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Post-assembly Functionalization of Organoplatinum(II) Metallacycles via Copper-free Click Chemistry

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Supporting Information

ABSTRACT: We describe the use of a strain-promoted copper-free click reaction in the post-self-assembly functionalization of organoplatinum(II) metallacycles. The coordination-driven self-assembly of a 120° cyclooctyne-tethered dipyridyl donor with 60° and 120° di-Pt(II) acceptors forms molecular rhomboids and hexagons bearing cyclooctynes. These species undergo post-self-assembly [3+2] Huisgen cycloaddition with a variety of azides to give functionalized ensembles under mild conditions.

The functionalization of supramolecular assemblies has been extensively investigated over the past few years with an aim to develop nanoscale ensembles that can find applications in diverse fields such biological systems, host–guest chemistry, cavity-directed synthesis, catalysis, photonics, redox activity, magnetic behavior, self-organization, and sensing.[1] Although various functionalized nanoscopic systems have been developed through conventional covalent synthesis, the control of functional groups and structural precision, the ability to perform selective encapsulation, and synthetic ease and building-block versatility make coordination-driven self-assembly a powerful tool to assemble functional supramolecules with relative simplicity. However, potential incompatibilities and interferences by various functional groups with the self-assembly process often limit the library and scope of the functionalized tectons. Thus, post-self-assembly modification of supramolecular ensembles through transformation of the organic component of the assemblies may be a way to circumvent the problem. We have recently been able to achieve post-assembly functionalization of metallosupramolecular prisms via covalent modifications to incorporate new functionalities under mild conditions.[2] The free amino groups tethered on the edges of the prisms allowed facile reactions with isocyanate or maleic anhydride. Similarly, the free malemide groups tethered on the edges of these prisms underwent Diels–Alders reaction with anthracenyl ferrocenoate. However, the range and scope of using an amino group as a handle to introduce various functional groups is limited. The azide–alkyne-based "click" reactions are attractive alternatives in this context since they usually involve weakly polarized reactants, minimizing undesired side reactions, and thus could be an efficient method for expanding the range of chemical functionalities that can be tethered onto the metallosupramolecules. Post-synthetic modification of metal–organic frameworks[3] has been achieved in recent years through copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions.[4] However, the application of click chemistry to functionalize discrete assemblies has received much less attention. In a rare example, Zhou et al.[5] described the functionalization of porous nanocages bearing free alkyne groups via the CuAAC reaction with azide-terminated PEG to transform the nanocages into water-stable colloids, which showed controlled release of the anticancer drug 5-fluorouracil. However, the use of CuAAC reactions in living systems is limited due the cytotoxicity of the Cu(I) catalyst toward living cells. Copper-free strain-promoted azide–alkyne cycloaddition (SPAAC) reactions[6] recently developed between cyclooctynes and azides have found wide utility in chemical biology, such as labeling of biomolecules (glycans,[7] proteins,[8] lipids,[9] and nucleotides,[10]), modification of oligonucleotides[11] and enzymes,[12] and cell and tissue surface engineering.[13] In the field of material science, SPAAC reactions have been used for surface functionalization of dendrimers,[14] polymers,[15] nanoparticles,[16] and nanowires,[17] surface patterning,[18] and cross-linking of polymers and hydrogels.[19]

Herein we report post-self-assembly functionalization of supramolecular ensembles through "copper-free click chemistry". The 120° cyclooctyne-tethered dipyridyl donor was synthesized via the amide coupling reaction of 3,5-bis(4-pyridylethynyl)aniline with 1-cyclooctyne-3-glycolic acid[20] in dichloromethane, leading to the formation of the cyclooctyne-tethered donor **1** (Supporting Information, Scheme S1).

