 2.81 Å), and (c) the ketone oxygen in one molecule and AcOC−H hydrogen in its neighbor (2.28 Å) are noticeable.

Encouraged by this observation, we expanded our study to other guests with linear functional groups: aliphatic and aromatic terminal alkynes and nitriles. Cocrystals of cyclobenzoin esters were obtained with five additional guests **3**−**7**, shown in Figure 1.

Three terminal alkynes were crystallized with macrocyclic host **1a**: propargyl alcohol (**3**, Figure 2, second structure from the left), 3-butyne-2-one (**4**, Figure 2, second structure from the right), and 4-phenyl-1-butyne (**5**, Figure 2, right). Whereas crystallization of these guests was attempted with all three cyclotetrabenzoin esters **1a**−**c**, only **1a** produced X-ray-diffraction-quality cocrystals. For all three guests, the terminal C≡C—H group was included in the center of the intrinsic pore of **1a**. Just like in the case of **1a**·**2**, complexes of **1a** with **3** and **4** show these two guests disordered around four positions. In contrast, the 4-phenyl-1-butyne (**5**) guest was disordered over two positions. The triple bonds of **3** and **4** are inserted deeper into **1a**'s cavity than was the case with **2**: the distance between the centroids of the C≡C bonds and the average horizontal planes of **1a** is 0.60 Å. In the **1a**·**5** complex, this distance is slightly longer: 1.43 Å. Once again, the relative positioning of the aromatic walls of **1a** and the guests' triple bonds is very suggestive of [$\pi\cdots\pi$] stacking between these moieties. The distances between the centroids of the C≡C bonds and the aromatic walls of **1a** are 3.42 and 3.53 Å in **1a**·**3**, 3.45 and 3.54 Å in **1a**·**4**, and 3.36 and 3.55 Å in **1a**·**5**. The triple bonds fit perfectly within the cavity of **1a**, allowing virtually equidistant interactions with all four surrounding aromatic rings. Overall, guest **5** distorts the structure of **1a** the most compared with the empty host, causing significant twisting between aromatic rings on the opposite sides of the macrocycle. Tentatively, this can be explained by the interactions that the phenyl ring of **5** establishes with structural elements of **1a** positioned outside of the cavity. Namely, this phenyl ring finds itself sandwiched between two aromatic planes of two different molecules of **1a** (C^{Ar}−centroid distances of 3.78 Å), and its hydrogen atoms establish short contacts (2.70 Å) with the C═O group of **1a**'s ester moiety.

As Figure 3 shows, the packing of **1a** is almost identical regardless of whether **2**, **3**, or **4** is included as the guest. These structures are also very much like the packing structure of **1a** devoid of any guests.[19] The molecules of **3** form two additional

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short contacts between their oxygen atoms and the aromatic hydrogen atoms of **1a** (2.32 and 2.61 Å). The molecules of **4** form two short contacts with **1a** within the same layer (a) between the ester carbonyl and hydrogen of the methyl group of 3-butyne-2-one (2.78 Å) and (b) between a hydrogen on the methyl group of **1a** and the ketone oxygen of **4** (2.97 Å).

Guest **5** causes a significant change in this organization of its host, that is best appreciated when viewed down the crystallographic *a* axis (Figure 3, bottom right). In this view, the square intrinsic pore of **1a** is filled with molecules of 4-phenyl-1-butyne pointing their alkyne triple bonds into the cavity of **1a**, whereas the ester groups form a narrow channel between macrocycles. Vertical sheets stack offset where the macrocycles are not directly on top of one another. These sheets are held together by a series of short contacts. Two-dimensional sheets are established through [C−H···O] contacts between (a) the ester carbonyl oxygen and the AcOC—H hydrogen in its neighbor (2.28 Å) and (b) the ester carbonyl oxygen of one molecule and the hydrogen of the methyl group on another molecule (2.78 Å). Neighboring sheets are connected by [C−H···O] contacts between (a) the ketone oxygen in one molecule and an aromatic hydrogen on its neighbor (2.39, 2.83, and 2.92 Å) and (b) the ketone oxygen in one molecule and hydrogen atoms on the methyl group of its neighbor (2.58 Å).

