

Kinetically Trapped Tetrahedral Cages via Alkyne Metathesis

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S Supporting Information

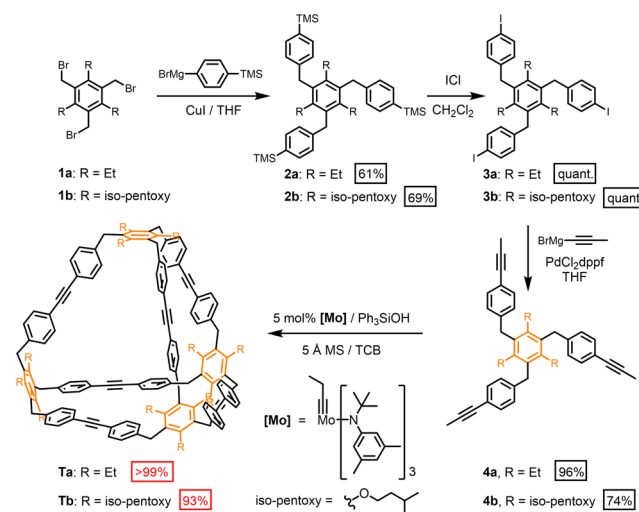
ABSTRACT: In dynamic covalent synthesis, kinetic traps are perceived as disadvantageous, hindering the system from reaching its thermodynamic equilibrium. Here we present the near-quantitative preparation of tetrahedral cages from simple tritopic precursors using alkyne metathesis. While the cages are the presumed thermodynamic sink, we experimentally demonstrate that the products no longer exchange their vertices once they have formed. The example reported here illustrates that kinetically trapped products may facilitate high yields of complex products from dynamic covalent synthesis.

Dynamic covalent chemistry (DCC)^{1,2} is a powerful strategy for synthesizing shape-persistent molecular architectures such as macrocycles,^{3,4} cages,^{5,6} and covalent organic frameworks.^{7–9} The common view of successful DCC syntheses is that they proceed reversibly, ultimately allowing for “error correction” and convergence toward thermodynamic products. Kinetic aspects of DCC are often overlooked, however, as only in a few cases have kinetically trapped intermediates been identified to hinder the reaction pathway.¹⁰ For instance, Moore et al. synthesized imine condensation-based ladders that become kinetically trapped beyond formation of four imine rungs.¹⁰ The higher rung ladders formed misaligned byproducts that were trapped, preventing perfect rung registry expected for the thermodynamic product. Thus, only when the reaction proceeds through a kinetically viable pathway, a pathway which does not fall in a kinetic trap, can the thermodynamic product form in appreciable yields.

Although kinetic traps are generally considered as encumbrances, in some cases, they may yield useful outcomes. Sanders et al. prepared hydrazone-based macrocycles that become trapped in a dynamic combinatorial system.¹¹ The irreversible nature of this macrocycle provided the stability for its usage as an anion receptor. In addition, they synthesized a trefoil knot architecture using dynamic disulfide chemistry and found that it was both thermodynamically and kinetically favored.¹² Otto et al. created a system which disulfide-based six-membered macrocycles become trapped while self-assembling into tubular stacks.¹³ Beuerle and Klotzbach prepared various boronic ester-based cage complexes and identified two that were kinetically trapped.¹⁴ Here, we present high-yield syntheses of organic tetrahedral cages (Scheme 1), which become kinetically trapped after the exchange of six alkynyl bonds during alkyne metathesis.

While the vast majority of organic cage syntheses have been achieved using disulfide,^{15,16} imine,^{17,18} and boronic ester^{19,20}

Scheme 1. Syntheses of Tetrahedral Cages Ta and Tb^a



^aCentral phenylene groups forming the vertices are colored in orange for clarity. TCB: 1,2,4-trichlorobenzene.

formations and alkyne metathesis,^{21,22} only a handful of studies have been reported using alkyne metathesis.^{23,24} Pioneering research by Zhang et al. has shown that alkyne metathesis serves as a reaction well-suited for preparing shape-persistent cages. They were able to synthesize porphyrin-based cages,²⁵ D_{2h} symmetric cages²⁶ and interlocked cages²⁷ in moderate to high yields. Yet, the use of alkyne metathesis is in its infancy compared to other DCC systems.

Previously, Zhang et al. attempted to synthesize tetrahedral cages using tritopic precursors.²⁶ However, they found that their precursors rapidly formed macrocyclic dimers, which directed the reaction pathway toward the formation of D_{2h} -symmetric cages. In order to bias the pathway away from dimer formation, we utilized a 1,3,5-tribenzyl-2,4,6-triethylbenzene derivative, **4a** (Scheme 1). The well-defined angles and alternating up–down conformation direct preorganization into a bowl-shaped structure^{28–31} (see X-ray crystal structure of **3a** in Figure S24). Based on results from conformational modeling calculations, the trialkoxy derivative, **4b**, was chosen as a more dynamic and less well-defined bowl-shaped vertex (Figure S21) designed to test the importance of “tight” vs “loose” preorganization.

