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Synthesis of Cycloparaphenyleneacetylene via Alkyne Metathesis: C_{70} Complexation and Copper-Free Triple Click Reaction

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Supporting Information

ABSTRACT: Alkyne metathesis provided an efficient macrocyclization route to a cycloparaphenyleneacetylene derivative in high yield. The cavity size was suitably matched for C_{70} which was tightly bound in an induced-fit fashion. The strained alkynes enabled a copper-free, 3-fold azide−alkyne cycloaddition at 50 °C.

Fully conjugated molecular belts[1,2] with radially oriented π-systems have garnered great interest in the past two decades due to their intriguing photophysical[3−5] and electronic properties[6,7] as well as their ability to form host−guest complexes.[8−13] Cycloparaphenyleneacetylene (CPPA)[3] was one of the earliest classes of molecular belts prepared by Kawase and Oda in 1996 (Figure 1). CPPA was synthesized by

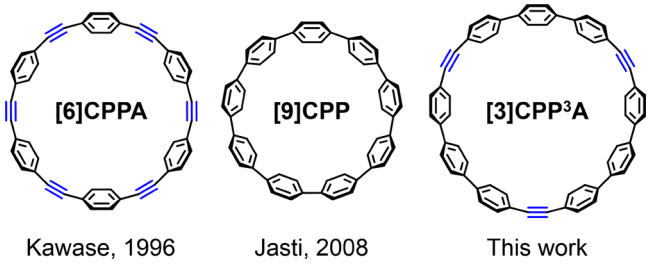
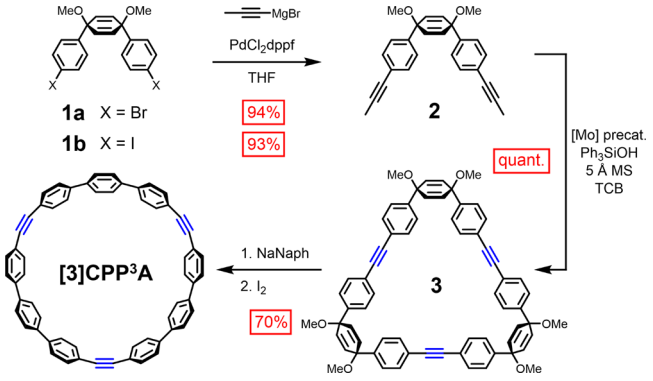


Figure 1. Representative examples of fully conjugated molecular belts, cycloparaphenyleneacetylene (CPPA),[3] cycloparaphenylene (CPP),[14] and [3]**CPP³A** (this work).

McMurry coupling of dialdehyde precursors followed by a sequence of bromination and elimination reactions.[15] Others have used Sonogashira coupling[11,16] or Glaser coupling[17] to prepare CPPA derivatives. More recently, cycloparaphenylenes (CPP, Figure 1) have been widely explored with pioneering work by Jasti,[14] Itami,[18] and Yamago.[19] Despite the great accomplishments to realize CPPAs and CPPs, the macrocyclization step remains a major bottleneck in these syntheses. For instance, "shotgun" macrocyclization[3,14] in a one-pot reaction using simple monomeric building blocks resulted in mixtures of macrocycles of various sizes and low yields. In order to improve the selectivity and yield, multistep reaction sequences[20,21] were used to prepare macrocyclic precursors. In addition, the majority of macrocyclization reactions were performed in high-dilution conditions (≤ 5 mM)[20,21] and in some instances stoichiometric amounts of precious metals were required.[19,22] Furthermore, in most cases, column chromatography was used to purify the cyclized products. Here, we report the synthesis of a CPPA precursor in quantitative yield using alkyne metathesis on the gram-scale without the need for chromatographic separation. The subsequent reductive aromatization resulted in a fully conjugated CPPA derivative, [3]cyclopara*ter*phenyleneacetylene, [3]**CPP³A** (Scheme 1).

