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Fuel-Driven Formation of Covalent Basket Cages

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ABSTRACT: Essential functions that sustain life including reproduction, signaling and mechanical motion, persist through the consumption of chemical fuels. Despite recent advances in developing dissipative assemblies that mimic such systems, the fuel-driven formation of covalent organic cages with the capacity to promote catalysis, folding, delivery and sequestration has yet to be demonstrated. In this work we describe the transient formation of a nanosized, tetrahedral cage ($V = 5 \text{ nm}^3$, $M_w = 6150 \text{ Da}$) with four molecular baskets at its vertices linked via imine bonds to four aromatic amines forming the faces. Tribromoacetic acid (TBA) acts as the chemical fuel that drives assembly of the cage via imine metathesis in addition to controlling its formation over time. Our study sets the stage for constructing large dissipative cages with spatiotemporal modes of operation resembling the action of biological molecular machines.

Introduction

Porous organic cages (POCs)¹ are discrete molecular structures composed of two or more multivalent organic components linked through labile covalent bonds (Figure 1A).² These fascinating compounds are rigid enough³ to retain their shape in the solid state and give micro- and mesoporous materials comprising a hollow interconnected network of channels.⁴ In contrast to conventional porous frameworks (MOFs, COFs, HOFs, etc.),⁵ solution processibility of POCs has facilitated their implementation in devices for gas separation⁶ and sensing⁷ of organic compounds. Thus far, the studies pertaining POCs have mostly focused on investigating their capacity for trapping gases under equilibrating conditions.^{1,3} However, one can easily envision POCs acting as rigid but dynamic containers⁸ for encapsulation of one or more pharmaceuticals, toxins, or even biological macromolecules (proteins, nucleic acids, etc.).⁹ Furthermore, it has been recognized that the emergence of complexity in natural systems arises from vast networks of dynamic assemblies¹⁰ operating out-of-equilibrium.¹¹ For instance, the binding of ATP (i.e. chemical fuel, Figure 1C) to chaperonin GroEL produces a transient intermediate capable of encapsulating an unfolded protein (along with GRoES lid) to direct its folding within the chamber.¹² With GroEL acting as an ATPase, the hydrolysis of ATP triggers a departure of now folded protein (and the GRoES lid) followed by the binding of ATP to repeat the process. To mimic the complex natural machinery,¹³ a variety of self-assembled systems¹⁴ and autonomous molecular machines¹⁵ have, in recent years, been developed to operate out of equilibrium. However, there have been no reports describing a transient formation of dynamic covalent cages (e.g., POCs, Figure 1B) in which chemical fuel could regulate their lifetime for enabling spatiotemporal catalysis,¹⁶ sequestration,¹⁷ and delivery.¹⁸

If the system is set to favor the building components of a cage (Figure 1B), then a chemical fuel could be added to push the equilibrium out of balance giving rise to the cage which dissipates as the fuel is consumed.¹⁹ Several challenges in constructing an abiotic dissipative system include: (a) configuring the equilibrium in Figure 1B to favor reactants, (b) developing chemical reaction cycle^{13a} that incorporates rapid formation and slow breakdown of the cage and (c) having the assembly of the covalent cage proceed with high fidelity²⁰ to allow continuous operation²¹ since an irreversible loss of the material would hamper its effectiveness. In regard to the last point, POCs are obtained via single-pot syntheses²² using polyvalent components capable of, in most cases, forming imine and/or boronic ester bonds in a reversible fashion.²³ Dynamic equilibria are important for correcting errors,²⁴ albeit the formation of kinetic traps²⁰ is possible necessitating optimization of the reaction conditions. Since the outcome of reversible-bond condensations correlates well with the degree of preorganization of the reacting molecules,²⁵ we hypothesized that trivalent *tris*-aldehyde basket **2**,²⁶ with the bite angle²⁰ close to 60° (Figure 1D) and semi-flexible bicyclic framework,²⁷ could undergo imine condensation with trivalent 1,3,5-*tris*-(4-aminophenyl)benzene **3** to give covalent basket cage **1** (CBC, Figure 1D). Nanosized **1** ($d = 3.0 \text{ nm}$ and $V = 5 \text{ nm}^3$) is a truncated [4+4] tetrahedron²⁸ with four trigonal panels made of triphenyl benzenes and four vertices composed of abiotic cavitands, baskets,²⁹ known to act as allosteric hosts²⁷ capable of trapping haloalkanes,³⁰ cationic molecules,³¹ nerve agents,³² pesticides,³³ and anticancer drugs.³⁴ Accordingly, we reasoned that obtaining non-collapsible CBCs of type **1** and developing a method for their transient formation via consumption of chemical fuel will set the stage for examining temporal control of their action¹⁷ resembling GRoEL chaperone in Figure 1C.¹⁸ For the first time, we herein describe a method to drive the out