Received: January 13, 2016

Published: February 8, 2016

The synthesis started from a copper(I)-catalyzed coupling reaction²⁹ to convert tribromomethyl compound **1a** to a tribenzylic compound **2a** (Scheme 1). The trimethylsilyl groups were converted to the corresponding iodide using ICl to furnish triiodo compound **3a** in quantitative yields. Kumada coupling³² between **3a** and 1-propynylmagnesium bromide yielded **4a**. Precursor **4b** was prepared using identical procedures as **4a** starting from compound **1b**. Alkyne metathesis of precursors **4a** and **4b** (10 mM) was performed at 70 °C for overnight using an active molybdenum catalyst, preformed by mixing 5 mol % of a molybdenum(VI) propylidyne precatalyst, [Mo],^{33,34} and excess triphenylsilanol ligand (30 mol %).³⁵ Molecular sieves (5 Å, 800 mg/mmol of propynyl groups) were used to capture the 2-butyne byproducts.^{35,36} To our delight, alkyne metathesis resulted in tetrahedral cages **Ta** (>99%) and **Tb** (93%) in high yields. ¹H NMR spectra (Figures S7 and S19) showed two aromatic doublets, indicating the highly symmetric structure of the product. Contrary to our original hypothesis, the level of preorganization within precursors **4a** and **4b** had only minor effects on the cage yields under the conditions that were used.

Tetrahedral cage **Ta** crystallized in a tetragonal space group, $I4_1/a$, (Figure 1b) from a mixture of chloroform and toluene.

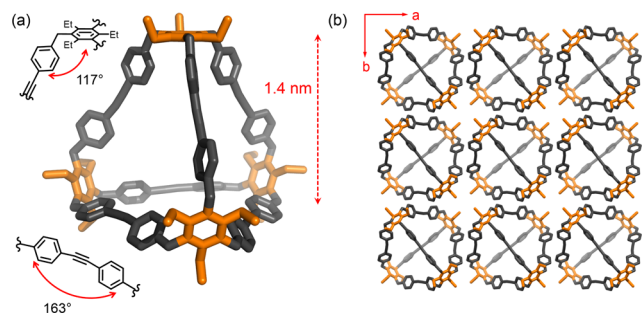


Figure 1. (a) X-ray crystal structure of **Ta** and its (b) packing structure viewed along the *c*-axis. Hydrogen atoms, disordered solvent molecules, and disordered phenylene groups were omitted for clarity.

Due to the disordered solvent molecules and lack of heavy atoms, the crystal diffracted weakly. A synchrotron light source was required to obtain reasonable diffraction data for analysis. The X-ray crystal structure unambiguously showed the tetrahedral geometry of cage **Ta** (Figure 1a). The angle between the benzylic edges and the central benzene moiety on the vertices was found to be 117.3° on average (Figure 1a), which did not deviate much from the X-ray crystal structure of a tritopic precursor **3a** (117.8° on average, Figure S24). However, this angle was smaller compared to the ideal 125.2° angle for a perfect tetrahedron. As a result, the six diphenylene-acetylene groups on the edges are bent toward the central cavity with an average angle of 163°. The size of the cavity is 1.4 nm in height. Thus far, no host–guest complexes have resulted from a screen of potential guest molecules with similar sizes (e.g., C₆₀, PMo₁₂O₄₀³⁻, Ph₄B⁻, Ph₄P⁺).

Alkyne metathesis is driven under thermodynamic control and normally gives high yields in macrocycle synthesis.^{37–39} However, the near-quantitative yields for cages **Ta** and **Tb** were not originally anticipated.^{25–27} We hypothesized that such high yields may have originated from the thermodynamic stability of the products as well as kinetic trapping. In order to test this hypothesis, dynamic scrambling experiments were performed (Figure 2). A mixture of equimolar amounts of **Ta** and **Tb** was subjected to alkyne metathesis (Figure 2a) in higher