In contrast with the aliphatic guests **2**−**5**, their aromatic counterparts **6** and **7** did not cocrystallize with **1a**. However, switching to **1b** and **1c** as the hosts provided three cocrystals of sufficient quality for X-ray diffraction. Benzonitrile (**6**) cocrystallized with both **1b** and **1c**, whereas phenylacetylene (**7**) formed crystals just with **1c**. In all of these cocrystal structures, the aromatic guests were found to reside outside of the cavity of **1b**/**1c**. In the crystal structure of **1b**·$\mathbf{6}_2$ (Figure 4, top left), two molecules of **6** are located on the outside of the central cavity of **1b**, establishing [$\pi\cdots\pi$] stacking interactions with the two aromatic walls on the opposite sides of **1b**. The distances between centroids of the benzene rings of **6** and the average planes of the two aromatic walls of **1b** are 3.52 and 3.89 Å. This [$\pi\cdots\pi$] stacking is extended through the slipped stacking of two molecules of **6**, which are in an antiparallel arrangement with an interplanar distance of 3.47 Å. Short contacts are also observed between molecules of **1b** and **6**: (a) the ester carbonyl oxygen and two aromatic hydrogen atoms of **6** (2.58 and 2.78 Å) and (b) the ketone oxygen and two aromatic hydrogen atoms of **6** (2.45 and 2.77 Å). There are also two [C−N···H] contacts between the nitrile nitrogen and hydrogen atoms on two aromatic rings of **1b** (2.51 and 2.71 Å). The ethyl groups of **1b** are found to pack directly below the cyclobenzoin cavity, establishing short [C−H···C] contacts with aromatic walls that range in length from 2.88 to 3.36 Å. Other contacts include [C−H···O] contacts between (a) the ester's alkoxy oxygen and an aromatic hydrogen in **1b** (2.90 Å), (b) the ketone oxygen and an aromatic hydrogen (2.61 Å), and (c) the ester carbonyl oxygen and an aromatic hydrogen (2.61 Å).

Macrocycle **1c** also crystallizes with benzonitrile, with the guest located outside of the intrinsic pore (Figure 4, center left) and engaging in [$\pi\cdots\pi$] stacking with the outside walls of **1c** (centroid-plane distance of 3.54 Å). Here again, the molecules of **6** engage in slipped [$\pi\cdots\pi$] stacking with each other in an antiparallel arrangement and with an interplanar distance of 3.52 Å. Multiple short contacts are formed between **1c** and **6**, including [C−N···H] contacts between the nitrogen

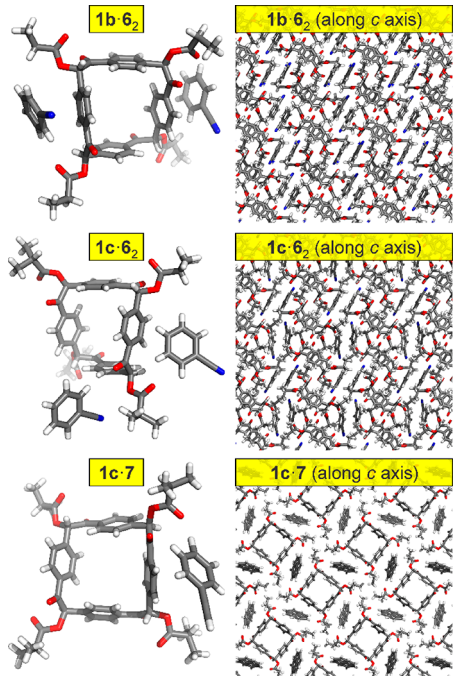

Figure 4. Crystal structures and backing diagrams of complexes **1b**·$\mathbf{6}_2$, **1c**·$\mathbf{6}_2$, and **1c**·**7** show the guests outside of the cavity of hosts **1b** and **1c**. This orientation allows the aromatic groups of the guests to stabilize by stacking interactions with benzene rings from multiple molecules of **1b** or **1c**. Element colors: C, gray; O, red; N, blue; H, white.

of the nitrile and both aromatic and aliphatic hydrogen atoms of **1c** as well as between aromatic hydrogen atoms of **6** and carbonyl and ester oxygen atoms of **1c**. Crystal packing results in no discernible pores (Figure 4, center right) due to the efficient packing from the ester group stacking in the cyclobenzoin cavity, establishing short [C−H···C] contacts that range in length from 2.84 to 3.12 Å. Other contacts include [C−H···O] contacts between (a) the ketone oxygen and $(CH_3)_2$C−H hydrogen (intramolecular, 2.62 Å) and (b) the ketone oxygen and two aromatic hydrogen atoms on two aromatic rings (2.54 and 2.65 Å).

The last diffraction-quality crystal produced was of **1c** with phenylacetylene (**7**) as the guest, where molecules of **7** were also located outside of the central pore (Figure 4, bottom left). Molecules of **1c** pack in such a way that two different pores are visible when viewed along the crystallographic *c* axis (Figure 4, bottom right): one square-shaped pore derived from the intrinsic pore of **1c** and a second oval-shaped pore formed between two molecules of **1c**. The disordered molecules of **7** are located within these oval pores. Curiously, they do not engage in aromatic [$\pi\cdots\pi$] stacking interactions with the outer walls of **1c** but are instead organized into parallel planes with interplanar distances of 2.61 Å. The oval pores are held together by four short [C−H···O] contacts between the ester carbonyl oxygen and the hydrogen atoms of the CH_3 group (2.87 and 3.10 Å). To create a 2D motif, there is a series of short contacts between (a) the ketone oxygen and two aromatic hydrogen atoms (2.71 and 2.75 Å) and (b) the ketone oxygen and AcOC—H hydrogen on its neighbor (2.82 Å). There are also contacts formed between the ketone and ester carbonyl oxygen atoms of **1c** and the aromatic hydrogen atoms of **7** (2.49 and 3.00 Å, respectively) and the methyl hydrogen atoms of **1c** and an aromatic carbon of **7** (2.80 Å).

