Hetero-Diels-Alder Reaction between Singlet Oxygen and Anthracene Drives Integrative Cage Self-Sorting

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ABSTRACT: A Zn$_{10}$L$_6$ pseudo-cube containing anthracene-centered ligands, a Zn$_{11}$L', tetrahedron with similar side length as the cube, and a trigonal prism Zn$_{10}$L$_6$L'$_2$ formed in equilibrium from a common set of subcomponents. Hetero-Diels-Alder reaction with photogenerated singlet oxygen transformed the anthracene-containing “L” ligands into endoperoxide “L’” ones, ultimately driving the integrative self-sorting to form trigonal prismatic cage Zn$_{10}$L$_6$L'$_2$ exclusively. This Zn$_{10}$L$_6$L'$_2$ structure lost dioxygen in a retro-Diels-Alder reaction after heating, resulting in reversion to the initial Zn$_{10}$L$_6$ + Zn$_{10}$L'$_2$ ⇌ 2 × Zn$_{10}$L$_6$L'$_2$ equilibrating system. Whereas the Zn$_{10}$L$_6$ pseudo-cube had a cavity too small for guest encapsulation, the Zn$_{10}$L$_6$L'$_2$ and Zn$_{10}$L$_6$L'L'$_2$ trigonal prisms possessed peanut-shaped internal cavities, with two isolated compartments divided by bulky anthracene panels. Guest binding was also observed to drive the equilibrating system towards exclusive formation of the Zn$_{10}$L$_6$L'$_2$ structure, even in the absence of reaction with singlet oxygen.

Self-sorting processes in chemical systems enable multi-ple structures to form from a common pool of subunits, potentially exercising their functions in parallel within the same solution. Understanding these processes can shed light on the complex self-assembly pathways in natural systems, as well as enabling the design of chemical systems that serve useful purposes. Artificial self-sorting systems have been developed where subunits are bound together by hydrogen bonds, metal-ligand coordination, aromatic stacking interactions, and electrostatic attraction.

Coordination cages can be produced in self-sorting systems, where selectivity is driven by thermodynamic and geometrical parameters. These cages can undergo structural changes in response to different stimuli, such as post-assembly modification.

As shown in Figure 1, Zn$_{10}$L$_6$ pseudo-cubic cage 1 and Zn$_{11}$L$_6$ tetrahedral cage 2 self-assembled from trigonal subcomponent A and anthracene-centered tetragonal subcomponent B, respectively. As a consequence of the matching side lengths of A and B, mixing solutions of 1 and 2, led to the emergence of a third cage, trigonal-prismatic 3,4 in equilibrium with the other two.

Singlet oxygen ($^1$O$_2$) reacted with the anthracene-containing B residues within both 1 and 3, generating the hetero-Diels-Alder endoperoxide product. This post-assembly modification impacted the relative stabilities of the members of the system, favoring the oxidized trigonal prismatic cage 4, and thus tilting the system towards integrative self-sorting. This modified trigonal prism 4 was observed to thermally revert to the precursor system following retro-Diels-Alder removal of O$_2$ thermally, thus allowing for reversible switching between the mixed and integratively self-sorted states of the system.

The bulky anthracene panels of trigonal prismatic coordination cages 3 and 4 separated the internal cavity into two isolated compartments. Neutral guest molecules were encapsulated in the trigonal prisms 3 and 4, but not in pseudo-cube 1 or tetrahedron 2. Reaction with $^1$O$_2$ thus set in a cascade of events that resulted in guest binding, as the system of cages reconfigured.

In the absence of $^1$O$_2$, the strong binding of adamantane within 3 also reconfigured the 1 + 2 ⇌ 3 equilibrium. This binding stabilized 3, favoring its formation. Adamantane binding thus served as an alternative signal triggering the system to integratively self-sort.

