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Covalent Stabilization: A Sturdy Molecular Square from Reversible Metal-Ion-Directed Self-Assembly

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Supporting Information

ABSTRACT: Supramolecular self-assembly using weak interactions under quasi-equilibrium conditions has provided easy access to very complex but often quite fragile molecules. We now show how a labile structure obtained from reversible transition-metal-directed self-assembly of rods and connectors serves as a template that can be converted into a sturdy structure of identical topology and similar geometry. The process consists of Cu(I)-catalyzed replacement of all rods or connectors terminated with pyridines for analogues terminated with ethynyls, converting dative N→Pt^+ bonds into covalent C−Pt bonds. The procedure combines the facility and high yield of reversible self-assembly with the robustness of covalent synthesis.

Self-assembly of molecular objects under the effect of weak interactions at or near equilibrium conditions has become an important area of study in chemistry and biochemistry.[1] Over the past two decades, investigators such as Fujita,[2] Mirkin,[3] Raymond,[4] Stang,[5] and others[6−8] have developed Tinkertoy-like[9,10] single-step self-assembly of molecular rods and connectors based on transition-metal cation−ligand interaction into a powerful tool for the synthesis of very large symmetric polygonal and polyhedral molecules, including structures as complex as a giant spherical cage ($M_{24}L_{48}$)[11] or a dodecahedron ($M_{60}L_{120}$).[12] The products not only are esthetically pleasing but also promise to be useful in various applications,[13] e.g., molecular encapsulation for enzyme-like catalysis,[14] molecular flasks,[15] catalysis,[16] or selective anion binding.[17]

Most often, the molecular constituents of this transition-metal-ion-directed self-assembly carried uncharged ligating groups, such as pyridine, at the termini. The metal cations either were free and carried two good leaving groups, or were covalently attached to a terminus of a rod or a connector and carried one good leaving group. The self-assembly was performed under equilibrium conditions, taking advantage of the facile formation of ligand-to-metal-ion dative bonds whose reversible nature offers easy error correction. A thermodynamically favored polycation product was often formed rapidly in nearly quantitative yield. This contrasts with the outcome of most attempts to assemble analogous covalent structures directly by covalent bonding under nonequilibrium conditions, which tend to produce the desired structures mixed with oligomers or polymers.[18−20]

A frequent consequence of the reversible mode of assembly is a regrettable fragility of the self-assembled structure under the conditions of its formation and, more generally, in the presence of nucleophilic solvents or reagents.[21,22] The polygons and polyhedra usually fall apart upon attempted chromatographic purification, and sometimes upon mere dilution of their solutions. The fragility of the self-assembled structures has been exploited for tuning the molecular shape through hydrogen bonding[23] or irradiation.[24] In general, however, this feature of metal-ion-directed self-assembly limits its practical utility. If a pure chemical species is to be obtained, it also constrains its scope, since in most cases only one kind of each structural element can be used. Then, all connectors throughout the assembled structure are identical, all rods are identical, and only highly symmetric polygons and polyhedra are accessible. When more than one type of connector or more than one type of rod is used simultaneously,[25] in most cases a mixture of labile self-assembled lower-symmetry products results, and there currently is no easy way to separate its components. In certain cases, however, heteroleptic structures were obtained by judicious use of topological constrains and maximum site occupancy.[26−28]

A similar concern with product instability is encountered in other types of equilibrium self-assembly and has been addressed by the use of assembly reactions that proceed reversibly only under certain specialized conditions that are unlikely to be encountered in the later use of the assembled structures. Examples are the formation of Schiff bases,[29,30] hydrogen bonding,[31] and cation templating.[32] Nevertheless, to our knowledge, a general solution to the problem has not been found in the case of transition-metal-ion-directed self-assembly of polygons and polyhedra.