of equilibrium formation of covalent basket cages in a tunable manner using an acidic chemical fuel in organic media.

Results and Discussion

Synthesis and Characterization of Covalent Basket Cages: After adding *tris*-aldehyde **2** to *tris*-amine **3** (Figure 1D) in DMSO, the condensation took place giving oligomeric materials although mass spectrometry (MALDI, Figure S1) also showed that desired **1** formed as a minor product. Encouraged

Figure 1. (A) An energy minimized structure (PM3, Spartan) of a previously studied [4+4] porous organic cage (POC). (B) A scheme showing the formation of a dynamic covalent cage driven by a dissipation of fuel. (C) GroEL is a biological molecular machine that uses ATP as a fuel for forming a transient intermediate capable folding a protein in its cavity. The hydrolysis of ATP drives the departure of the folded molecule. (D) The proposed formation of covalent basket cage **1** (CBC **1**, PM3) from 1,3,5-*tris*-(4-aminophenyl)benzene **3** and *tris*-aldehyde basket **2**. CBC **1** is a truncated tetrahedron with a trigonal side panel having edges $a = 3.5$ nm and volume 5 nm^3 . Diameter of a circumscribed sphere is $D = 2.8$ nm.

by the result, we decided to probe the condensation in differently sized and shaped solvents since, we posited, they might template the formation of the [4+4] cage.^{25b} From solvent screening (Figure S2), it appeared that 1,2-dichloroethane (DCE) and chloroform would, in the presence of catalytic TFA,³⁵ assist the formation of **1**. Despite such optimization, cage **1** would under preparative conditions precipitate from the solution as a pale-yellow solid being sparingly soluble in organic media. To address the issue, we prepared *tris*-amine **4** (Figure 2A) to include solubilizing groups (hexoxide, OC_6H_{13}) conjugated to the benzene core. In DCE containing catalytic TFA, the reaction of *tris*-aldehyde basket **2** and *tris*-amine **4** resulted in the formation of CBC **5** as the sole product (Figure 2A; Figure S18), which remained soluble in chlorinated solvents after isolation, including dichloromethane and chloroform. ^1H NMR spectrum of **5** showed a set of signals corresponding to, on average, a T_d symmetric imine (Figure 2A; for 2D COSY, HMBC and HSQC of CBC **5** see Figures S7-8) with resonances arising from the basket and linker components in equal ratio. A greater magnetic deshielding of $\text{H}_{\text{C/H}}$ signals from *tris*-imine panels is in line with the conversion of the amine functional groups into more electron withdrawing imines. From 2D NOESY spectrum of **5** (Figure S9), we noted cross peaks between H_f and H_e as well as H_f and CH_2 from hexyl groups to corroborate the proximity of the two building blocks and *trans* configuration of the imine double bond (Figure 2A). DOSY NMR spectrum of **5** had all proton resonances

leveled (Figure S10) therefore corroborating that the amine and aldehyde components reside within the same molecule.

Molecular Encapsulation within CBC 5: A slow vapor diffusion of methanol into 1,1,2,2-tetrachloroethane (TCE) solution of *tris*-aldehyde basket **2** gave single crystals. After being subjected to X-ray diffraction analysis (Figure 2B), we found the unit cell of **2** includes two baskets entangled into a centrosymmetric capsule surrounded with six additional capsules as a part of the honeycomb array (Figure 2B). Each capsule incorporates two molecules of TCE, holding onto southern and northern benzenes via $\text{C}-\text{Cl}\cdots\pi$ halogen bonds ($R =$

