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Cofacial Organic Click Cage to Intercalate Polycyclic Aromatic Hydrocarbons

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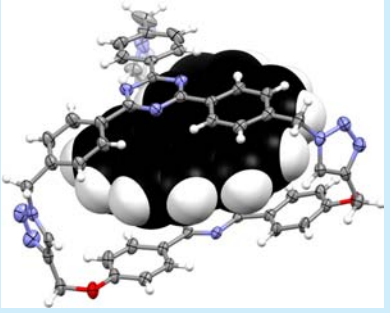
Supporting Information

ABSTRACT: The synthesis of a 3-fold symmetric cofacial organic cage (COC) through Cu(I)-catalyzed azide−alkyne cycloaddition is reported. The COC can function as an efficient receptor for carcinogenic polycyclic aromatic hydrocarbons to intercalate them in its intrinsic cavity through donor−acceptor and $\pi\cdots\pi$ stacking interactions. The association constants (K_a) are in the range of 3.7×10^4 to 1.3×10^6 M^{-1}. X-ray diffraction analysis authenticated that the polycyclic aromatic hydrocarbons (PAHs) are intercalated in the interior of the COC.



Design and synthesis of organic cage-like molecules with vast interior space, capable of intercalating large organic guest molecules, has been a longstanding research activity[1] and gained significant attention in recent years.[2] Among those various cages with different topologies, cofacial organic cage (COC), with convergent recognition surfaces on top and bottom panels and three or more bridges linking them together, is a challenging target for synthetic supramolecular chemist.[3]

The major utility of the COCs includes being an efficient host to intercalate guest molecules such as polycyclic aromatic hydrocarbons (PAHs) among others.[3] Crucially, PAHs, composed of two or more fused benzene rings, are prevalent and persistent in the environment due to anthropogenic activities and are carcinogenic.[4] Synthetic hosts, such as cages and cyclophanes with convergent recognition surfaces, capable of binding PAHs are in great demand. However, there exists only a few such receptors based on specific donor−acceptor interactions,[5] including Stoddart's hexacationic ExCage[3a] and BlueCage.[3b] The COCs might further be useful as transport vehicles in biomedical applications and in enzyme-mimetic catalysis.

Nevertheless, the few COCs, demonstrated with inclusion of PAHs, were obtained in challenging synthetic conditions with limited yield,[3a,b] in comparison with similar cofacial metal−organic cages.[6] High yielding reversible bond forming reactions,[7] especially imine condensation,[8] are often used to form the COCs; however, no such cages capable of intercalating PAHs are known so far. Thus, there remains a strong and urgent need for ready access to COCs with convergent recognition surface capable of intercalating PAHs and other large organic molecules by any synthetic means.[3a]

We hypothesized that Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) reaction, a better known example for the click chemistry,[9] might be a possible tool to obtain COCs, with convergent recognition surface, when carefully chosen building blocks are used. Although CuAAC reaction was often used to synthesize large macrocycles,[10] only limited organic cages, of any topology, are known.[11] In fact, there exists only two COCs obtained through CuAAC reaction: one having limited guest entry portal, thus reported to bind small azide anions only,[11d] and the other having solubility issues for any host−guest complexation.[11a]

Herein, we report the synthesis of a shape persistent COC, obtained thorough CuAAC reaction in high yield, along with its demonstrated ability to intercalate PAHs with great affinity, confirmed by NMR, fluorescence, and single-crystal X-ray diffraction (SCXRD) analyses.

Our strategy of accessing a COC relies on careful choice of building blocks. We chose to utilize the C_3-symmetric 2,4,6-triaryl-1,3,5-triazine moieties with necessary azide and alkyne functional groups on the aryl rings, separately.

Accordingly, we synthesized the necessary building blocks **1a** and **1b** readily (Scheme 1).[12] We subsequently performed the CuAAC reaction by adding equimolar mixture of **1a** and **1b** in THF/toluene (1:3, 0.4 mM, 20 mL), into a toluene (300 mL) solution of CuI and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 75 °C over 18 h, and further stirring the reaction mixture at the 110 °C over additional 24 h (Scheme 1). Subsequent purification of the crude product by column chromatography resulted in the desired COC **1**, in 58% yield. The yield is remarkable considering that the irreversible nature of the reaction and no other major products were isolated during purification. ^{1}H NMR and mass

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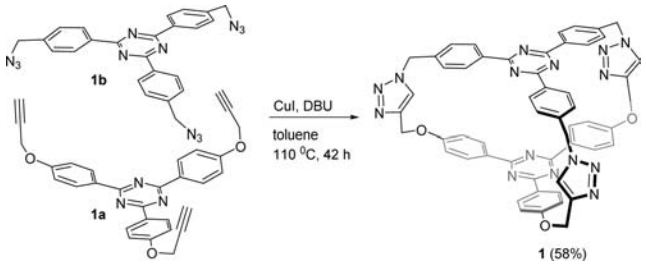
Scheme 1. Synthesis of the COC 1



spectral (see Supporting Information) analysis confirmed formation of **1**.