Scheme 1. Synthetic Procedure of [3]CPP³A[a]



[a][Mo] precat.: tris(*tert*-butyl(3,5-dimethylphenyl)amino)-(propylidyne)molybdenum precatalyst. MS: molecular sieves. TCB: 1,2,4-trichlorobenzene. NaNaph: sodium naphthalenide.

This new molecular belt formed a stable 1:1 complex with C_{70} fullerene and exhibited an intriguing columnar assembly in the solid state. The strained alkynes within [3]**CPP³A** resulted in a triple, copper-free azide−alkyne cycloaddition at 50 °C.

Alkyne metathesis is a powerful technique to synthesize arylene-ethynylene-based molecular architectures including macrocycles[23] and cages[24−28] in one pot via dynamic covalent chemistry.[29,30] By applying this method to the U-shaped building blocks (Scheme 1, **1a** and **1b**) reported by Jasti,[14,31] we envisioned a simple synthetic pathway toward a CPPA−CPP hybrid molecular belt. The cyclohexadienyl-building blocks **1a** and **1b** were prepared using previously reported methods[14,31] and then subjected to a Kumada coupling reaction with propynylmagnesium bromide to give the dipropynyl-building block **2** in excellent yields (Scheme 1). Gratifyingly, molybdenum(VI)-catalyzed alkyne metathesis of **2** resulted in the desired CPPA precursor **3** in quantitative yields. Molecular sieves (5 Å) were used to remove the 2-butyne byproduct from

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the reaction. Macrocycle **3** exhibited poor solubility in most organic solvents and precipitated out of the solution during the reaction, thus driving the equilibrium completely toward the product. Soxhlet extraction with $CHCl_3$ was used to separate **3** from the molecular sieves. The reductive aromatization was successfully performed with sodium naphthalenide (NaNaph) to give [**3**]**CPP^{3}A** in 70% yield. Due to the poor solubility of precursor **3** in THF, it was necessary to sonicate the suspension in order to break apart large aggregates into small particulates before initiating the reaction. Consistent with previously reported CPPAs, [**3**]**CPP^{3}A** was unstable and decomposed into a yellow insoluble material when exposed to air. A similarly sized [6]CPPA was previously reported to decompose "explosively" at 80 °C in air.[3] While we have seen no evidence that [**3**]**CPP^{3}A** was shock sensitive, we advise using extra precaution such as protective gloves and eye protection when working with dry samples. We stored [**3**]**CPP^{3}A** as a dry solid under an argon atmosphere or as a solution in degassed organic solvents such as acetone, dichloromethane, and toluene below 0 °C. The molecular belt was fully characterized using 1D (Figures S5, S6, S9) and 2D (Figures S10, S11) NMR spectroscopy and mass spectrometry (Figure S12).

Both CPPA and CPP derivatives are known to exhibit rich host–guest properties with fullerenes and their derivatives.[8,9,11−13] Computational studies (DFT B3LYP 6-31G*, Figure S15) suggested [**3**]**CPP^{3}A** to have a diameter of 1.5 nm. This was similar to that of a naphthalene-fused CPPA (1.4 nm)[8] and [11]CPP (1.5 nm),[13] which bind C_{70} fullerene with large association constants ($K_a > 10^5$ M^{-1}) in organic solvents. The ^{1}H NMR chemical shifts of [**3**]**CPP^{3}A** in 1,1,2,2-tetrachloroethane-d_2 were monitored at room temperature with added C_{70} (Figure 2a). All proton signals showed gradual

