Fuel-Driven Formation of Covalent Basket Cages

Jovica Badjic (badjic.1@osu.edu)  
The Ohio State University

Vageesha Liyana Gunawardana  
The Ohio State University

Tyler Finnegan  
The Ohio State University

Carson Ward  
The Ohio State University

Curtis Moore  
The Ohio State University  https://orcid.org/0000-0002-3311-7155

Article

Keywords:

Posted Date: February 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1299975/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Fuel-Driven Formation of Covalent Basket Cages

Vageesha W. Liyana Gunawardana,[a] Tyler J. Finnegan,[a] Carson E. Ward,[a] Curtis E. Moore,[a] Jovica D. Badjić*[a]

[a]Department of Chemistry & Biochemistry, The Ohio State University, 100 West 18th Avenue, 43210 Columbus, Ohio

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 nm³) 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 nm³) 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 equilibriating conditions.¹³ 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 cycle²⁰ that incorporates rapid formation and slow breakdown of the cage and (c) having the assembly of the covalent cage proceed with high fidelity²¹ to allow continuous operation²² since an irreversible loss of the material would hamper its effectiveness. In regard to the last point, POCs are obtained via single-pot syntheses²³ using polyvalent components capable of, in most cases, forming imine and/or boronic ester bonds in a reversible fashion.²⁴ Dynamic equilibria are important for correcting errors,²⁴ albeit the formation of kinetic traps²⁶ 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,²⁷ we hypothesized that trivalent Tris-aldehyde basket ²⁶ with the bite angle²⁹ 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 nm and V = 5 nm³) is a truncated ⁴ tetrahedron with four trigonal panels made of triphenyl benzenes and four vertices composed of abiotic cavities, baskets, known to act as allosteric hosts³⁰ capable of trapping haloalkanes,³¹ cationic molecules,³¹ nerve agents,³¹ pesticides,³¹ and anticancer drugs.³¹ 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 action³¹ resembling GRoEL chaperone in Figure 1C.³⁻¹ 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 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,\(^{23}\) 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, \(\text{OC}_6\text{H}_4\)) 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.\(^{1}\) NMR spectrum of 5 showed a set of signals corresponding to, on average, a \(T_2\) 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 \(\text{H}_3\text{imine}\) signals from \(\text{tris-imine}\) 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 \(\text{H}_r\) and \(\text{H}_t\) as well as \(\text{H}_t\) and \(\text{CH}_2\) from hexyl groups to corroborate the proximity of the two building blocks and \(\text{trans}\) 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 part of the honeycomb array (Figure 2B). Each capsule incorporates two molecules of TCE, holding onto southern and northern benzenes via C–Cl–…π halogen bonds (\(R = 3.334 \text{ Å} \text{ and } \alpha = 171.67^{\circ}\)).\(^{36}\) Benzaldehyde groups employ \(\text{C}_2\text{p}^2\)–\(\text{H}\) groups to form a seam of edge-to-face \(\text{C}_2\text{p}^2\text{H}–\pi\) hydrogen bonds at the capsule’s equator (\(d_{\text{C}–\text{Cl}} = 3.705-4.418 \text{ Å} \text{ and } \alpha = 112.41-143.59^{\circ}\), Figure 2B).\(^{37}\) With tetrachloroethane (108 Å) 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 Å)\(^{39}\). 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 \(\text{H}_c\) 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 plot\(^{41}\) 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 CBr₄ 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 CBr₄: these guests are nested inside basket cavities forming a C–Br···π halogen bond (R = 3.229 Å and α = 170.09°) with the benzene base and placing the remaining three bromides between the phthalimide sides. The unit cell has four [(CBr)₄CBC 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 porous with its channels providing access to basket cavities. The uptake of potential guests (i.e., gas molecules or compounds from a liquid phase) remains to be studied in the future.