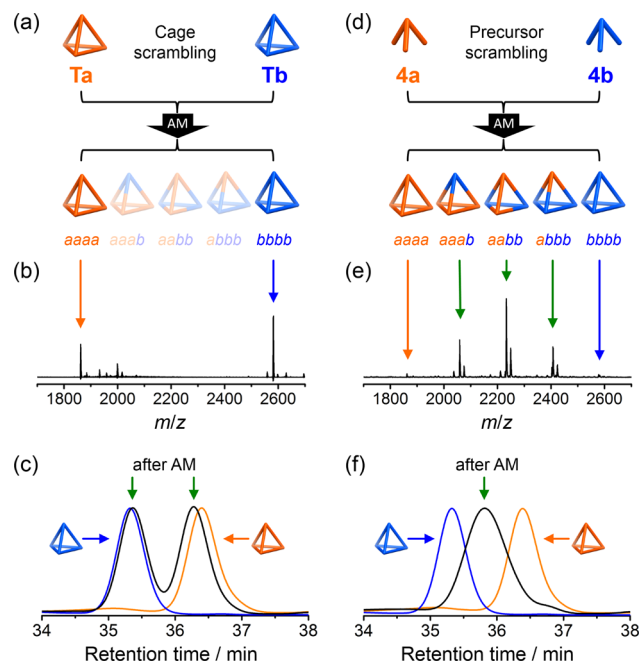


Figure 2. Scrambling experiments. (a) Cage scrambling experiment and its (b) MALDI spectrum and (c) GPC trace. (d) Precursor scrambling experiment and its (e) MALDI spectrum and (f) GPC trace. AM: alkyne metathesis.

concentrations ($\times 4$) and larger catalyst loading ($\times 4$) compared to the individual cage syntheses (Table S1). The non-scrambled cages **Ta** (aaaa) and **Tb** (bbbb) were recovered in quantitative yields after the reaction. ¹H NMR (Figure S22), MALDI spectra (Figures 2b and S23), and GPC traces (Figure 2c) all consistently showed no evidence of the scrambled cages (aaab, aabb, abbb). To eliminate the possibility of narcissistic self-sorting of cages **Ta** and **Tb**, a mixture of equimolar amounts of **4a** and **4b** was subjected to alkyne metathesis (Figure 2d). The resulting MALDI spectrum (Figure 2e) clearly showed the formation of all five possible cages. The GPC trace (Figure 2f) exhibited a new peak with a retention time in between that of **Ta** and **Tb**. These results show that precursors **4a** and **4b** do not self-sort. Hence, the tetrahedral cages, regardless of their compositions, are kinetically trapped once they are formed under these reaction conditions.

Kinetic trapping of the tetrahedral cages can be rationalized by effective molarity. In a situation where a single alkynyl bond of the tetrahedral cage is opened up, it would still have five alkynyl bonds that lock the four vertices in a tetrahedral geometry. This preorganized intermediate would provide a high effective molarity allowing it to rapidly close again before another alkynyl bond opens up. Sanders et al. have observed a similar kinetic trapping phenomenon in their organic trefoil knot.¹² Cleavage of a single disulfide bond in a trefoil knot would result in an oligomeric intermediate that retains the folded structure of the knot through hydrophobic effects. Therefore, the ring closure would be faster than unfolding the entire structure.

There are two possible explanations regarding the thermodynamics of the tetrahedral cages. First, the cages are thermodynamically very stable and thereby create large kinetic barriers preventing them from breaking apart. Second, the actual thermodynamic product has not been reached^{14,40–42} due to the kinetic trapping in the tetrahedral intermediate stage.

However, we were not able to model any other cage compounds with appreciable stability compared to the tetrahedron, and no other cage complexes have been observed in the reaction time scale of alkyne metathesis. Thus, the first explanation is more plausible based on the experimental results at hand. The energy landscape picture that emerges for this example is that of the Levinthal “golf-course” landscape,⁴³ where the starting precursor is located only a few short steps from the “hole”. The flat playing surface enables rapid exploration of intermediate and undesirable constitutions that, through random exchange and ring closure, find their way to a deep, monotonic energy well which siphons off the desired product once it forms.

In conclusion, we synthesized tetrahedral cages in high yields; the high yields realized in part because the desired product becomes kinetically trapped under the reaction conditions. This also marks the first platonic solid that has been prepared via alkyne metathesis to date. We are currently investigating the precursor design parameters (e.g., angles, degree of preorganization) that affect the formation of kinetic traps. In addition, strategies to escape from kinetic traps, allowing the system to return to thermodynamic control, are being investigated.⁴⁴ We envision that these tetrahedral cages will provide a simple platform to systematically study kinetic aspects of cage formations in alkyne metathesis and help guide the way toward more complex polyhedral cages.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00468.

Synthetic procedures and characterization including ¹H NMR, ¹³C NMR, mass spectroscopic data (PDF)

X-ray crystallographic data (CIF, 3a, CCDC 1452250)

X-ray crystallographic data (CIF, Ta, CCDC 1452245)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.L. thanks the Beckman Postdoctoral Fellows Program for their financial support. The authors thank Dr. Danielle Gray and Dr. Jeffrey Bertke for single crystal X-ray diffraction experiments. This work was supported by the NSF CHE 1300313 grant. Crystallographic data of Ta was collected through the SCrALS (Service Crystallography at the Advanced Light Source) program at Beamline 11.3.1 at the Advanced Light Source (ALS), Lawrence Berkeley National Laboratory. The Advanced Light Source is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under contract no. DE-AC02-05CH11231.

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