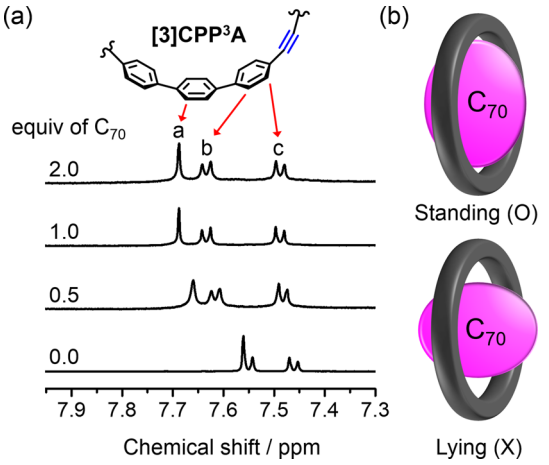

Figure 2. (a) Room temperature ^{1}H NMR spectra of [**3**]**CPP^{3}A** (5 mM in 1,1,2,2-tetrachloroethane-d_2) with added C_{70} shows downfield shifts that correspond to a (b) "standing" orientation of C_{70} within the central cavity.

downfield shifts that saturated upon addition of 1 equiv of C_{70}. The downfield shift likely results from the interaction of aromatic protons with the two apical pentagons of C_{70}, which are known to have strong deshielding effects.[32] Therefore, it was possible to deduce that C_{70} binds in a "standing"[13,33] orientation (Figure 2b) within the cavity of [**3**]**CPP^{3}A**. The association constant between [**3**]**CPP^{3}A** and C_{70} was determined by a titration experiment in toluene, monitored by the change in ultraviolet–visible (UV–vis) absorbance (Figure S14). Equilibrium restricted factor analysis[34] of UV–vis spectra generated a K_a value of 102 000 ± 4000 M^{-1} (ΔG = −28.6 ± 0.1 kJmol^{-1}), which is similar to the reported C_{70} association constant of [11]CPP[13] and naphthalene-fused CPPA.[8] On account of the strong association constant, it was possible to separate out the [**3**]**CPP^{3}A**⊃C_{70} complex by flushing the mixture with CH_2Cl_2 through a silica gel column. Furthermore, the [**3**]**CPP^{3}A** was substantially stabilized by C_{70} complexation and its crystals (from toluene and CH_2Cl_2) did not decompose in open air for more than three months. C_{60}, on the other hand, did not show significant association and was not able to stabilize [**3**]**CPP^{3}A**.

Single crystals of the [**3**]**CPP^{3}A**⊃C_{70} complex suitable for X-ray analysis were prepared by slow evaporation of a degassed solution in CH_2Cl_2 and *m*-xylene (1:1 mixture). The X-ray crystal structure was solved in a *Pnma* orthorhombic space group and clearly showed a 1:1 complex between [**3**]**CPP^{3}A** and C_{70} (Figure 3a,b). Agreeing with the downfield shifts observed in the ^{1}H NMR spectra (Figure 2a), C_{70} was standing in the center of the ring and the C_5 axis of C_{70} was closely