Cages 1 and 2 were synthesized individually via subcomponent self-assembly, as shown in Figure 1a, where dynamic coordination (N→Zn) and covalent (C=N) bonds formed during the same overall process. Subcomponent A was synthesized from commercially available anthracene-9,10-diboronic acid bis(pinacol) ester (SI section 2.1). The reaction of A (6 equiv) with zinc(II) bis(trifluoromethanesulfonylimide) (Zn(NTf$_2$)$_2$, 8 equiv) and 2-formylpyridine (24 equiv) in acetonitrile at 70 °C produced Zn$_{10}$L$_6$ cubic cage 1. Electrospray ionization mass spectrometry (ESI-MS) confirmed the Zn$_{10}$L$_6$ composition (Figure S11, S12), in line with diffusion-ordered spectroscopy (DOSY) NMR measurements (Figure S10), which provided a hydrodynamic radius of 20.9 Å. The reaction of commercially-available subcomponent B (4 equiv) with 2-formylpyridine (12 equiv) and Zn(NTf$_2$)$_2$ (4 equiv) provided cage 2, following published procedures.31
Figure 1. (a) Self-assembly and structural transformation of pseudo-cubic cage 1 and tetrahedral cage 2 from tetramine A and triamine B, respectively; (b) Construction of trigonal prismatic cage 3 and its transformation into cage 4 via hetero-Diels-Alder reaction with photo-generated O2; (c) Schematic illustrating how the ligands panel the faces of cages 1-4.

Single crystals of cage 1 suitable for analysis by X-ray diffraction were obtained by slow diffusion of diethyl ether into an acetonitrile solution. The solid-state structure (Figure 2a) revealed six anthracene ligands bridging eight octahedral ZnII in an S6-symmetric framework, with four metal centers adopting a Λ configuration, and the other four adopting a Δ configuration.12 Within cage 1, the metal-metal distances between adjacent vertices range from 14.8 Å to 16.4 Å. The bulky anthracene panels protrude into the cage cavity, leaving only a small cavity volume of 9.0 Å³, calculated using MoloVol13 (Figure S88).

Cages 1 and 2 were mixed in acetonitrile and heated at 65 °C for 24 hours. The formation of trigonal prismatic cage 3 was observed through integrative self-sorting,1b in equilibrium with the narcissistic products 1 and 2 (Figure 1). The presence of all three products was confirmed by 1H NMR, DOSY spectra (Figure S14, S15) and ESI-MS (Figure S16, S17). Two-dimensional NMR techniques provided structural information consistent with a D3-symmetric trigonal prismatic framework for cage 3 (Figure S52-S55). DFT calculations were undertaken using Gaussian 16 program14 to obtain an energy-minimized structure for cage 3, shown in Figure 2c. This structure gave conformations of the three bulky anthracene panels that projected inwards, separating the internal cavity into two isolated compartments.

Figure 2. (a) X-ray structure of cage 1 (Zn: yellow, N: blue, O: red, C: gray, H: white); DFT-minimized structures of (b) trigonal-prismatic cages 3 and (c) 4; (d) DFT-minimized structure of pseudo-cubic 5.
We then investigated the [4+2] hetero-Diels-Alder reaction between anthracene and \(^1\)O\(_2\) involving both anthracene-based cubic cage 1, and the self-sorted system containing cages 1, 2 and 3. Pioneering work employing this reaction in supramolecular structures has been conducted by the groups of Stang,\(^{15}\) Shionoya\(^{16}\) and Bibal,\(^{17}\) involving structural transformations of host species and changes of their binding affinities. Building upon this work, cage 1 was mixed with the photosensitizer methylene blue (MB, 0.05 equiv) in acetonitrile. This solution was irradiated (\(\lambda_{max} = 630\) nm) for 2 hours at room temperature under air (Figure 1). After irradiation, the anthracene moieties of the cages were found to have reacted to form endoperoxides, generating oxidized cubic cage 5, as shown in Figure 3b. ESI-MS and \(^1\)H NMR analyses confirmed complete 1 \(\rightarrow\) 5 transformation (Figures S28, S36, S37). Comparison of the \(^1\)H NMR spectra of cages 1 and 5 revealed the same number of signals, but with different chemical shift values (Figures S3, S28), which implied that the \(S_6\) symmetry of the framework was maintained. The structure of cage 5 was further confirmed by 2D NMR spectroscopy (Figure S31-S35), and it was also minimized by DFT calculation (Figure 2b, see supporting information Section 7).