$3.334 \text{ \AA}$ and $\alpha = 171.67^\circ$).³⁶ Benzaldehyde groups employ $\text{C}_{\text{sp}2}-\text{H}$ groups to form a seam of edge-to-face $\text{C}_{\text{sp}2}-\text{H}\cdots\pi$ hydrogen bonds at the capsule's equator ($d_{\text{C}-\pi} = 3.705\text{--}4.418 \text{ \AA}$ and $\alpha = 112.41\text{--}143.59^\circ$, Figure 2B).³⁷ With tetrachloroethane ($108 \text{ \AA}^3$) residing in the cavity of **2** and the known propensity of baskets to trap haloalkanes in solution,³⁸ we wondered if CBC **5** could use its four compartments for complexing complementary and polarizable CBr_4 ($108 \text{ \AA}^3$)?³⁹ If so, could there be any homotopic cooperativity characterizing the four consecutive binding events?⁴⁰ An incremental addition of a standard solution of CBr_4 to tetravalent CBC **5** caused a notable magnetic deshielding of its aromatic H_C protons (Figure 2A; Figure S20) resulting from the guest occupying the host's cavities.³⁹ The titration isotherm fit well to 1:1 binding model ($K_a = 108 \pm 2 \text{ M}^{-1}$, Figure 3A) with the linear Scatchard plot⁴¹ corroborating the statistical population of the four compartments ($K_a = 100 \text{ M}^{-1}$, Figure 3A); for fitting to the 1:1 binding model, the known concentration of CBC **5** was multiplied by a factor of four. Interestingly, the complexation of the cage by CBr_4 was also found to be more favorable than monomeric **2** ($K_a = 46 \pm 4 \text{ M}^{-1}$, Figure S21). We posit that a more rigid and preorganized cavities of CBC **5** (Figure 2A) should be responsible for a more effective complexation of the guest. As for the statistical complexation of CBr_4 by tetravalent **5**, the consecutive binding events must have caused insufficient change in the conformation of the cage and its solvation to result in measurable outcome.⁴²

A slow diffusion of methanol into 1,1,2,2-tetrachloroethane solution of CBC **5** containing CBr_4 resulted in the formation of single crystals. X-ray diffraction analysis of the sample revealed rigid CBC **5** with the shape of a truncated tetrahedron having four molecular baskets at its corners conjugated to four trivalent aromatic panels by imine bonds (Figure 3B). Fascinatingly, each cage **5** would in the solid state encapsulate four molecules of CBr_4 : these guests are nested inside basket cavities forming a $\text{C}-\text{Br}\cdots\pi$ halogen bond ($R = 3.229 \text{ \AA}$ and $\alpha = 170.09^\circ$)³⁶ with the benzene base and placing the remaining

three bromides between the phthalimide sides. The unit cell has four $[(\text{CBr})_4\text{C}\text{--}\mathbf{5}]$ complexes (Figure 3C) packed in an arrangement that forms nanosized channels (1.26 nm wide, Figure 3C) extending throughout the entire crystal. The channels are lined with four conformationally dynamic hexyl chains, two at the front and two at the back (Figure 3C). The solid material is thus expected to be porous⁴ with its channels providing access to basket cavities. The uptake of potential guests (i.e., gas molecules or compounds from a liquid phase)⁴³ remains to be studied in the future.

Figure 2. (A) ^1H NMR spectra (850 MHz, CD_2Cl_2) of *tris*-amine **4** (top), *tris*-aldehyde basket **2** (middle), and CBC **5** (bottom). Energy-minimized structures (PM3) of **2**, **4** and **5** (hexoxide groups are shown as red spheres). (B) ORTEP diagrams (50% probability) of the solid-state structures of complexes $[\text{C}_2\text{H}_2\text{Cl}_4\text{C}\text{--}\mathbf{2}]$ and $[(\text{C}_2\text{H}_2\text{Cl}_4)_2\text{C}\text{--}\mathbf{2}_2]$.