Stirring a mixture of 120° cyclooctyne-tethered donor **3** and the 60° organoplatinum(II) acceptor, 3,6-bis[*trans*-Pt-$(PEt_3)_2(NO_3)_2$]phenanthrene (**4**), in a 1:1 ratio in CD_2Cl_2 for 8 h led to the formation of self-assembled [2+2] metallacyclic rhomboid **6**. Similarly, self-assembled [3+3] hexagon **7** was prepared by mixing the 120° donor ligand **3** with organoplatinum(II) acceptor, 4,4′-[*trans*-Pt-$(PEt_3)_2(NO_3)_2$]diphenyl ketone (**5**), in a 1:1 ratio in CD_3OD for 8 h (Scheme 1). Multinuclear NMR (^{31}P and ^{1}H) of the reaction products supports the formation of discrete, highly symmetric assemblies. These metallacycles contain a pendant cyclooctyne moiety at their vertices. The $^{31}P\{^{1}H\}$ NMR spectra of **6** and **7** displayed sharp singlets at 12.7 and 14.1 ppm with concomitant ^{195}Pt satellites corresponding to a single phosphorus environment (Figure 1). The peaks were shifted upfield from those of their respective platinum acceptors **4** and **5** by approximately 6.4 and 5.1 ppm, respectively. The upfield shift as well as the decrease in coupling constant (ΔJ) for the

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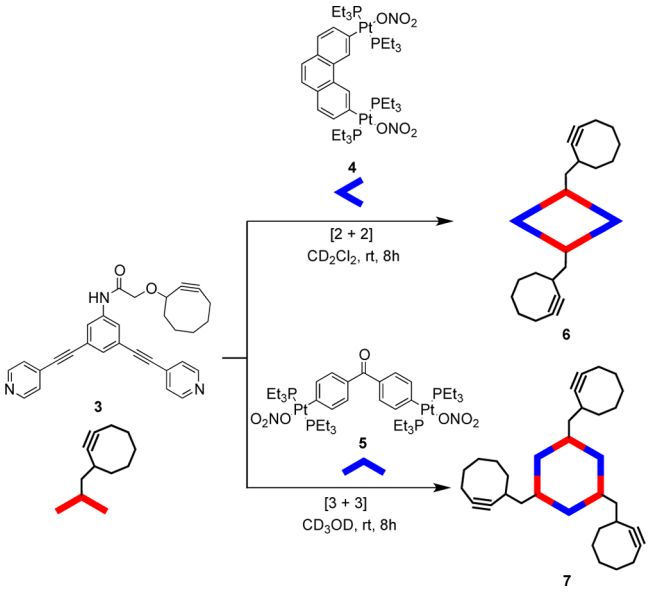
Scheme 1. Self-Assembly of Discrete Metallacyclic Rhomboids and Hexagons Bearing Cyclooctyne Functionality



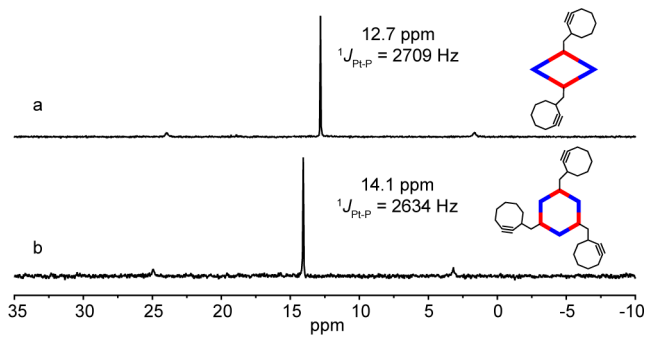


Figure 1. $^{31}P\{^{1}H\}$ NMR spectra of (a) rhomboid **6** and (b) hexagon **7**.

^{195}Pt satellites is consistent with back-donation from the platinum atoms. In the ^{1}H NMR spectrum of **6**, signals due to the α- and β-protons of the pyridine rings showed the expected downfield shifts relative to those of **3** due to the loss of electron density that occurs upon coordination of the pyridyl N-atom to the Pt(II) metal center. As shown in Figure 2, the α- and β-protons on the pyridine rings are split into two sets of two doublets upon coordination, which is consistent with previous observations of similar Pt-based rhomboids.[21] The signal for the α-pyridyl protons of cyclooctyne-tethered donor **3**, which appears as a doublet at 8.62 ppm, splits into two doublets at 9.34 and 8.68 ppm. Similarly, the β-pyridyl proton signal (δ = 7.42 ppm) is split into two doublets at 7.96 and 7.81 ppm. The signal at δ = 9.18 ppm was assigned to the amide proton. In the ^{1}H NMR spectrum of **7**, sharp signals corresponding to coordinated α- and β-pyridyl protons were identified at 8.89 and 7.87 ppm with downfield shifts relative to **3** (Figure 2).