Next, we applied the same oxidation conditions to the mixture of cages 1-3. All anthracene panels in this geometric self-sorting system also underwent complete transformation into endoperoxides after irradiation. The hetero-Diels-Alder reaction triggered integrative self-sorting, resulting in the exclusive formation of oxidized trigonal prismatic cage 4, the formulation of which was confirmed by \(^1\)H NMR and ESI-MS (Figure S18, S26, S27). DFT geometry minimization provided a structure for oxidized trigonal prismatic cage 4 (Figure 2c) that was again consistent with 2D NMR spectra (Figures S21-25), which reflected \(C_3\) point symmetry.

As the cycloaddition reaction between \(^1\)O\(_2\) and anthracene is thermally reversible,\(^{15,\,17}\) we studied the recovery of parent cage 1 from oxidized 5 (Figure S38). This transformation occurred after heating 5 in acetonitrile at 120 °C under microwave irradiation for 2 h. Trigonal prismatic cage 4 also underwent deoxygenative retro-cycloaddition, transforming back into the initial mixture of 1-3 following microwave heating. After five cycles of photooxygenation/cyclolysis, NMR integration indicated that 84% of the oxidized trigonal prism was formed, relative to the amount initially present (Figures 3e, S40).

Oxidized trigonal prismatic cage 4 also assembled directly following the mixture of tetrahedral cage 2 and oxidized cubic cage 5 (Figures 3c, S39). We infer that the addition of singlet oxygen stabilized oxidized cage 4 relative to 3, rendering the 2 \(\rightarrow\) 5 \(\rightarrow\) 2 \(\times\) 4 transformation more thermodynamically favorable than the corresponding 1 \(\rightarrow\) 2 \(\rightarrow\) 2 \(\times\) 3 process.

Variable temperature \(^1\)H NMR measurements were used to construct a van ‘t Hoff plot, from which thermodynamic parameters were obtained\(^{18}\) for the 1 \(\rightarrow\) 2 \(\rightarrow\) 2 \(\times\) 3 equilibrium (Figure S41). Conversion into 3 was an endothermic and entropically favored process, with \(\Delta H = 48.35 \pm 1.61 \) kJ mol\(^{-1}\) and \(\Delta S = 150.6 \pm 4.7 \) K mol\(^{-1}\) (Figure S42).

By contrast, the 2 \(\rightarrow\) 5 \(\rightarrow\) 2 \(\times\) 4 transformation (Figure 3d) was found not to be reversible between 25 °C and 65 °C, consistent with high thermodynamic stability of 4 relative to 2 and 5 (Figure S43). The relative energetic favorability of structure 4 was also supported by DFT calculations (Figures S85, S86). DFT structures also suggested that the bent anthracene endoperoxide moieties reduced hindrance inside the cage, further stabilizing cage 4 (Figure S84).