Figure 3. (A) An incremental addition of a standard solution of CBr₄ to CBC 5 (0.15 mM) was in CH₂Cl₂ monitored with ¹H NMR spectroscopy (600 MHz, 300 K). A nonlinear least-square analysis of the binding isotherm (SigmaPlot; Figure S20) fit well to the formation of a binary complex with $K_a = 108 \pm 2 \text{ M}^{-1}$; note that for the analysis, the concentration of 5 was increased by a factor of four. A Scatchard plot for the supramolecular titration of CBr₄ to 5 was fit to a linear function (SigmaPlot). The population of the four binding sites in 5 ($r = 1-4$) was calculated using the observed change in the chemical shift of H_C (top) while the equilibrium concentration of [CBr₄] was assumed to be equal to its overall concentration. (B) A ball and stick representation of CBC 5 in the solid state (X-ray diffraction) with four CBr₄ molecules in its cavity (only one is shown for clarity). (C) A ball and stick representation of the unit cell of CBC 5 in the solid state, showing cylindrical channels extending along the crystallographic c axis.

Figure 4. (A) Equilibrium I is populated with *tris*-amine 4, *tris*-aldehyde basket 2 and CBC 5 and shifted toward the cage formation at 298 K. (B) Equilibrium II is populated with *tris*-amine 7, *tris*-aldehyde basket 2 and [1+1] capsule 6 and shifted toward the capsule formation at 298 K. (C) Equilibrium III includes CBC 5 reacting with *tris*-amine 7 to give *tris*-amine 4 and [1+1] capsule 6. With an excess of 7, equilibrium III is shifted to the right with predominant formation of [1+1] capsule 6. (D) A stick representation of the solid-state structure of [1+1] capsule 6 packing into supramolecular nanotubes.

Fuel-driven formation of CBCs: Catalytic TFA was used in the preparation of CBC 5 (Figure 2A) to increase the rate of imine exchange and thereby allow “error corrections” to give the thermodynamically controlled outcome.²⁴ However, adding an excess of TFA to 5 caused its conversion into 2 and [4-H₃]³⁺ driven by favorable protonation of the *tris*-amine (Figure S19). On the contrary, subsequent addition of base (Et₃N) resulted in deprotonation of [4-H₃]³⁺ followed by the exclusive formation of cage 5. We reasoned that this high fidelity in cycling between the covalent cage and its building components makes it well suited for developing an acid-fueled dissipation system.^{14c, 44} However, equilibrium I (Figure 4A) with 2, 4, 5, and catalytic TFA favors the cage and this must be reversed to drive its transient formation using a chemical fuel.⁴⁵ To address the quandary, we hypothesized that arresting *tris*-aldehyde 2 in the form of stable [1+1] capsule 6 (equilibrium II, Figure 4B) could, on the account of entropy, have 5-to-6 process (equilibrium III, Figure 4C) favoring the latter. First, preorganized⁴⁶ *tris*-amine 7 and basket 2 reacted in the presence of catalytic TFA to form [1+1] capsule 6 with no ¹H

NMR signals suggesting the formation of other species (Figures S12-S17).^{25b, 47} The solid-state structure of 6 (X-ray diffraction, Figure 4D) showed these hollow capsules with no guests occupying their interior. Interestingly, they packed into supramolecular nanotubes by stacking (head-to-tail, Figure 4D) on top of one another. The tubes also extend throughout the crystal along the crystallographic *a* axis in the opposite directions. Importantly, adding an excess of *tris*-amine 7 to CBC 5 (catalytic TFA) resulted in capsule 6 populating equilibrium III (Figure 4C; Figure S22). Now that we developed a process in which desired CBC 5 was an unfavorable product (equilibrium III, Figure 5A), adding an excess of tribromoacetic acid (TBA, chemical fuel, p*K*_a = 0.8) was expected to disturb it by predominantly protonating aliphatic amine 7 (p*K*_a = 9) thereby triggering the removal of the smaller [1+1] capsule from the equilibrium (Figure 5A). Condensation of the released *tris*-aldehyde basket 2 and aromatic amine 4 (p*K*_a = 4) should then result in the out-of-equilibrium formation of CBC 5. The tribromoacetate ion formed through protonation of 7 undergoes thermal decarboxylation to give CHBr₃ and CO₂

