Dynamic Covalent Assembly

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Solution-Phase Dynamic Assembly of Permanently Interlocked Aryleneethynylene Cages through Alkyne Metathesis**

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Abstract: *Highly stable permanently interlocked aryleneethynylene molecular cages were synthesized from simple triyne monomers using dynamic alkyne metathesis. The interlocked complexes are predominantly formed in the reaction solution in the absence of any recognition motif and were isolated in a pure form using column chromatography. This study is the first example of the thermodynamically controlled solution-phase synthesis of interlocked organic cages with high stability.*

Interlocked molecular architectures represent a particularly appealing topology whose molecular self-assembly poses a great synthetic challenge.[1,2] These mechanically bonded molecules exhibit intriguing properties, such as the presence of multiple stable conformations and the combination of both robustness and a greatly enhanced flexibility.[3,4] These unique properties of interlocked assemblies could provide an entirely new class of materials and open up new fields of research in fundamental science as well as in modern nanotechnology.[5] Most interlocked assemblies have been prepared through template-assisted interlocking of multiple rings.[6–8] However, very few examples of interlocked molecular cages have been reported. The first assembly of interlocked cages was reported by Fujita et al. in 1999.[9] Triply interlocked metal–organic dimeric cages were formed as the predominant product in the absence of template or a strong directing effect. Later, metal-coordination-based interlocked cages with various topologies were reported by Kuroda et al.,[10] Hardie et al.,[11] and Clever and co-workers.[12,13] Purely organic interlocked cages are even rarer. The first example of such a complex was reported by Cooper et al. through dynamic imine reactions,[14] with a subsequent example by Mastalerz and co-workers employing boronic acid condensation reactions.[15] In both cases, a kinetically interrupted thermodynamic approach was employed, in which the interlocked species were precipitated as crystals and irreversibly removed from the dynamic system.[16,17] These interlocked complexes have limited stability in solution, undergoing decomposition over time, because of the labile imine or B–O bonds. For example, the boronic-ester-linked interlocked cage only exists in crystalline form and rapidly disassembles in solution to form monomeric cages.[15] Herein, we report the first example of permanently interlocked aryleneethynylene cages which are assembled in solution through a thermodynamic process involving alkyne metathesis. The interlocked dimers **2a**/**2b** are formed preferably over the independent dimer **1a**/**1b** at equilibrium (Figure 1). The advantage of interlocked aryleneethynylene cages is their superior stability provided by the robust ethynylene linkages, whose disconnection and formation generally require the use of a catalyst.

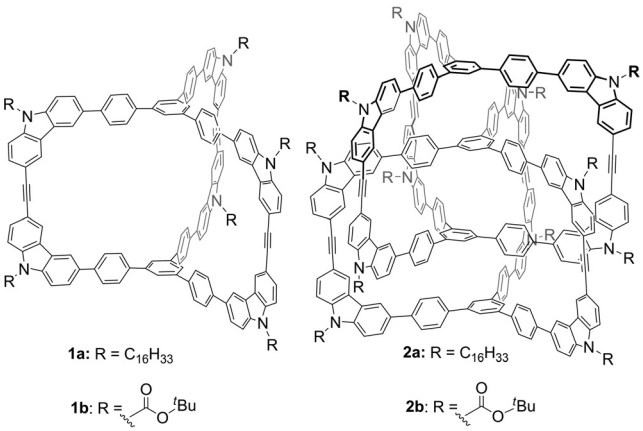

Figure 1. Structures of independent dimers **1a**/**1b** and interlocked dimers **2a**/**2b**.

Self-reacting tritopic building blocks **7a**/**7b** with C_3 symmetry were designed and synthesized as monomers (Scheme 1). Starting from readily available diiodocarbazoles **3a** and **3b**, Sonogashira cross-coupling reactions with (benzoyldiphenyl)acetylene yielded mono-substituted iodocarbazoles **4a** and **4b**. The compound **4b** was then directly coupled with pinacol boronic ester **6b** to form building block **7b**. Alternatively, the iodo group of **4a** was converted into pinacol borate to form **5a**, which underwent Suzuki–Miyaura coupling with 1,3,5-tris(4-bromophenyl)benzene to yield compound **7a**.