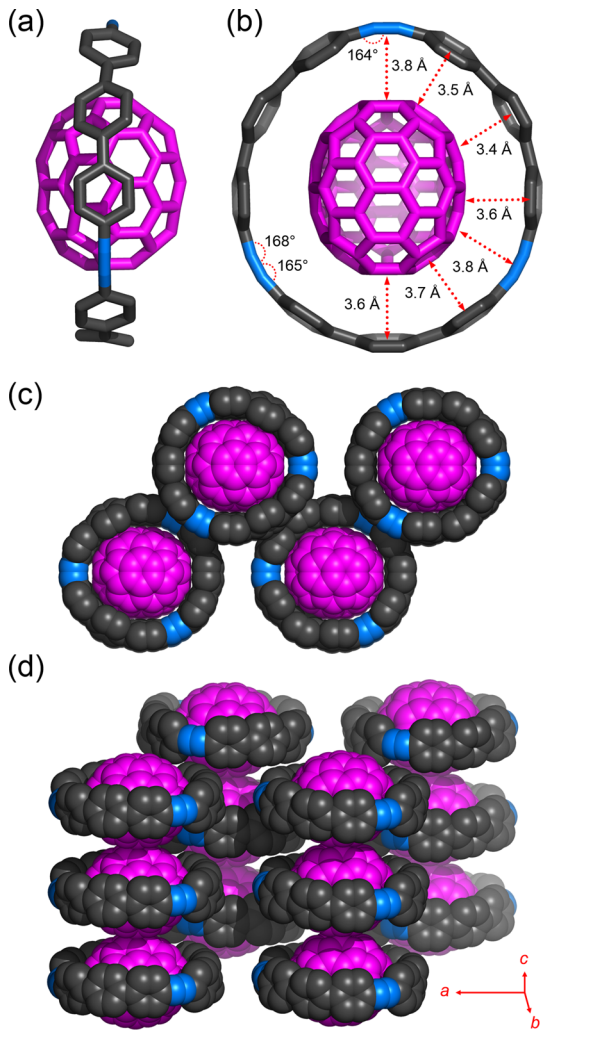

Figure 3. X-ray crystal structure of [**3**]**CPP^{3}A**⊃C_{70}: (a) Side view showing the "standing" orientation. (b) Top view with alkyne bond angles (∠C–C≡C) and [**3**]**CPP^{3}A**–C_{70} distances labeled. (c) Top view and (d) side view of crystal packing showing columnar stacks of C_{70}. Hydrogen atoms and solvent molecules are omitted for clarity. Alkynes are colored in blue.

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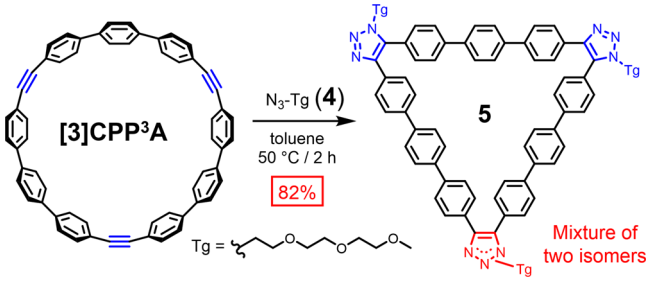
aligned against the plane of [3]CPP^{3}A with a 2° tilt (Figure S19). The complexed molecular belt was slightly distorted into an ellipsoid with an aspect ratio of 1:1.08 to accommodate C_{70} (aspect ratio 1:1.12) in an induced-fit fashion. The alkyne bond angles (∠C−C≡C) were 164°, 165°, and 168°. The distance between [3]CPP^{3}A and the bound C_{70} ranged from 3.4 to 3.8 Å (Figure 3b), suggesting attractive van der Waals interactions. The crystal packing shows columnar stacks of C_{70} (Figure 3c,d) that are separated by 3.1 Å along the *c*-axis. Such self-assembly resembles the nanopeapod assembly of fullerenes within single wall carbon nanotubes,[35] suggesting potential applications in organic electronics.[36]

Strain-promoted azide−alkyne cycloaddition (SPAAC), so-called copper-free click reaction, occurs between azides and strained alkynes with bond angles that deviate significantly from 180°. Representative examples of cyclooctyne-based compounds by Bertozzi[37] have alkyne bond angles around 160°.[38,39] The alkyne bond angle of [3]CPP^{3}A was calculated (DFT B3LYP 6-31G*) to be 165°, and the overall strain energy[40] of the macrocycle was estimated as 47.76 kcal/mol (Figure S16). The SPAAC reaction was put to test by stirring a solution of [3]CPP^{3}A (5 mM in toluene) with 9 equiv of azido-compound **4** at 50 °C for 2 h (Scheme 2). The reaction

Scheme 2. A Triple SPAAC Reaction between [3]CPP^{3}A and an Azido-Compound (N_3-Tg, 4) Resulted in a Tris-triazoloterphenylene Macrocycle 5



progress was monitored by thin-layer chromatography which showed the appearance and then disappearance of intermediate spots which hints at a stepwise reaction. The SPAAC reaction successfully resulted in tris-triazoloparaterphenylene macrocycle **5** as a mixture of two isomers that were not separable by column chromatography. Despite the complexity of the aromatic region in the ^{1}H NMR spectrum, their integrated intensity ratio against the aliphatic region clearly showed 1:3 reaction stoichiometry between [3]CPP^{3}A and the azido-compound **4** (Figure S7). The mass spectrum exhibited isotope signatures that correspond with the triply clicked product **5** (Figure S13). To the best of our knowledge,[41,42] this is the first example of a macrocycle that undergoes three successive SPAAC reactions.