Electrospray ionization mass spectroscopic (ESI-MS) studies further supports the formation of discrete supramolecular assemblies. The ESI mass spectrum for rhomboid **6** (Supporting Information) showed peaks at m/z = 1560.5, corresponding to $[M - 2NO_3]^{2+}$, and m/z = 1019.02, attributable to $[M - 3NO_3]^{3+}$. All the peaks were isotopically resolved and agreed very well with the calculated theoretical

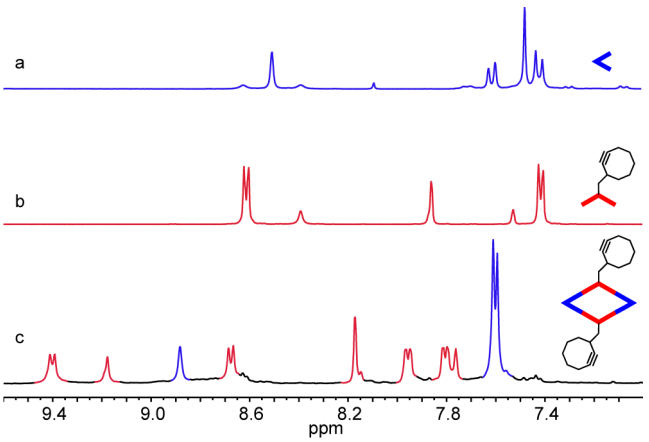


Figure 2. Partial ^{1}H NMR spectra (in CD_2Cl_2) of (a) Pt(II) acceptor **4**, (b) cyclooctyne-tethered donor **3**, and (c) rhomboid **6**.

distribution. In the ESI-MS of **7**, no parent ion peak was observed due to fragmentation. However, unique fragments were observed that support the formation of the hexagonal structure when analyzed in conjunction with the NMR spectra (Supporting Information).

In order to gain structural information about the metallacycles, single-point density functional theory (DFT) energy minimizations were performed using the Gaussian09 package.[22] All calculations were performed using the B3LYP hybrid DFT functional[23,24] and a split basis set wherein the 6-31G** basis set[25] was used for C, H, N, O, and P atoms, while the LANL2DZ basis set[26] and pseudopotential were used for Pt. To minimize the computational cost, PEt_3 ligands were modeled as PH_3. In rhomboid **6**, the two cyclooctyne moieties at the vertices lie above and below the plane of the central metallacyclic core (Figure 3). The cyclooctyne groups adopt a more stable boat conformation.[27] The alkyne bonds in the cyclooctynes are bent from linearity. Previous studies[28] using

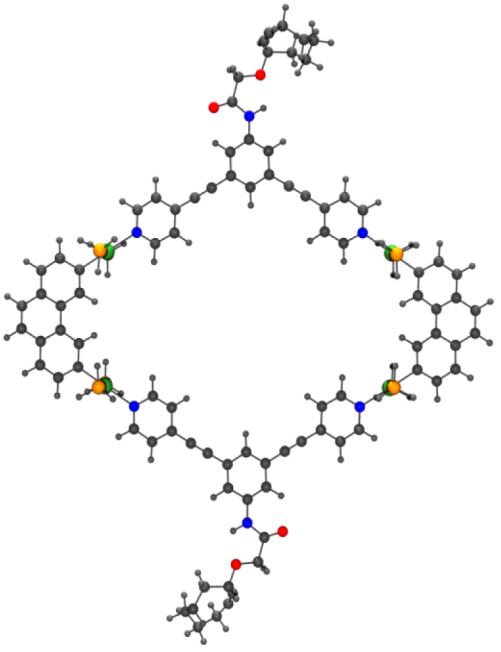


Figure 3. DFT-optimized structure of metallacyclic rhomboid **6**. Color code: gray, C; light gray, H; blue, N; red, O; orange, P; green, Pt.