As alkyne metathesis is a dynamic equilibrium reaction,[18–24] continuous removal of one of the alkyne products is important to drive the equilibrium toward product formation.

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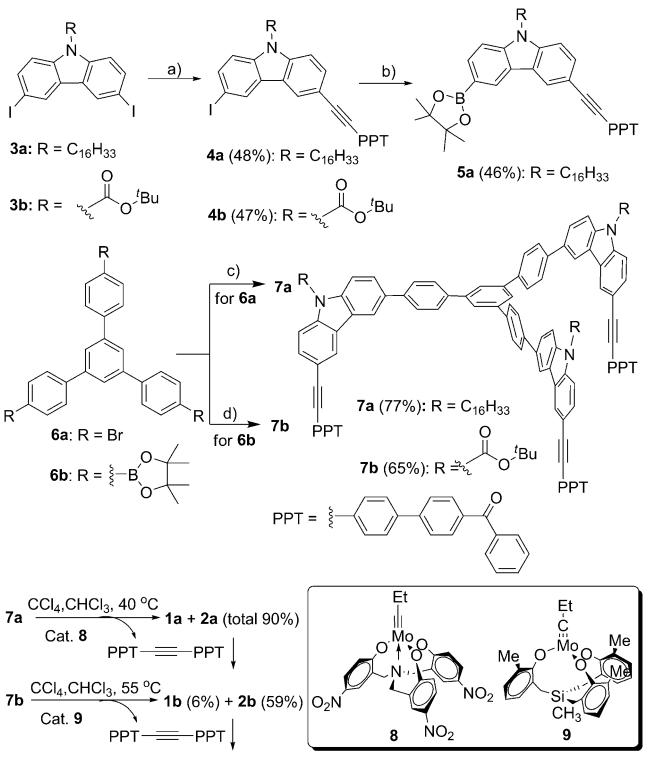

Scheme 1. Synthesis of interlocked complexes: a) PPT–C≡C–H, [Pd(PPh$_3$)$_2$Cl$_2$], CuI, THF, piperidine, RT; b) Pinacolborane, [Pd(PPh$_3$)$_2$Cl$_2$], triethylamine (TEA), toluene, reflux; c) **5a**, [Pd(PPh$_3$)$_4$], Na$_2$CO$_3$, toluene–EtOH–H$_2$O (v/v/v, 25:3:3), 90 °C; d) **4b**, [Pd(PPh$_3$)$_4$], Na$_2$CO$_3$, toluene–EtOH–H$_2$O (v/v/v, 25:3:3), 90 °C.

Methyl-substituted alkynes are generally preferred substrates because they are synthetically facile to use and the 2-butyne byproduct can be easily removed under vacuum or using molecular sieves as scavengers.[25–28] However, in our study, we used benzoylbiphenyl-substituted alkynes **7a**/**7b** as the substrates to drive the equilibrium by precipitation of bis(benzoylbiphenyl)acetylene (PPT–C≡C–PPT).[29,30] We had difficulty in separating tris-propyne-substituted monomers from di-, or mono-substituted products. The installation of benzoylbiphenyl substituents facilitates the purification of the monomers by increasing their polarity.[31]

Next, we explored the covalent assembly of the monomer **7a**/**7b** through reversible alkyne metathesis. The metathesis of **7a**/**7b** was performed in CCl$_4$/CHCl$_3$ at slightly elevated temperature (40–55 °C). A high-activity multidentate molybdenum carbyne complex (**8** or **9**, Scheme 1) was used as the catalyst.[26,32] Upon the addition of the catalysts, precipitation of the metathesis byproduct bis(benzoylbiphenyl)acetylene occurs. After stirring overnight, the precipitates were filtered off and the crude product left in solution was analyzed by MALDI-TOF mass spectrometry. We were intrigued to detect mass signals corresponding to two, four, six, and eight monomer units, with the species containing four monomer units (**2a**/**2b**) being predominant. We were able to isolate the relatively major products **1b** (6%) and **2b** (59%), where R = *tert*-butoxycarbonyl (^{t}Boc), in pure form using flash column chromatography. Although a small amount of pure **1a** and **2a** (R = C$_{16}$H$_{33}$) were isolated, the majority of the product was obtained as a mixture (90% combined yield). An accurate assessment of the relative product ratios was difficult as a result of their very similar polarities.