Crystals of **1**, SCXRD, were readily grown by slow evaporation from either $CHCl_3$ or $C_2H_4Cl_2$ and the analysis confirmed the expected molecular structure with the desired COC topology (Figure 1).

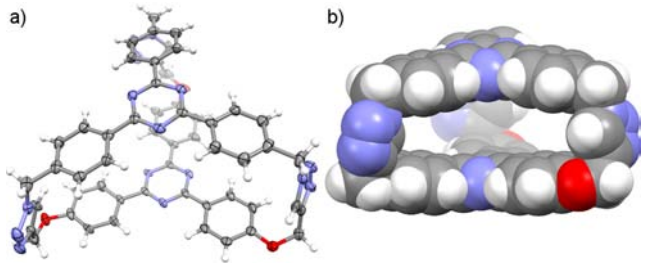


Figure 1. X-ray determined molecular structure of **1**. (a) Thermal ellipsoid plot in 50% probability level and (b) space filling representation. The solvent molecules are not shown for clarity.

The crystal structures reveal that in **1** the atom-to-atom (i) interplanar distances between the two triazine moieties are 6.5–6.7 Å and (ii) interbridge distances between any two triazole moieties are ca. 13 Å. Expectedly, **1** crystallized with the solvent molecules ($CHCl_3$ or $C_2H_4Cl_2$) included in the cavity and in the crystal lattice.

In order to study the ability of **1** to complex the PAH guests (Figure 2) in solution phase, we performed the initial host–guest binding studies by ^{1}H NMR analysis. We prepared equimolar solutions of the host–guest complexes in $CDCl_3$ and then examined for any upfield shift for the guest resonances due to magnetic shielding offered by **1** upon intercalation. Among the PAHs of **2**–**6**, naphthalene (**2**) and pyrene (**5**), curiously, did not show any upfield shift (Figures S4 and S10); presumably their

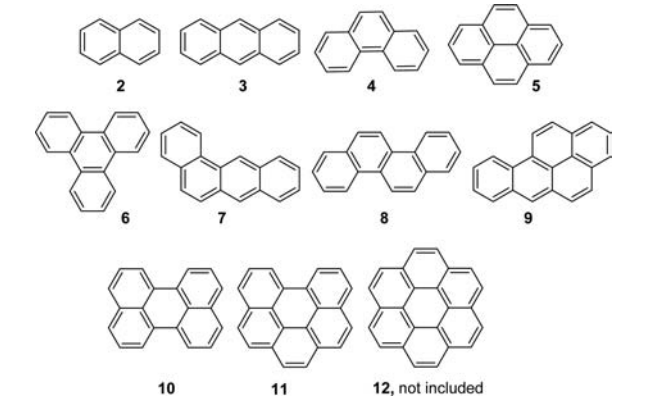


Figure 2. PAH guest molecules examined for intercalation.

size and shape favors fast exchange between in-and-out of the COC **1** in NMR time scale. However, anthracene (**3**), phenanthrene (**4**), and triphenylene (**6**) showed mild upfield shifts ($\Delta\delta$ = 0.1 ppm, Figures S6, S8, and S12) of their proton resonances.

We reasoned that complexation might be favorable in more polar solvent for the nonpolar guests and nonpolar host.[14] Subsequent ^{1}H NMR analysis of the host–guest complexes of **2**–**6** with **1** in THF-d_8/$CDCl_3$ (2:1) revealed significant upfield shift ($\Delta\delta$ = up to 0.5 ppm) for the guest resonances (Figures 3a,

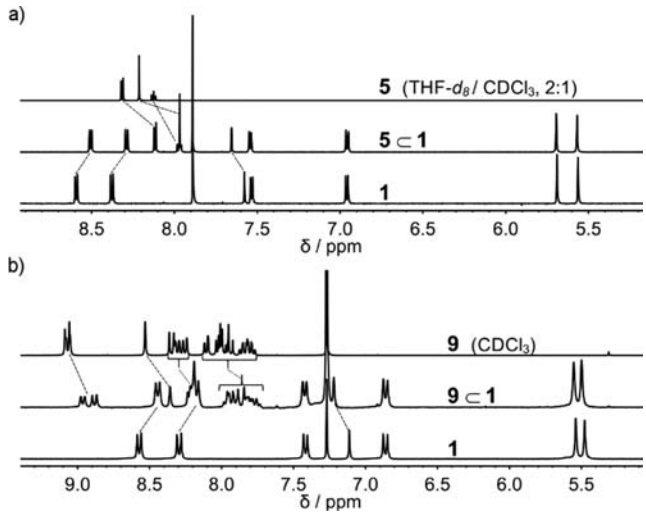


Figure 3. ^{1}H NMR spectra of **5** ⊂ **1** (a) and **9** ⊂ **1** (b).