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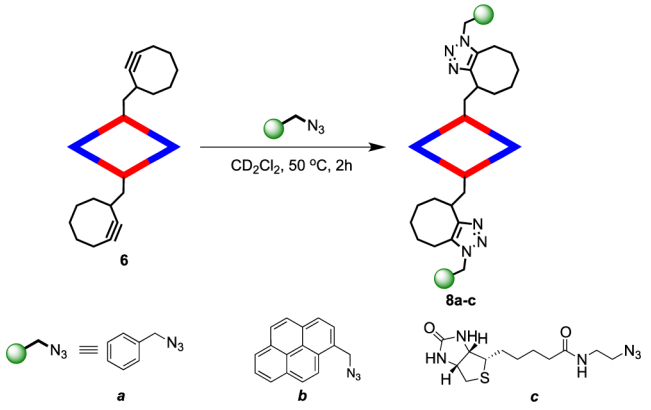
DFT-based models for the 1,3-dipolar cycloaddition of cyclooctynes with azides have shown that such deviation from linearity distorts the cyclooctynes toward the transition-state geometry, thus requiring less distortion energy to reach their preferred transition-state geometry relative to a linear alkyne.

The metallacyclic rhomboid **6** was tested for post-assembly functionalization via "copper-free click chemistry". The rhomboid **6** undergoes efficient [3+2] Huisgen-type SPAAC reactions with a variety of functionalized azides to give functionalized metallacycles under mild conditions (Scheme 2). Molecular rhomboids **8a**–**c** were obtained upon treatment

Scheme 2. Post-assembly Modification of Discrete Metallacyclic Rhomboids with Different Azides via Copper-Free Click Chemistry



of **6** with azidomethylbenzene, 1-(azidomethyl)pyrene, and 2-(azidoethyl)biotinamide, respectively, in a 1:5 ratio in CD_2Cl_2 for 2 h at room temperature. In all cases, the only products observed were the two regioisomeric 1,4,5-trisubstituted 1,2,3-triazoles in varying ratios, as identified from ^{1}H NMR spectra of **8a**–**c**. The ^{31}P{^{1}H} NMR spectra for all the assemblies remained unchanged, with the peaks appearing at about the same positions relative to those of their unfunctionalized counterparts. The ^{31}P{^{1}H} NMR spectra of the functionalized rhomboids **8a**–**c** show sharp singlets at 12.7 ppm, identical to the spectrum of the unfunctionalized rhomboid **7**. The ^{1}H NMR spectra of the ensembles showed additional peaks attributable to benzyl, pyrenyl, and biotinyl protons (Supporting Information). In the ^{1}H NMR spectrum of **8a**, the phenyl protons originating from the benzyl azide appear as a multiplet at 7.38 ppm, while the benzylic protons appear at 5.60 ppm and are consistent with previous observations.[29] The pyrenyl protons in **8b** appear as a multiplet at 8.27–8.11 ppm, with the benzylic proton appearing at 6.38 ppm.

ESI-MS data provided further evidence for the formation of the discrete functionalized species. The ESI mass spectrum for **8a** showed isotopically resolved peaks at m/z = 1693.6, corresponding to $[M - 2NO_3]^{2+}$, and m/z = 1108.1, attributable to $[M - 3NO_3]^{3+}$ (Supporting Information). Similarly, isotopically resolved peaks due to $[M - 2NO_3]^{2+}$ and $[M - 3NO_3]^{3+}$ were observed at m/z = 1817.6 and 1190.8 respectively, in the ESI-MS spectrum of **8b**. The ESI-MS spectrum of biotin-functionalized species **9c** also showed an isotopically resolved peak at m/z = 1228.1, corresponding to $[M - 3NO_3]^{3+}$.

In conclusion, we have demonstrated that copper-free strain-promoted azide–alkyne cycloaddition reactions can be effectively used to functionalize metallacycles having pendant cyclooctyne groups. In contrast to other methodologies for construction of functionalized supramolecules where a pre-functionalized unit is used, this method provides a facile way to incorporate a wide range of chemical functionalities on appropriate supramolecular assemblies with relative synthetic ease. The ready access to a multi-biotin scaffold permits the formation of a biotin multimeric structure for potential enhancement of avidin–biotin assays. Since a multivalent biotin scaffold allows many biotin binding proteins to dock simultaneously and form larger complexes,[30] these conjugates may recruit more detection molecules to bind at the site of an analyte that can have a direct effect on the sensitivity of immunoassays, fluorescent detection, enzyme-linked immunosorbent assays, and Western blotting procedures. Use of this methodology to functionalize three-dimensional supramolecular cages, having large cavities, with biologically relevant homing devices may lead to better drug delivery devices. Investigation along these lines is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all metallacyclic assemblies; complete ref 22. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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