![Figure 2](image.png)

Figure 2. (A) ¹H NMR spectra (850 MHz, CD₂Cl₂) 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 [C₃H₆Cl₂2] and [(C₃H₆Cl₂)₂2].
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 Hc (top) while the equilibrium concentration of [CBr]₄ 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.23,24 However, adding an excess of TFA to 5 caused its conversion into 2 and [4–H]3+ driven by favorable protonation of the tris-amine (Figure S19). On the contrary, subsequent addition of base (Et3N) resulted in deprotonation of [4–H]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.23,24 However, equilibrium 1 (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.25 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 5–6 process (equilibrium III, Figure 4C) favoring the latter. First, preorganized26 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).27 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, pKₐ = 0.8) was expected to disturb it by predominantly protonating aliphatic amine 7 (pKₐ = 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 (pKₐ = 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 CHBr₂CO₂− 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).\textsuperscript{15a}

\textit{1}H NMR spectrum of [1+1] capsule 6, tris-amines 4 and 7 along with TFA in CD\textsubscript{2}Cl\textsubscript{2} showed the presence of 6 and 4 while [7–H\textsubscript{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 tribro-moacetate, illustrated by the formation of CHBr\textsubscript{2}Cl\textsubscript{2} and CHBr\textsubscript{3}Cl showed the presence of 6 and 4 while [7–H\textsubscript{n+}][n] (n=1~3) stayed as a precipitate (Figure 5B).

Important, 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 tribromooacetate, illustrated by the formation of CHBr\textsubscript{3}Cl showed the presence of 6 and 4 while [7–H\textsubscript{n+}][n] (n=1~3) stayed as a precipitate (Figure 5B).

The long-term goal is to exploit the function-al characteristics of covalent cages for gas chromatography separations. Chem. Mater. 2015, 27, 3207-3210; (c) Zhang, G.; Hua, B.; Dey, A.; Ghosh, M.; Moosa, B. A.; Khashab, N. M., Intrinsi-cally Porous Molecular Materials (IPMs) for Natural Gas and Ben-zene Derivatives Separations. Acc. Chem. Res. 2021, 54, 155-168; (d) Zhang, J.-H.; Xie, S.-M.; Chen, L.; Wang, B.-J.; He, P.-G.; Yuan, L.-M., Homochiral Porous Organic Cage with High Selectivity for the Separation of Racemates in Gas Chromatography. Anal. Chem. 2015, 87, 7817-7824; (e) Chai, A.; Mouchaham, G.; Shkurenko, A.; Hong, P.; Moosa, B.; Bhatt, P. M.; Adil, K.; Salama, K. N.; Eddaoudi, M.; Khashab, N. M., Trianglamine-Based Supramolecular Organic Framework with Permanent Intrinsic Porosity and Tunable Selectivity. J. Am. Chem. Soc. 2018, 140, 14571-14575.

7. Brutschy, M.; Schneider, M. W.; Mastalerz, M.; Waldvogel, S. R., Porous Organic Cage Compounds as Highly Potent Affinity Materials for Sensing by Quartz Crystal Microbalances. Adv. Mater. 2012, 24, 6049-6052.

8. (a) Ono, K.; Iwasawa, N., Dynamic Behavior of Covalent Organic Cages. Chem. Eur. J. 2018, 24, 17856-17868; (b) Chen, Y.; Lei, Y.; Tong, L.; Li, H., Stabilization of Dynamic Covalent Architectures by Multivalence. Chem. Eur. J. 2021, Ahead of Print.

9. (a) Fujita, D.; Suzuki, K.; Sato, S.; Yagi-Utsumi, M.; Yamaguchi, Y.; Mizuno, N.; Kumasaka, T.; Takata, M.; Noda, M.; Uchiyama, S.; Kato, K.; Fujita, M., Protein encapsulation within synthetic molecular hosts. Nat. Commun. 2012, 3, 2093/1-2093/7; (b) Xu, D.; Warmuth, R., Edge-Directed Dynamic Covalent Synthesis of a Chiral Nanocube. J. Am. Chem. Soc. 2008, 130, 7520-7521; (c) Yang, X.; Sun, J.-K.; Kitto, M.; Pang, H.; Xu, Q., Encapsulating highly catalytic-

**ASSOCIATED CONTENT**

**Supporting Information**

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

**AUTHOR INFORMATION**

**Corresponding Author**

badjic.1@osu.edu

**ACKNOWLEDGMENT**

This work was supported with funds from the NSF under CHE-2002781. Generous computational resources from the OSC are gratefully acknowledged.