We now introduce a "covalent stabilization" procedure that treats an initial fragile self-assembled structure as a template and converts it in a high yield into a topologically equivalent sturdy structure that can be geometrically nearly equivalent as well. The process consists of a single-step reaction which exploits the lability of the metal ion−ligand bonds in the template to effect a facile replacement of all the rods or all the connectors attached by such weak bonds with counterparts attached by sturdy covalent bonds. In reality, the reaction is only formally a single-step process, since the replacements need to occur one at a time to preserve the overall bonding pattern. The rate at which the new connector replaces a donor ligand from the first metal cation

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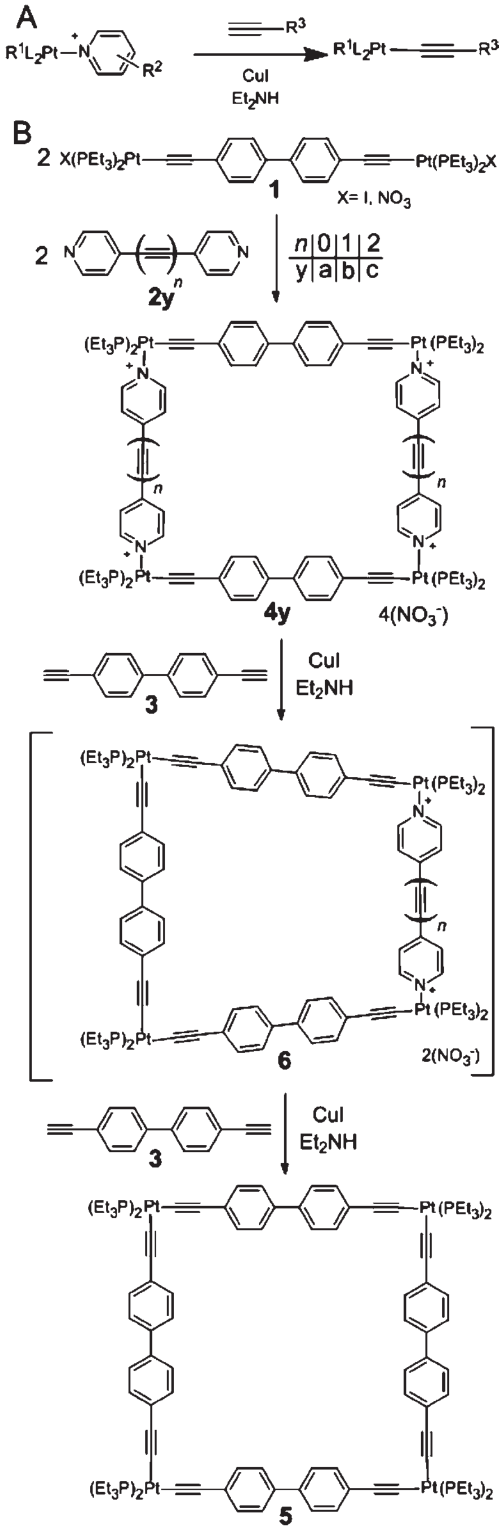
Scheme 1. Covalent Stabilization: (A) Key Reaction (R^1 = alkyne; L = trialkylphosphine; R^2, R^3 = aryl, alkynyl, alkenyl, or alkyl) and (B) Synthesis of Templates 4y (y = a, b, c) and of the Sturdy Square 5



in the template with a carbon-based covalent ligand using one of its reactive termini may be slow, but the replacement of the donor ligands from the remaining metal cation or cations to which the new connector is to bind, using its other covalently reactive termini, needs to be fast to minimize the chances of bimolecular processes that would lead to oligomeric products. Some reactivity differentiation will be naturally provided by a difference of activation entropies, since the first reaction step is bimolecular and the subsequent ones are unimolecular, but it was not obvious at the outset whether this difference would be sufficient.

We illustrate the procedure on the high-yield conversion of three labile charged molecular rectangles into the same topologically equivalent and sturdy uncharged molecular square. One of the initial rectangles and the final square have nearly identical dimensions, too. We provide evidence that the covalent stabilization occurs without loss of integrity of the initial self-assembled structure. We also show that the two-step, metal-ion-directed self-assembly of a template and its covalent stabilization can be performed consecutively in a single reaction vessel without isolation of the template, effectively representing a quantitative self-assembly of an irreversible and kinetically stable yet thermodynamically directed product.

Covalent stabilization is conceptually somewhat related to "covalent capture" that has been developed for the stabilization of biomolecular complexes[33] and cation-templated structures,[34] but perhaps the best pictorial analogy is the petrification of wood by gradual replacement of all its organic constituents with silica.