S5, S7, S9, S11, and S13). The aromatic protons, adjacent to the 1,3,5-triazine moieties, of **1** also underwent significant upfield shift ($\Delta\delta$ = up to 0.2 ppm), thereby suggesting efficient intercalation of the PAHs **2**–**6** inside **1** in favorable solvent. Other larger PAHs, namely, benz(*a*)anthracene (**7**), benzo(*a*)-phenanthrene (**8**), benzo(*a*)pyrene (**9**), perylene (**10**), and benzo(*ghi*)perylene (**11**) exhibited significant upfield shift ($\Delta\delta$ = up to 0.7 ppm) for their proton resonances upon complexation with **1** (1:1 ratio) in $CDCl_3$ itself and more pronounced shifts in THF-d_8/$CDCl_3$ (2:1) (Figures 3b and S14–S23). Due to signal overlap of the host and the guest resonance, NMR titration to obtain the association constant appeared impossible. Subsequent ^{1}H NMR analyses of still larger PAH coronene (**12**) and **1** in $CDCl_3$, as well as in THF-d_8/$CDCl_3$ (2:1), in 1:1 or 1:2 ratio, even after heating the mixture at 60 °C for 3 days, did not show any shift for the guest resonance (Figures S24 and S25); thereby suggesting that **1** might not intercalate **12**. Thus, it is quite remarkable to note that the COC **1** can selectively intercalate **11** ($C_{22}H_{12}$) against **12** ($C_{24}H_{12}$).

UV–vis spectral analysis of 1:1 mixture of the COC **1** with PAHs **2**–**11** and **12** as well showed enhanced molar absorption coefficient, suggesting donor–acceptor interaction, but without any new red-shifted charge-transfer band (Figures S26–S28). We expected that the electron rich PAH guests (**2**–**11**), upon being intercalated with the COC **1**, might transfer the excited energy to the low lying LUMO of the 1,3,5-triazine linked aromatic panels of **1** and thus become nonemissive.[6b] Accordingly, we performed the fluorescence titration experiments, in $CHCl_3$, by adding increasing amounts of **1** in excess (up to 4–9 equiv) into the PAHs (**2**–**11**) solution placed in the cell; thus, the guest molecules should be completely intercalated in **1** at the completion. As anticipated, we observed that fluorescence

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intensities of the PAHs (**2**–**11**) were quenched upon the addition of **1**. The observed reduction in emission maxima was plotted against the change in host concentration, and the association constants (K_a) were calculated for a 1:1 binding model by using nonlinear least-squares curve fitting (Figures S29–S38).[15] The association constants (K_a), listed in Table 1,

Table 1. Thermodynamic Parameters for Binding of PAHs with 1[a]

PAH ⊂ **1**	K_a (M^{-1})	$-\nabla G°$ (kJ/mol)
2 ⊂ **1**	$(1.2 \pm 0.26) \times 10^6$	34.63 ± 0.54
3 ⊂ **1**	$(3.7 \pm 0.42) \times 10^4$	26.04 ± 0.28
4 ⊂ **1**	$(1.56 \pm 0.07) \times 10^5$	29.62 ± 0.11
5 ⊂ **1**	$(5.1 \pm 0.19) \times 10^5$	32.55 ± 0.09
6 ⊂ **1**	$(6.27 \pm 0.37) \times 10^4$	27.36 ± 0.15
7 ⊂ **1**	$(8.6 \pm 0.27) \times 10^4$	28.15 ± 0.08
8 ⊂ **1**	$(1.39 \pm 0.18) \times 10^5$	29.81 ± 0.17
9 ⊂ **1**	$(1.47 \pm 0.04) \times 10^5$	29.48 ± 0.07
10 ⊂ **1**	$(4.3 \pm 0.18) \times 10^4$	26.42 ± 0.1
11 ⊂ **1**	$(7.2 \pm 0.21) \times 10^4$	27.65 ± 0.13
12 + **1**	$(6.75 \pm 0.5) \times 10^4$	27.53 ± 0.2

[a]Measured at 25 °C in $CHCl_3$.

are in the range of 10^4 to 10^6 (M^{-1}) for all PAHs. The measured affinities clearly demonstrated the ability of COC **1** with convergent recognition surface exerting aromatic $\pi\cdots\pi$ stacking and donor–acceptor interactions with the nonpolar PAHs to form favorable inclusion complexes even in nonpolar solvent. Comparatively, other macrocycles and cyclophanes showed similar affinities in polar solvents only.[13,16] A similar fluorescence titration of **1** against **12** also showed a remarkable quenching, and the data can be fit into 1:1 binding model (Figure S39, Table 1). However, based on the ^{1}H NMR data, we suggest that the observed quenching should primarily be due to external binding, instead of intercalation.