**REFERENCES**

1. Hasell, T.; Cooper, A. I., Porous organic cages: soluble, modular and molecular pores. Nat. Rev. Mater. 2016, 1, 16053.

2. Lauer, J. C.; Zhang, W.-S.; Rominger, F.; Schroeder, R. R.; Mastalerz, M., Shape-Persistent [4+4] Imine Cages with a Truncated Tetrahedral Geometry. Chem. Eur. J. 2018, 24, 1816-1820.

3. Mastalerz, M., Porous Shape-Persistent Organic Cage Compounds of Different Size, Geometry, and Function. Acc. Chem. Res. 2018, 51, 2411-2422.

4. Cooper, A. I., Porous Molecular Solids and Liquids. ACS Cent. Sci. 2017, 3, 544-553.

5. (a) Das, S.; Heasman, P.; Ben, T.; Qiu, S., Porous organic material strategic design and structure-function correlation. Chem. Rev. 2017, 117, 1515-1563; (b) Luo, J.; Wang, J.-W.; Zhang, J.-H.; Lai, S.; Zhong, D.-C., Hydrogen-bonded organic frameworks: design, structures and potential applications. CrystEngComm 2018, 20, 5884-5898; (c) Gropp, C.; Canossa, S.; Wuttke, S.; Gandara, F.; Li, Q.; Gagliardi, L.; Yaghi, O. M., Standard Practices of Reticular Chemistry. ACS Cent. Sci. 2020, 6, 1255-1273.

6. (a) Chen, L.; Reiss Paul, S.; Chong Samantha, Y.; Holden, D.; Jelfs Kim, E.; Hasell, T.; Little Mare, A.; Kewley, A.; Briggs Michael, E.; Stephenson, A.; Cooper Andrew, I.; Thomas, K. M.; Armstrong Jayne, A.; Bell, J.; Busto, J.; Noel, R.; Liu, J.; Strachan Denis, M.; Thallapally Praveen, K., Separation of rare gases and chiral mole-cules by selective binding in porous organic cages. Nat Mater 2014, 13, 954-60; (b) Kewley, A.; Stephenson, A.; Chen, L.; Briggs, M. E.; Hasell, T.; Cooper, A. I., Porous Organic Cages for Gas Chromatog-raphy Separations. Chem. Mater. 2015, 27, 3207-3210; (c) Zhang, G.; Hua, B.; Dey, A.; Ghosh, M.; Moosa, B. A.; Khashab, N. M., Intrinsi-cally Porous Molecular Materials (IPMs) for Natural Gas and Benzene Derivatives Separations. Acc. Chem. Res. 2021, 54, 155-168; (d) Zhang, J.-H.; Xie, S.-M.; Chen, L.; Wang, B.-J.; He, P.-G.; Yuan, L.-M., Homochiral Porous Organic Cage with High Selectivity for the Separation of Racemates in Gas Chromatography. Anal. Chem. 2015, 87, 7817-7824; (e) Chai, A.; Mouchaham, G.; Shkurenko, A.; Hong, P.; Moosa, B.; Bhatt, P. M.; Adil, K.; Salama, K. N.; Eddaoudi, M.; Khashab, N. M., Trianglamine-Based Supramolecular Organic Framework with Permanent Intrinsic Porosity and Tunable Selectivity. J. Am. Chem. Soc. 2018, 140, 14571-14575.

7. Brutschy, M.; Schneider, M. W.; Mastalerz, M.; Waldvogel, S. R., Porous Organic Cage Compounds as Highly Potent Affinity Materials for Sensing by Quartz Crystal Microbalances. Adv. Mater. 2012, 24, 6049-6052.

8. (a) Ono, K.; Iwasawa, N., Dynamic Behavior of Covalent Organic Cages. Chem. Eur. J. 2018, 24, 17856-17868; (b) Chen, Y.; Lei, Y.; Tong, L.; Li, H., Stabilization of Dynamic Covalent Architectures by Multivalence. Chem. Eur. J. 2021, Ahead of Print.