We found that an electron-withdrawing substituent (such as a *tert*-butyl ester group) on the monomer significantly slowed down the metathesis reaction. Although monomer **7a** substituted with alkyl group successfully formed **1a** and **2a** under catalysis by **8**, ^{t}Boc-protected monomer **7b** only yielded oligomers with a broad molecular weight distribution under the same conditions. The predominant formation of products **1b** and **2b** was achieved using the triphenolsilane-based complex **9** (Scheme 1) which had a slightly higher catalytic activity than **8**.[26] These results suggest that the success of dynamic covalent assembly is predicated on the ability of catalysts to rapidly reach the point of equilibrium.

The assignment of complexes **1a**/**1b** consisting of two monomer units was straightforward. Based on their simple ^{1}H NMR spectra (see the Supporting Information, Figures S4 and S5), which indicate high structural symmetry, the compounds were assigned as the C_3-symmetric dimers **1a**/**1b**. In contrast to the sharp resonance signals of protons on dimers **1a**/**1b**, the ^{1}H NMR spectra of the species containing four monomer units are quite broad and complicated (Figure S8). Similar line broadening and signal complication were observed previously by Cooper et al. when a monomeric imine-linked cage was converted into triply interlocked complexes.[14] Generally, the interlocked complexes lose the original symmetry of the monomeric cage upon catenation, leading to the complication of their proton resonance signals. Based on the literature precedent and careful inspection, we assigned **2a**/**2b** as the interlocked dimer complexes. Conformational heterogeneity was then expected for such mechanically connected complexes. Indeed, at low temperature, we detected much sharper and well resolved signals in the ^{1}H NMR spectra of **2a**/**2b**, whereas the coalescence of multiple peaks was detected at higher temperature (Figure S9). This indicates that the conformational exchange occurs within the NMR timescale and causes the broadening and complexity of NMR resonance signals. The hydrodynamic radii of **2b** and **1b** ($r_{1b}/r_{2b} = 0.72$), estimated through a diffusion-ordered NMR spectroscopic experiment (DOSY), also agree well with the expected size difference between a dimer and an interlocked complex. Gel permeation chromatography (GPC) traces of **1b** and **2b** show a sharp single peak with retention volumes of 16.25 mL and 16.55 mL, respectively, indicating a larger size of **2b** compared to the cage **1b** (Figure 2a). Additionally, the possible presence of higher-order interlocked complexes containing three or four molecules of the dimer **1b** in the MALDI-TOF mass spectra of the crude product mixture (Figure 2b) also supports the formation of interlocked dimers.

Our structure assignment was further substantiated by the subsequent decatenation experiments in which the interlocked complexes are broken down to release independent dimer cages. Upon cleavage of alkyne bonds in **2b** through ruthenium- or iron-catalyzed oxidation (RuO$_2$/oxone or FeCl$_3$/H$_2$O$_2$), we detected the appearance of signals corre-