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To shed light on the energetics of guest inclusion in complexes of **1a** with **2**–**5**, we performed density functional theory calculations. They revealed interaction energies (ΔE_{int}) of −12.7 kcal mol^{-1} for **1a**·**2**, −12.9 kcal mol^{-1} for **1a**·**3**, −14.5 kcal mol^{-1} for **1a**·**4**, and −16.1 kcal mol^{-1} for **1a**·**5**. These ΔE_{int} values were computed based on the total electronic energy of the host–guest complex minus that of the isolated host and the isolated guest at the B3LYP-D3/6-31+G(d) level. Optimized geometries at the same level of theory show averaged distances (d_{avg}) between the average planes of the four π-rings of **1a** and the centroids of triple bonds of **2** (d_{avg} = 3.48 Å), **3** (d_{avg} = 3.50 Å), **4** (d_{avg} = 3.52 Å), and **5** (d_{avg} = 3.54 Å), in good agreement with the crystallographically observed values.[22] These calculated structures suggest an attraction between the guests and the cyclobenzoin host, which could be interpreted as favorable slipped-stack interactions of host's π-rings with either the π-clouds of the triple bonds or the acidic acetylenic H atoms in the case of **3**–**5**. The calculated stabilization energies, per host to guest interaction, are comparable to those seen for the slip-stacked benzene dimer (~2.7 kcal mol^{-1} per interaction).[23] Computed electrostatic potential maps of host **1a** show that the guests interact with a neutral interior of the host (green color, Figure 5), suggesting the importance of dispersion stabilizations in the host–guest interactions.

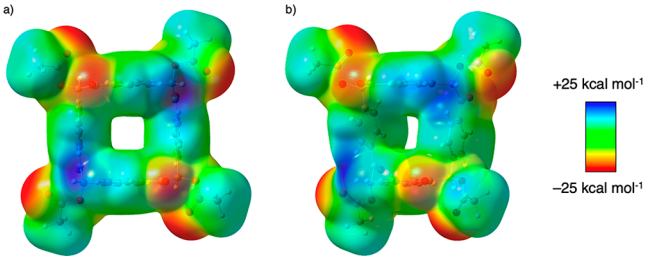

Figure 5. Computed electrostatic potential maps for the host **1a**: (a) front view and (b) side view on a 0.001 au contour surface. Blue indicates positive potential and red indicates negative potential.

Solution-phase experiments were conducted to probe the association of **1a**–**c** with the alkyne and nitrile guests. Nuclear magnetic resonance (NMR) spectroscopy (in solvents too large to fit into the cyclotetrabenzoin cavity) revealed no significant shifts, and diffusion-ordered NMR spectroscopy indicated no change in the size of the host upon the addition of a guest.

In conclusion, we have crystallographically and computationally shown that the central pore of cyclobenzoins can be used to complex thin guests. Crystal growth of host–guest complexes showed that the triple bonds of aliphatic guests can enter the pores of **1a**–**c**, whereas those of aromatic guests cannot. This differentiation is tentatively a consequence of the competition of triple bonds and aromatic rings for [$\pi\cdots\pi$] sites of hosts **1a**–**c**. Guests with sterically undemanding triple bonds can insert those functional groups into the cyclotetrabenzoin cavity. In contrast, guests with aromatic groups prefer to stabilize those moieties by interaction with aromatic rings from multiple molecules of **1b**/**1c**; these interactions take place on the outside of the macrocycle cavity because aromatic rings cannot enter the pores of cyclotetrabenzoin.[24]

Our future work will focus on: (a) exploring other linear guests, for example, CO_2, for inclusion into cyclotetrabenzoin cavities, (b) modifying the electronic properties of **1a** by substituting its aromatic rings in a way that strengthens the association with nitrile and alkyne guests and allows the observation of their inclusion in the solution phase, and (c) exploring guest binding in the recently prepared expanded cyclotetrabenzoins.[25,26]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00383.

General methods and materials, X-ray crystallographic analysis, computational methods, and optimized Cartesian coordinates at B3LYP-D3/6-31+G(d) (PDF)

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Author Contributions

C.M.M. crystallized all of the complexes. X.W. solved the crystal structures. L.J.K. performed the computations with insights from J.I.W. O.Š.M. wrote the manuscript with input from all authors, who have given their approval to the final version.

Notes

The authors declare no competing financial interest.

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