Taking advantage of our prior experience with metal-directed self-assembly,[35−37] we have chosen to work with cyclic structures self-assembled through the binding of Pt(II) cations to pyridine ligands. The Pt cations are covalently attached to each end of a molecular rod, X-$Pt(PEt_3)_2$-C_2-$(C_6H_4)_2$-C_2-$Pt(PEt_3)_2$-X (**1**, X = ONO_2), and to pyridine-terminated connectors NC_5H_4-$(C_2)_n$-C_5H_4N (**2a**−**2c**, with $n = 0-2$, respectively). Covalent stabilization then consists of a replacement of all the connectors **2** in the self-assembled template, where they are held by weak $[\text{Pt-pyridine}]^+$ dative bonds, with deprotonated ethynyl-terminated connectors $^-C_2$-$(C_6H_4)_2$-C_2^- (**3**) that will be held by much stronger Pt−C covalent bonds (Scheme 1). The exchange should not only stabilize the structure, hopefully sufficiently for chromatographic separations, but also remove net charges from the molecule. This is essential for differential barrier height imaging,[38] dielectric studies, and other work in which the presence of counterions with ill-defined locations and mobility is undesirable.

In order to effect the desired replacement of pyridine-ligand-terminated connectors **2y** (**y** = **a**, **b**, **c**) with deprotonated acetylide-terminated connectors **3**, we needed a substitution reaction that replaces a pyridine ligand on a Pt cation with an acetylide ligand. To our surprise, we were unable to find a report of such a reaction in the published literature. After some searching, we found that the use of a terminal triple bond in the presence of copper iodide and diethylamine easily leads to the desired outcome (Scheme 1A).

The rod **1** (X = NO_3) was prepared by standard procedures (Supporting Information). The connector **2a** was purchased, and **2b**[39] and **2c**[40] were prepared by slightly modified published procedures. The self-assembly of **1** and **2a**, **2b**, or **2c** proceeded rapidly and quantitatively at room temperature in CH_2Cl_2, and the rectangular templates **4a**−**4c** precipitated upon addition of diethyl ether. They are soluble in nitromethane and have been fully characterized spectroscopically. 2D DOSY NMR[41] at 20 and 45 °C established that in each of the three cases a single product is formed (Figure S1). The products are fragile under ESI mass spectrometry conditions, yielding many fragment ions

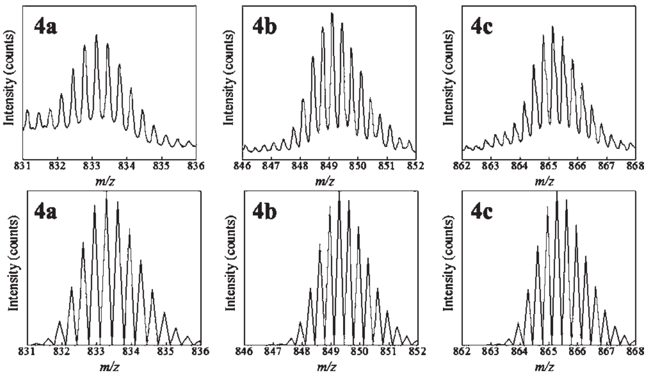


Figure 1. ESI$^+$−HRMS: observed (top) and calculated (bottom) isotopic distribution for **4a**−**4c** $[M - 3NO_3]^{3+}$.

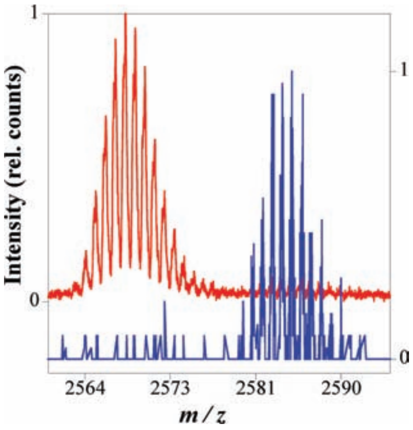


Figure 2. ESI$^+$−HRMS: **5** (top, red) and **5** with two perdeuterated edges (bottom, blue) in CH_2CL_2 containing 5−10% of CH_3CN.

of easily rationalized m/z ratios (Figure S2). Figure 1 shows the high-resolution spectra of the trication $[M^{4+},NO_3^{-}]$ for all three templates.