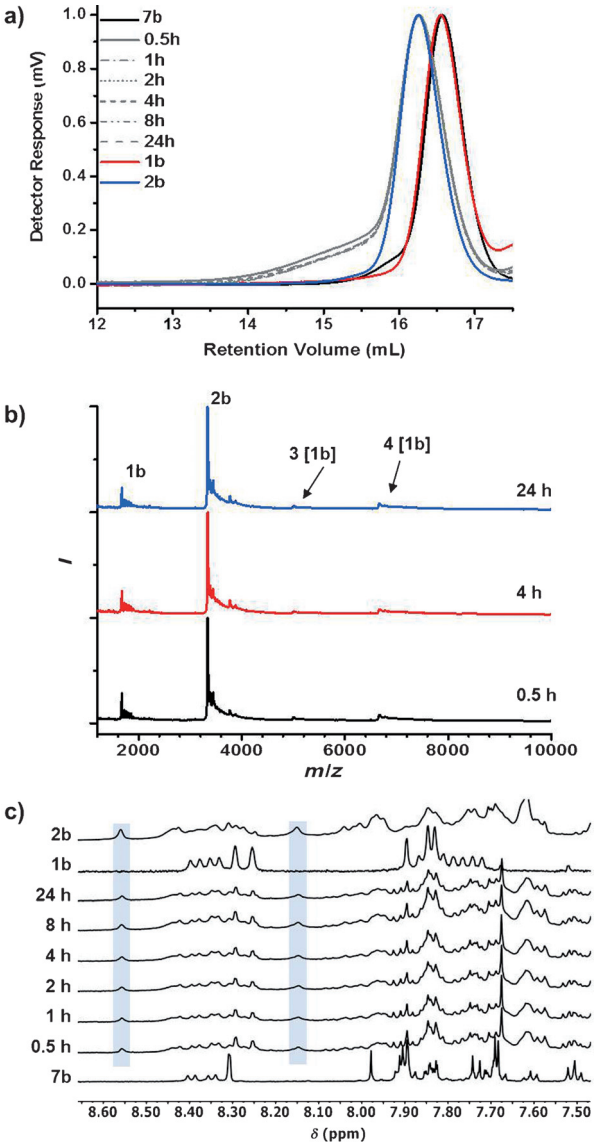

Figure 2. Reaction progress for the formation of interlocked complex **2b** monitored by a) GPC, b) MALDI-TOF mass spectrometry, and c) ^{1}H NMR spectroscopy. Complete cleavage of the Boc groups occurs during MALDI-TOF analysis.

sponding to the free dimer **1b** in the MALDI-MS traces of the crude reaction mixture (Figure S1). This observation confirms our assignment that the product **2b** is an interlocked complex and rules out the possibility of the formation of a single large tetrameric covalent cage.

To gain some insight into the formation of interlocked cage complexes, we monitored the progress of the reaction for the formation of **2b**. Aliquots of the reaction mixture (monomer concentration = 3 mM) taken after 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h were analyzed by GPC, MALDI mass spectroscopy, and ^{1}H NMR spectroscopy (Figure 2). Our study shows that the monomer was consumed and the interlocked complex **2b** was predominantly formed within 30 min. No obvious conversion of dimers into interlocked complexes was found afterwards during a 24 h time period. This result indicates that equilibrium has been reached and the product distribution reflects the relative thermodynamic stabilities of the equilibrium compositions. Although the formation of dimers **1a**/**1b** and their interlocked complexes **2a**/**2b** appears to be simultaneous, the possibility of the initial formation of the monomeric cage **1a** or **1b** followed by their rapid conversion into interlocked complexes cannot be excluded. Nevertheless, in either case the thermodynamic preference toward the interlocked species **2a**/**2b** over **1a**/**1b** is evident under the tested conditions.

We found that the formation of the interlocked complexes can be further promoted by increasing the initial monomer concentration. A higher ratio of interlocked complexes to dimers (2.5:1 versus 9.8:1) was detected when the concentration of the monomer **7b** was increased from 2.6 mM to 4.9 mM under otherwise identical conditions (catalyst concentration, reaction time, and temperature). Conversely, when toluene was used as the solvent, the formation of the dimer **1b** was predominant, presumably as a result of the template effect of the solvent.[33] When pure interlocked cage **2b** was subjected to the alkyne metathesis conditions in toluene, we detected significant conversion of **2b** into monomeric cage **1b**. These results further illustrate the thermodynamically controlled dynamic nature of the assembly process.

Previously, the purely organic interlocked cages were obtained as crystals from the solution containing monomeric cages or precursors.[14,15] Thus the formation of interlocked complexes is likely driven by the preference of the cages to achieve the most dense packing motif with their internal cavities filled. Although the imine-linked interlocked cages are relatively stable in solution in the absence of a catalyst such as trifluoroacetic acid (TFA), boronic-ester-linked interlocked cages immediately decompose to form the non-interlocked species upon dissolution. This result indicates that the formation of the interlocked species is favored in the solid state but not in the solution phase. As the exchange between the solution and precipitation is considerably slow, precipitation or crystallization of a component from a dynamic covalent system can be considered as irreversible quenching.[17] Therefore, although it is possible that the interlocked cages formed as crystals are the thermodynamically most stable species, the possibility that they exist as kinetic traps cannot be ruled out.