SCXRD experiments of the host–guest complexes unequivocally confirmed that the PAHs (**2**–**11**) are intercalated inside the COC **1** through aromatic face-to-face $\pi\cdots\pi$ stacking interaction (Figure 4). Further, in several instances, one of the three 1,2,3-triazole bridges of **1** appears to be rotatable to allow the guest molecules readily into the interior of **1**. The intercalated

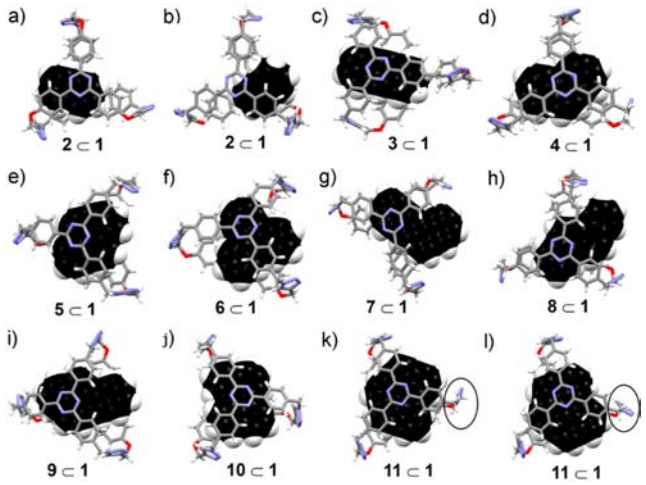

Figure 4. X-ray determined intercalation complexes of **1** with PAHs. The solvent molecules are not shown for clarity.

PAHs, buried inside the COC **1**, appear to be highly solvated in the crystalline state. The solvent molecules are in close contacts with the intercalated PAHs ($d_{C-Cl\cdots C}$ = 3.0 to 4.2 Å) and propagate to form solvent-clustered canals.

The crystal structure of **2** ⊂ **1** provided an explanation for higher affinity observed in the fluorescence titrations. Contrary to other 1:1 PAHs ⊂ **1** complexes (**3**–**11**), the PAH **2** crystallized with **1** along with three molecules of it, one bound inside the cage and other two are outside, but all in close contact, and with a solvent molecule. The bound guest **2** inside the cage **1** is located in two orientations (85:15) with an interplanar angle of 26.3°, to form more favorable edge-to-face aromatic interaction with the host (Figure 4b). This augments the reason for stronger affinity of **1** toward **2** as observed in fluorescence experiments.

Closer inspection of the **11** ⊂ **1** complex confirms that the size of **11** appears to be the maximum that can fit in **1** (Figures 4k,l and S75). The whole of guest **11** and one of the triazole linkers of the cage, closer to the bay area of the guest, were found to be in two different orientations, i.e., disordered over two positions, in order to reach the best fit. It suggests that a larger PAH in which the bay area of **11** was closed with further annulation, i.e., the PAH **12**, cannot fit inside the cage, as suggested by ^{1}H NMR results. Despite our repeated efforts, all our attempts to obtain the crystals of **12** intercalated with **1** did not result in any desired result. This further supports that the size of **11** appears to be the largest PAH that can be intercalated in **1**.

In summary, we have synthesized an organic cage **1**, with two cofacial aromatic platforms bridged through three triazole units, using the exemplary click chemistry of CuAAC reaction, which is otherwise unexplored to synthesize organic cages capable of complexing large organic guests. We have demonstrated that the COC **1**, with a convergent aromatic recognition surface, can intercalate PAHs efficiently, for which available designer supramolecular receptors with specific recognition surfaces are only a few and are highly sought after due to their carcinogenic nature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01554.

Synthesis, details of NMR, UV–vis and fluorescence based binding studies, and details of X-ray diffraction studies (PDF)
X-ray data of $(CHCl_3)_n$ ⊂ **1** (CIF)
X-ray data of $(C_2H_4Cl_4)_n$ ⊂ **1** (CIF)
X-ray data of **2** ⊂ **1** (CIF)
X-ray data of **3** ⊂ **1** (CIF)
X-ray data of **4** ⊂ **1** (CIF)
X-ray data of **5** ⊂ **1** (CIF)
X-ray data of **6** ⊂ **1** (CIF)
X-ray data of **7** ⊂ **1** (CIF)
X-ray data of **8** ⊂ **1** (CIF)
X-ray data of **9** ⊂ **1** (CIF)
X-ray data of **10** ⊂ **1** (CIF)
X-ray data of **11** ⊂ **1** (CIF)

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Notes

The authors declare no competing financial interest.

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