Slow addition of a solution of 2 equiv of **3** in CH_2Cl_2 to a ~1 mM solution of any one of the rectangles **4y** (**y** = **a**, **b**, **c**) in a 1:1 CH_3NO_2/CH_2Cl_2 mixture at −25 °C in the presence of CuI and diethylamine, followed by slow warming to room temperature, caused the precipitation of the same nearly pure product **5** in 60−70% yield. Further purification was readily achieved by column chromatography on silica gel without any sign of decomposition.

The structure of **5** follows from its spectra. The ^{1}H NMR spectrum contains two doublets in the aromatic region, corresponding to the hydrogens of the biphenyl, and two complex multiplets (due to ^3J and ^4J couplings with the Pt nucleus) in the alkyl region, assigned to the protons of the CH_2 and CH_3 groups of the triethylphosphine ligands. The peaks of the aromatic protons are broader than those in the spectrum of the rod **1**, and this is attributed to a slower rotation rate of the large flat molecule. The equivalence of the protons shows that a single conformer is present on the NMR time scale; either the biphenyl moiety is oriented with its aromatic planes nearly perpendicular to the plane of the square, or it can rotate essentially freely without hindrance by the protons of the biphenyls located at the adjacent edges. The main UV−vis absorption peak of **5** is red-shifted compared to those of **1** and **4** (Figure S3). The ESI mass spectrum (Figure 2) exhibits the expected molecular mass and isotopic pattern for the molecular ion. Gel permeation chromatography (GPC) showed a single peak at ~2500 Da (Figure S4).

^{31}P NMR spectroscopy (Figure S5) and ESI mass spectrometry (Figure S6) were used to follow the conversion of **4c** to **5** after a set period of time as a function of the amount of **3** added. Both methods revealed the intermediate formation of the expected trapezoidal structure **6** in which only one of the two initial connectors **2c** has been replaced with the final connector, $-C_2-(C_6H_4)_2-C_2-$. No open chains were detectable, supporting the proposal that the second terminus of each newly introduced connector reacts too rapidly to allow the open-chain intermediate to accumulate.

To verify that the structural integrity of the self-assembled structure remains intact during the covalent stabilization process, the reaction of **4c** was repeated with **3** fully deuteriated on both rings. This produced a square **5** with two sides deuteriated and two protonated. As expected from the proposed mechanism, squares with other isotopic labeling patterns were not detectable (Figure 2). This result excludes the possibility that under the reaction conditions the initial self-assembled template **4c** falls apart partially or fully into its rod and connector constituents and then reassembles. Indeed, treatment of a mixture of the rods **1** and **3** with CuI and diethylamine yields a mixture of oligomeric products. According to GPC (Figure S4), the main constituents are oligomers containing 6−10 rods, and only a very small amount of **5** is present. It is possible that under high-dilution conditions[18] **5** could be formed efficiently, but the present procedure is much more convenient.

The synthesis of the square can be performed in a single reaction vessel. A stoichiometric mixture of **1** and **2c** in CH_2Cl_2 forms **4c** in 15 min, and subsequent addition of **3**, CuI, and diethylamine furnishes the square **5**. This one-pot route is simpler, but a drawback is that the product does not precipitate and needs to be isolated by column chromatography.

The results obtained for the synthesis of the square **5** by the process of covalent stabilization of **4a**−**4c** are encouraging and suggest that the procedure might be extendable to larger and more complex self-assembled structures, to additional transition metals, and to ligands other than pyridine and acetylide. It is noteworthy that the present process is quite tolerant of a mismatch between the length of the connector **2** that is being replaced and the length of the connector **3** that is being introduced, and the limits of this tolerance are also worth exploring. If the outcomes of these investigations are positive, covalent stabilization will represent a useful tool for the production of sturdy symmetrical molecular polygons and polyhedra. These can then be subjected to additional transformations, such as oxidative removal of Pt with concomitant C−C coupling.[42,43]

Moreover, covalent stabilization promises access to separable mixtures of low-symmetry, sturdy self-assembled species. More than one type of rod or ligating connector can now be used in the initial self-assembly, or more than one type of covalent connector can be used in the stabilization process, and chromatographic separation of the resulting mixture can be attempted for access to heteroleptic polygons and polyhedra.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedures and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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