9. (a) Fujita, D.; Suzuki, K.; Sato, S.; Yagi-Utsumi, M.; Yamaguchi, Y.; Mizuno, N.; Kumasaka, T.; Takata, M.; Noda, M.; Uchiyama, S.; Kato, K.; Fujita, M., Protein encapsulation within synthetic molecular hosts. Nat. Commun. 2012, 3, 2093/1-2093/7; (b) Xu, D.; Warmuth, R., Edge-Directed Dynamic Covalent Synthesis of a Chiral Nanocube. J. Am. Chem. Soc. 2008, 130, 7520-7521; (c) Yang, X.; Sun, J.-K.; Kitto, M.; Pang, H.; Xu, Q., Encapsulating highly catalytic-
cally active metal nanoclusters inside porous organic cages. *Nat. Catal.* **2018**, *1*, 214-220; (d) Hasell, T.; Schmidtmann, M.; Cooper, A. I., Molecular Doping of Porous Organic Cages. *J. Am. Chem. Soc.* **2011**, *133*, 14920-14923.

10. Whitesides, G. M.; Grzybowski, B., Self-assembly at all scales. *Science* **2002**, *295*, 2418-2421.

11. De, S.; Klajn, R., Dissipative Self-Assembly Driven by the Consumption of Chemical Fuels. *Adv. Mater.* **2018**, *30*, 1706750.

12. Hayer-Hartl, M.; Bracher, A.; Hartl, F. U., The GroEL-GroES Chaperonin Machine: A Nano-Cage for Protein Folding. *Trends Biochem. Sci.* **2016**, *41*, 62-76.

13. (a) Riess, B.; Groetsch, R. K.; Boekhoven, J., The Design of Dissipative Molecular Assembly Drives by Chemical Reaction Cycles. *Chem. 2020*, *6*, 552-578; (b) Das, K.; Gabrielli, L.; Prins, L. J., Chemically Fueled Self-Assembly in Biology and Chemistry. *Angew. Chem., Int. Ed.* **2021**, *60*, 20120-20143; (c) Podolsky, K. A.; Devaraj, N. K., Synthesis of lipid membranes for artificial cells. *Nat. Rev. Chem.* **2021**, *5*, 676-694.

14. (a) Amano, S.; Fielden, S. D. P.; Leigh, D. A., A catalysis-driven artificial molecular pump. *Nature* **2021**, *594*, 529-534; (b) Kriebisch, C. M. E.; Bergmann, A. M.; Boekhoven, J., Fuel-Driven Dynamic Combinatorial Libraries. *J. Am. Chem. Soc.* **2021**, *143*, 7719-7725; (c) Olivieri, E.; Quintard, G.; Naubron, J.-V.; Quintard, A., Chemically Fueled Three-State Chiropotical Switching Supramolecular Gel with Temporal Control. *J. Am. Chem. Soc.* **2021**, *143*, 12650-12657; (d) Ouyang, Y.; Zhang, P.; Manis-Levy, H.; Palitiec, Y.; Willner, I., Transient Dissipative Optical Properties of Aggregated Au Nanoparticles, CdSe/ZnS Quantum Dots, and Supramolecular Nucleic Acid-Stabilized Ag Nanoclusters. *J. Am. Chem. Soc.* **2021**, *143*, 17622-17632; (e) Rizzuto, F. J.; Platnich, C. M.; Luo, X.; Shen, Y.; Dore, M. D.; Lachance-Brais, C.; Guarne, A.; Cosa, G.; Sleiman, H. F., A dissipative pathway for the structural evolution of DNA fibres. *Nat. Chem.* **2021**, *13*, 843-849.

15. (a) Amano, S.; Borsley, S.; Leigh, D. A.; Sun, Z., Chemical engine driving systems away from equilibrium through catalyst reaction cycles. *Nat. Nanotechnol.* **2021**, *16*, 1057-1067; (b) Kariyawasam, L. S.; Hollmann, M. H.; Hartley, C. S., The Transient Covalent Bond in Abiotic Nonequilibrium Systems. *Angew. Chem., Int. Ed.* **2021**, *60*, 12648-12658.

16. Maiti, S.; Fortunati, I.; Ferrante, C.; Scrimin, P.; Prins, L. J., Dissipative self-assembly of vesicular nanoreactors. *Nat. Chem.* **2021**, *13*, 725-731.