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**Figure 3.** Interacting system of cages before and after the reaction of 1 with \(^1\)O\(_2\). (a) The reaction between 1 and 2 led to an equilibrium mixture containing 1, 2 and 3; (b) 1 reacted reversibly with in-situ generated \(^1\)O\(_2\), to form 5, (c) which in turn reacted with 2 to form only 4; (d) treatment of the equilibrium mixture of 1-3 with \(^1\)O\(_2\) gave only 4; both processes (b) and (d) were reversible following thermal retro-cycloaddition. (e) The reversibility of process (d) is charted over 5 cycles.
The host-guest properties of trigonal prismatic cages 3 and 4 were then investigated (Figure 4). In cages 3 and 4, the bulky meridional anthracene units were designed to separate the internal cavity into two isolated compartments, resembling a ‘peanut’ structure. The internal cavity volumes were calculated by Molvol to be 308.9 Å³ and 279.1 Å³ for 3, and 258.6 Å³ and 226.4 Å³ for 4, respectively (Figures 4a, S87). Cages 3 and 4 both bound a series of alkanes, including adamantane (G1) and norbornane (G2) in slow exchange on the NMR time scale (Figures S44, S67). Encapsulation was further confirmed by DOSY NMR (Figures S49, S57, S70 and S73), where the encapsulated guest and host were observed to diffuse at the same rate. Intriguingly, some terpenoid natural products such as verbenone (G3), (1S)-(-)-camphor (G4) and (-)-beta pinene (G5), which are similar in size to norbornane, were also observed to encapsulate within both 3 and 4 (Figures 4b, S59-S66, S75-S83), also in slow exchange on the NMR timescale.

Synthetic receptors have been shown to adjust their binding sites to better bind guests. Thus, we also studied guest-encapsulation-induced structural transformation in the equilibrium mixture of cages 1, 2 and 3. The addition of G1 to this mixture prompted re-equilibration, resulting in the formation of only cage 3 containing G1 (Figure 4c). ¹H NMR integrations indicated the formation of host-guest complex 2G1c3, which was also confirmed by ESI-MS, with no signals observed corresponding to cages 1 and 2. The host-guest complex 2G1c3 was characterized by 2D NMR spectroscopy (Figures S52-S55).

Entropy changes associated with guest encapsulation may help drive reconfiguration of the system. The freeing of solvent from the cavity of a cage provides an entropic driving force for guest binding. The entropy change associated with guest binding within 3 could thus result in the stabilization of heteroleptic 3 as opposed to homoleptic 2 and 1, which do not bind guest G1.

Using the reversible cycloaddition of ¹O₂ to anthracene to reconfigure a self-sorting system may thus open new possibilities for signal transduction within systems of cages, potentially involving guest uptake and release. The incorporation of enantiopure anthracene ligands may also enable the dynamic control of the chirotopic internal cavities of these coordination cages for potential applications of enantioselective guest recognition and separation.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge via the Internet at http://pubs.acs.org Experimental procedures; NMR characterizations; mass spectrometry data; volume calculations; DFT calculations; X-ray crystallographic data
CCDC 2255439 for cage 1

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Figure 4. a) DFT energy-minimized structures of 3 and 4 with the cavity volumes outlined in deep blue mesh; b) Guest molecules (G1-G5) were encapsulated by both 3 and 4; c) G1 induced conversion from 1 and 2 to form exclusively 2G1c3.

Figure 3. a) A perspective view of the crystal structure of 2G1c3 showing the encapsulated guest G1 encapsulated within cage 3. Red mesh indicates the cavity volume of cage 3.

Figure 2. a) Perspective and b) ball-stick views of the crystal structure of 2G1c3. The encapsulated guest G1 is positioned near the entrance of the cage. The meridional anthracene groups of 2G1c3 are colored light blue. The encapsulated guest is colored red. The crystallographic data for 2G1c3 contains 42 molecules (2G1c3) in the unit cell.

Figure 1. a) A perspective view of the crystal structure of 2G1c3 showing the encapsulated guest G1 encapsulated within cage 3. Red mesh indicates the cavity volume of cage 3. b) A ball-and-stick view of the crystal structure of 2G1c3. The encapsulated guest G1 is positioned near the entrance of the cage. The meridional anthracene groups of 2G1c3 are colored light blue. The encapsulated guest is colored red. The crystallographic data for 2G1c3 contains 42 molecules (2G1c3) in the unit cell.
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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

TOC Graphic

Geometric self-sorting

+ $O_2$

- $O_2$

Integrative self-sorting