In order to understand the thermodynamics of the three consecutive SPAAC reactions, computational analysis on the intermediates (**mono**, **bis-1**, **bis-2**, **bis-3**, Figure 4a) and the products (**tris-1**, **tris-2**) were performed. Methylazide (MeN_3) was used to simplify the calculation. The results show that all three reactions are exothermic (Figure 4b) and release strain energy (Figure 4c) on each step. The majority of the strain energy, 43 out of 48 kcal/mol (90%) combined, is released after the three reactions. The amount of energy released from each SPAAC reaction increases along the sequence. Interestingly, the first reaction is much less exothermic compared to the second

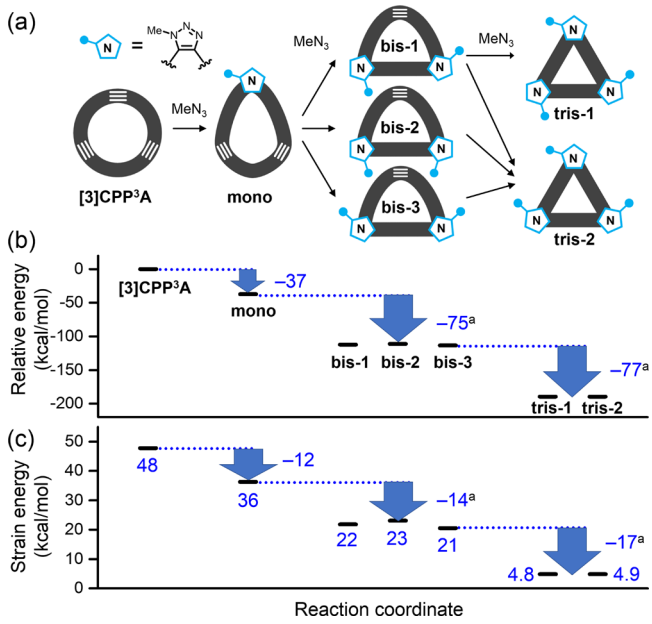


Figure 4. (a) Reaction pathway of three consecutive SPAAC reactions with MeN_3. (b) Calculated reaction enthalpy for each SPAAC reaction and (c) strain energy of intermediates and products. All values in kcal/mol, DFT B3LYP 6-31G*. [a] Average value of multiple reactions.

and third reaction. We presume that the triazole moiety in **mono** is more unstable compared to the ones in **bis** and **tris**, thereby being less exothermic during its formation. Further computational and experimental investigations will be pursued in the future to understand this outcome.

In conclusion, we have provided an efficient approach to prepare a CPPA derivative, [3]CPP^{3}A, using alkyne metathesis in the macrocyclization step. This new molecular belt formed a stable complex with C_{70} fullerene in an induced-fit fashion that distorted the structure into an ellipsoid. A triple SPAAC reaction was possible for the first time using the three strained alkynes within [3]CPP^{3}A. Computational studies showed that most of the strain is released during three consecutive SPAAC reactions. Transition state calculations of each reaction sequence and experimental reaction kinetics studies will be required to gain a better understanding of the triple SPAAC.[38,41,42] We envision that the high yielding synthetic method provided in this communication will allow us to prepare other molecular belts with different sizes and functionalities with ease. These studies may allow the molecular belts to be used in practical applications such as tritopic polymer cross-linkers.[43]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08752.

Synthetic procedures and characterization including ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data; computational studies and their corresponding Cartesian coordinates (PDF)

X-ray crystallographic data of compounds (CCDC #1500189) (CIF)

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Notes

The authors declare no competing financial interest.

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