17. Riess, B.; Boekhoven, J., Applications of Dissipative Supramolecular Materials with a Tunable Lifetime. *ChemNanoMat* **2018**, *4*, 710-719.

18. Wood, C. S.; Browne, C.; Wood, D. M.; Nitschke, J. R., Fuel-Controlled Reassembly of Metal-Organic Architectures. *ACS Cent. Sci.* **2015**, *1*, 504-509.

19. Ragazzon, G.; Prins, L. J., Energy consumption in chemical fuel-driven self-assembly. *Nat. Nanotechnol.* **2018**, *13*, 882-889.

20. Moneypenny, T. P.; Yang, A.; Walter, N. P.; Woods, T. J.; Gray, D. L.; Zhang, Y.; Moore, J. S.; Fatelnik, M. J.; Munoz, E.; Moore, C. E.; Hadad, C. M.; Badjic, J. D., On the encapsulation and assembly of anticancer drugs in a cooperative fashion. *J. Am. Chem. Soc.* **2019**, *141*, 12380-12384.

21. Chen, S.; Wang, L.; Polen, S. M.; Badjic, J. D., Gating the Trafficking of Molecules across Vesicular Membrane Composed of Dual-Cavity Basket. *Chem. Mater.* **2016**, *28*, 8128-8131.

22. Wang, W.; Wang, H.; Zhiquan, L.; Xie, H.; Cui, H.; Badjic, J. D., On the encapsulation and assembly of anticancer drugs in a cooperative fashion. *Chem. Sci.* **2019**, *10*, 5678-5685.

23. Ro, S.; Rowan, S. J.; Pease, A. R.; Cran, D. J.; Stoddart, J. F., Dynamic Hemicarcerands and Hemicarceplexes. *Org. Lett.* **2000**, *2*, 2411-2414.

24. Ang, S. J.; Mak, A. M.; Sullivan, M. B.; Wong, M. W., Site specificity of halogen bonding involving aromatic acceptors. *Phys. Chem. Chem. Phys.* **2018**, *20*, 8685-8694.

25. Nishio, M.; Umezawa, Y.; Fantini, J.; Weiss, M. S.; Chakrabarti, P., CH–X hydrogen bonds in biological macromolecules. *Phys. Chem. Chem. Phys.* **2014**, *16*, 12648-12683.

26. Rieth, S.; Hermann, K.; Wang, B.-Y.; Badjic, J. D., Controlling the dynamics of molecular encapsulation and gating. *Chem. Soc. Rev.* **2011**, *40*, 1609-1622.

27. Wang, B.-Y.; Bao, X.; Stojanovic, S.; Hadad, C. M.; Badjic, J. D., Encapsulation of Guests within a Gated Molecular Basket: Thermodynamics and Selectivity. *Org. Lett.* **2008**, *10*, 5361-5364.

28. Wang, W.; Finnegan, T. J.; Lei, Z.; Zhu, X.; Moore, C. E.; Shi, K.; Badjic, J. D., Tuning the allosteric sequestration of anticancer drugs for developing cooperative nano-antidotes. *Chem. Commun.* **2020**, *56*, 1271-1274.

29. Ercolani, G., Assessment of Cooperativity in Self-Assembly. *J. Am. Chem. Soc.* **2003**, *125*, 16097-16103.

30. Chen, S.; Yamasaki, M.; Polen, S.; Gallucci, J.; Hadad, C. M.; Badjic, J. D., Dual-Cavity Basket Promotes Encapsulation in Water in an AllostERIC Fashion. *J. Am. Chem. Soc.* **2015**, *137*, 12276-12281.