Figure 5. (A) A chemical reaction cycle showing tribromoacetic acid (TBA) acting as a fuel and driving equilibrium III to the right for a transient formation of CBC 5. Decarboxylation of CBr₃CO₂[−] into CHBr₃ and CO₂ (waste) brings the system back to its original state. (B) Partial ¹H NMR spectra (850 MHz, CD₂Cl₂) of [1+1] capsule 6 (0.44 mM), *tris*-amine 4 (0.44 mM), *tris*-amine 7 (0.62 mM) and TFA (1.7 mM). After an addition of TBA fuel (2.5 mM), ¹H NMR spectra were recorded after a few minutes, 5 h and 24 h (see also Figures S25-28). (C) A plot showing a normalized change in the concentration of [1+1] capsule 6, CBC 5 and CHBr₃ over time for the experiment described in (B). (D) A plot showing a change in the yield of CBC 5 over time for experiments similar to that described in (B) repeated with different concentrations of TBA: 2.0 mM (blue), 2.8 mM (red) and 3.6 mM (green) (see also Figures S29-S36).

(waste) with the overall loss of acid in solution. Next, the regeneration of aliphatic *tris*-amine **7** restores the original equilibrium III dominated by aromatic *tris*-amine **4** and [1+1] capsule **6**. In order to build a larger quantity of CBC **5** in solution, a faster degradation of **6** followed by slower dissipation of **5** must take place during the proposed reaction cycle (Figure 5A).^{13a}

¹H NMR spectrum of [1+1] capsule **6**, *tris*-amines **4** and **7** along with TFA in CD₂Cl₂ showed the presence of **6** and **4** while [7-H_n]ⁿ⁺ (n=1–3) stayed as a precipitate (Figure 5B). Importantly, an addition of TBA (fuel) prompted the immediate disintegration of [1+1] capsule **6** (Figure 5B). At the same time, CBC **5** started to form with a steady increase in its concentration over time (Figure 5B/C). When the concentration of **5** peaked (circa 5h, Figure 5C), the decarboxylation of tribromoacetate, illustrated by the formation of CHBr₃ (Figure 5C), became faster resulting in the release of *tris*-amine **7** and concomitant formation of [1+1] cage **6**. The system would, after circa 20h, return to its resting state comprising **6**, **4**, and [7-H_n]ⁿ⁺ (n=1–3). With CO₂ and CHBr₃ formed as waste, the process was cycled three times with minimal loss in its effectiveness (Figures S37–S39). By adding different quantities of TBA fuel, we found that the formation of CBC **5** could be tuned to peak at 1.7, 4.5 and 12 h (Figure 5D). Evidently, additional fuel requires longer time to convert into waste (second step in Figure 5A) therefore retarding the release of **7** and prolonging the dissipation of CBC **5**. Such fine tuning of the time-dependent concentration of CBCs will come handy for optimizing catalysis, delivery, and sequestration in complex chemical environments.⁴⁸

Conclusion

Dynamic covalent cages can now be made to exist for a fixed period of time,^{13a} using chemical fuel to tune the kinetics of their formation and dissipation. By combining trivalent and planar amines with trivalent and cup-shaped aldehydes (i.e., baskets) we obtained large [4+4] cages as rigid truncated tetrahedrons. These covalent basket cages (CBC) include four baskets at their vertices with four trivalent amines forming the face. In both solution and solid state, CBC **5** acted as an allosteric host holding up to four guest molecules in its four cavities. With the assistance of small [1+1] capsule **6**, we managed to establish a chemical equilibrium to favor its formation at the expense of CBC **5**. An addition of a labile acid as a fuel, shifted the equilibrium toward the formation of **5** and after the fuel dissipated by decarboxylation, the system returned to the starting equilibrium state. Our methodology for the temporary formation of large covalent cages can now be used as a roadmap for optimizing the action of similar molecules^{8a} including POCs.^{1,3} The long-term goal is to exploit the functional characteristics¹⁷ of covalent cages for promoting chemical reactions,⁴⁹ folding of molecules,³¹ delivery,⁵⁰ and sequestration³² in spatiotemporal fashion. After all, natural systems⁵¹ have evolved to build dynamic materials operating out-of-equilibrium and capable of doing work: converting chemical into mechanical energy (cytoskeleton),⁵² folding proteins (GroEL chaperone)¹² and controlling membrane transport (rotary ATPases).⁵³

ASSOCIATED CONTENT

Supporting Information

Additional spectroscopic and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website.

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