In contrast, the interlocked cages **2a** and **2b** are formed in solution and are stable in air, to moisture, and in silica-gel chromatography, which aids their isolation/purification and further application. They can be stored on the benchtop without noticeable decomposition. To our knowledge, this study is the first example of pure solution-phase template-free assembly of interlocked organic cages. The process is thermodynamically controlled without the aid of kinetic factors such as crystallization. In the absence of a recognition motif (for example a template) or the driving force of dimerization arising from a close-packing principle in the solid state, it is challenging to mechanically entangle two or more individual species. The entropy loss of holding two molecules together has to be compensated for by the enthalpy gain from the weak intermolecular bonding interactions. Presumably, the favorable π–π interactions between aromatic

moieties of interlocked cage complex **2a**/**2b** overcome the entropic penalty associated with the formation of the bimolecular architectures. In this regard, the design of building blocks appears to be critical for the successful formation of interlocked species.

Our group previously also studied the dynamic assembly of analogous C_4- or C_3-symmetric aromatic building blocks.[34,35] However, these building blocks only form a dimer with C_4 symmetry and a tetramer with D_{2h} symmetry, respectively, and no noticeable amount of interlocked species was detected. At this stage, our understanding of how molecules entangle and form interlocked molecular architectures is still very limited. Possible critical factors include structures of monomer units, the solvent template effect, and π–π interactions between aromatic moieties, which collectively influence the equilibrium compositions. Computer modeling was utilized to further evaluate the possible conformations of the interlocked cages. There are two possible ways to interlock two independent dimers: a) Conformer I (Figure 3a,b) in which all three windows are

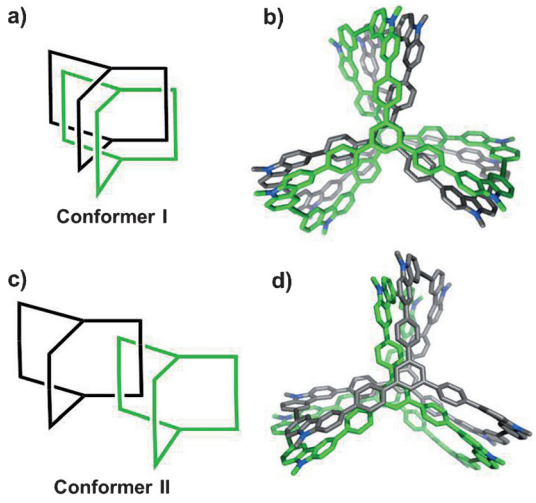

Figure 3. Schematic representations (a, c) and energy-minimized structures (b, d) of the two possible interlocked cage structures, namely conformer I (a, b) and conformer II (c, d). Methyl groups are used as the substituents on the carbazole moieties for simplicity.

penetrated, or b) conformer II (Figure 3c,d) in which two of three windows are penetrated. The coordination or covalent interlocked cages reported so far are mostly assembled in multiply interlocked conformations (all the windows are penetrated), achieving maximum π–π stacking or hydrogen-bonding interactions between the two interlocked species.[9–15] Computational calculations on the energy-minimized structures of conformer I and II show that triply-interlocked conformer I is 23 kcal mol^{-1} more stable than conformer II. Conformer I is stabilized by the π–π interactions between all three lateral arms and two panels of each trigonal prismatic cage, which likely represents the conformation of **2a**/**2b**. Our extensive crystallization trials with **2b** failed to produce single-crystals of sufficient quality for X-ray diffraction analysis.

In summary, by utilizing dynamic alkyne metathesis we successfully constructed the interlocked aryleneethynylene cages from simple triyne building blocks. This template-free, solution-phase covalent assembly approach is highly efficient, providing robust interlocked molecular cages in one step in good yield. The formation of the interlocked cage is thermodynamically favored over the simple dimer cage in solution. Our approach thus differs from solid-state catenation (crystallization from a solution), which is likely driven by the densest packing principle (nature abhors vacuum). Although the detailed mechanism of the molecular interlocking is unclear, the relative thermodynamic stability of the equilibrium components is a key factor, which can be manipulated by the choice of building blocks, solvent, and concentration. As a result of the unprecedented stability and the possibility to form higher-order oligomeric interlocked products, this template-free approach may have application in the development of polymeric interlocked structures with both greatly enhanced flexibility and the robustness provided by ethynylene bonds.

Keywords: alkynes · interlocked molecular cages · metathesis · supramolecular chemistry · thermodynamic control

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