31. Jie, K.; Zhou, Y.; Li, E.; Li, Z.; Zhao, R.; Huang, F., Reversible iodine capture by nonporous pillar[6]arene crystals. *J. Am. Chem. Soc.* **2017**, *139*, 15320-15323; (b) Zigon, N.; Duplan, V.; Wa dean, N.; Fujita, M., Crystalline Sponge Method: X-ray Structure Analysis of Small Molecules by Post-Orientation within Porous Crystals-Principle and Proof-of-Concept Studies. *Angew. Chem., Int. Ed.* **2021**, *60*, 25204-25222.
(a) Choi, S.; Mukhopadhyay, R. D.; Kim, Y.; Hwang, I.-C.; Hwang, W.; Ghosh, S. K.; Baek, K.; Kim, K., Fuel-Driven Transient Crystallization of a Cucurbit[8]uril-Based Host-Guest Complex. Angew. Chem., Int. Ed. 2019, 58, 16850-16853; (b) Abe, Y.; Okamura, H.; Nakazono, K.; Koyama, Y.; Uchida, S.; Takata, T., Thermoresponsive Shuttling of Rotaxane Containing Trichloroacetate Ion. Org. Lett. 2012, 14, 4122-4125; (c) Biagini, C.; Fielden, S. D. P.; Leigh, D. A.; Schaufelberger, F.; Di Stefano, S.; Thomas, D., Dissipative Catalysis with a Molecular Machine. Angew. Chem., Int. Ed. 2019, 58, 9876-9880; (d) Biagini, C.; Di Stefano, S., Abiotic Chemical Fuels for the Operation of Molecular Machines. Angew. Chem., Int. Ed. 2020, 59, 8344-8354.

45. Weissenfels, M.; Gemen, J.; Klajn, R., Dissipative Self-Assembly: Fueling with Chemicals versus Light. Chem 2021, 7, 23-37.

46. (a) Xie, H.; Finnegan, T. J.; Liyana Gunawardana, V. W.; Pavlovic, R. Z.; Moore, C. E.; Badjic, J. D., A Hexapodal Capsule for the Recognition of Anions. J. Am. Chem. Soc. 2021, 143, 3874-3880; (b) Hennrich, G.; Anslyn, E. V., 1,3,5-2,4,6-functionalized, facially segregated benzenes - exploitation of sterically predisposed systems in supramolecular chemistry. Chem. - Eur. J. 2002, 8, 2218-2224.

47. (a) Tromans, R. A.; Carter, T. S.; Chabanne, L.; Crump, M. P.; Li, H.; Matlock, J. V.; Orchard, M. G.; Davis, A. P., A biomimetic receptor for glucose. Nat. Chem. 2019, 11, 52-56; (b) Oh, J. H.; Kim, J. H.; Kim, D. S.; Han, H. J.; Lynch, V. M.; Sessler, J. L.; Kim, S. K., Synthesis and Anion Recognition Features of a Molecular Cage Containing Both Hydrogen Bond Donors and Acceptors. Org. Lett. 2019, 21, 4336-4339.

48. Mattia, E.; Otto, S., Supramolecular systems chemistry. Nat. Nanotechnol. 2015, 10, 111-119.

49. Catti, L.; Zhang, Q.; Tiefenbacher, K., Advantages of Catalysis in Self-Assembled Molecular Capsules. Chemistry 2016, 22, 9060-6.

50. Pavlovic, R. Z.; Border, S. E.; Li, Y.; Li, X.; Badjic, J. D., Photoinduced interruption of interannular cooperativity for delivery of cationic guests in water. Chem. Commun. 2020, 56, 2987-2990.

51. Merindol, R.; Walther, A., Materials learning from life: concepts for active, adaptive and autonomous molecular systems. Chem. Soc. Rev. 2017, 46, 5588-5619.

52. Pantaloni, D.; Le Clainche, C.; Carlier, M.-F., Mechanism of actin-based motility. Science 2001, 292, 1502-1506.

53. (a) Forgac, M., Vacuolar ATPases: rotary proton pumps in physiology and pathophysiology. Nat. Rev. Mol. Cell Biol. 2007, 8, 917-929; (b) Stewart, A. G.; Laming, E. M.; Sobti, M.; Stock, D., Rotary ATPases - dynamic molecular machines. Curr. Opin. Struct. Biol. 2014, 25, 40-48.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformation.pdf
- BadjicVagSmallCageCheckCIF.pdf
- BadjicVagAldehydeCheckCIF.pdf
- BadjicVagLrgCageCheckCIF.pdf
- BadjicVagSmallCage.cif
- BadjicVagAldehyde.cif
- BadjicVagLrgCage.cif