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# Modular Synthesis of Metal–Organic Complex Arrays Containing Precisely Designed Metal Sequences

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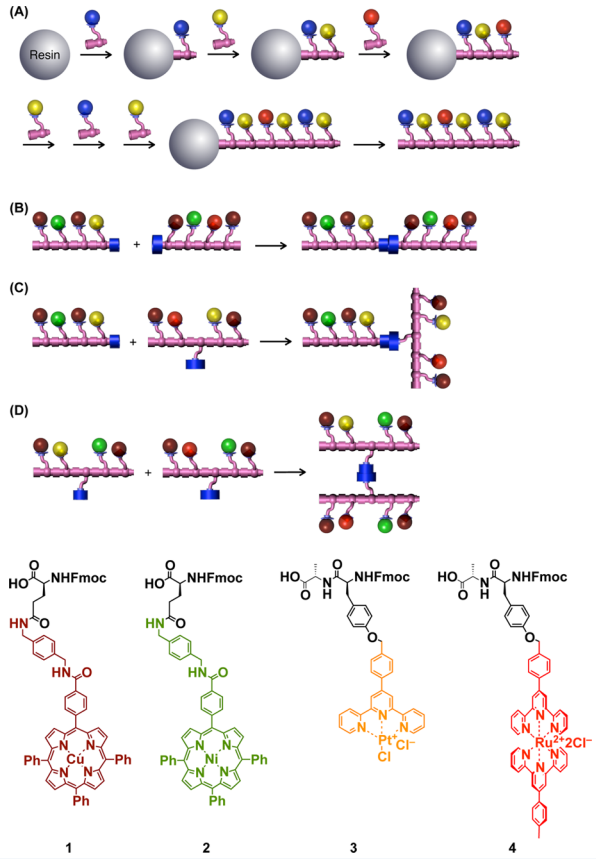
Supporting Information

**ABSTRACT:** A modular synthetic approach is reported for the synthesis of heterometallic metal–organic complex arrays (MOCAs). Modules of four metal centers containing three different metals copper(II), nickel(II), platinum(II), or ruthenium(II) are prepared using a solid-phase polypeptide synthesis technique and then linked in solution to make MOCAs of eight metal centers as linear, T-branched, and H-branched compounds. The MOCA molecular topologies thus have specific unique linear and branched sequences of metals along the peptide backbone.

Building chemical structures from multiple metallic centers of multiple different metals is an outstanding challenge because of phase separation and the increasing number of possible outcomes. Recently, we initiated a program aimed at developing synthetic methods to address this challenge. Our initial success was achieved in 2011 by adapting the sequential method of making peptides using solid-phase synthesis, where amino acids were functionalized, metalated, and then linked to make metal–organic complex arrays (MOCAs) containing up to six metal centers of three different metals arranged in a predetermined sequence (Scheme 1A).[1] In the present report, we show how this approach can be modularized to make larger and longer MOCAs by creating linkages between sequences of MOCAs in solution and then using these as modules in linking them into larger molecules in which metals are arranged in specific unique sequences along the peptide backbone. Specifically, modules of four metal centers containing three different metals are linked to make MOCAs of eight metal centers as linear, T-branched, and H-branched compounds (Schemes 1B–D and 2). Given the lack of reliable synthetic methods leading to multimetal assemblages containing different kind of metals,[2] our ability to produce such MOCAs and the facility with which we can design and place the metal units in specific sequences is a significant advance in the synthesis of unusual large molecules.

Here, our synthetic approach starts from the solid-phase synthesis of MOCA tetrads composed of three different metal complex monomers (Schemes 1B–D and 2). In our previous trials, we experienced that the detection of MOCAs by mass spectrometry became harder and then made their synthesis challenging when they had a large number of metal centers.[1] To help with detection of the expected large MOCAs, we designed a porphyrin-appended glutamate derivative whose copper(II) and

**Scheme 1. Modular Synthesis of MOCAs (A–D) and Molecular Structures of Monomers 1–4**




nickel(II) complexes (**1** and **2**), easily detectable by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry, were linked to a platinum(II) or ruthenium(II) complex of a terpyridine–tyrosine derivative (**3** and **4**) for construction of these modules. The N-terminal of the peptide backbone of a MOCA module served as the point of attachment to make a linear topology once linked to another module at its end (Schemes 1B and 2A). For the combination of modules intended to yield a branching topology, one glutamate was additionally placed at the middle of the peptide sequence so that its side residue

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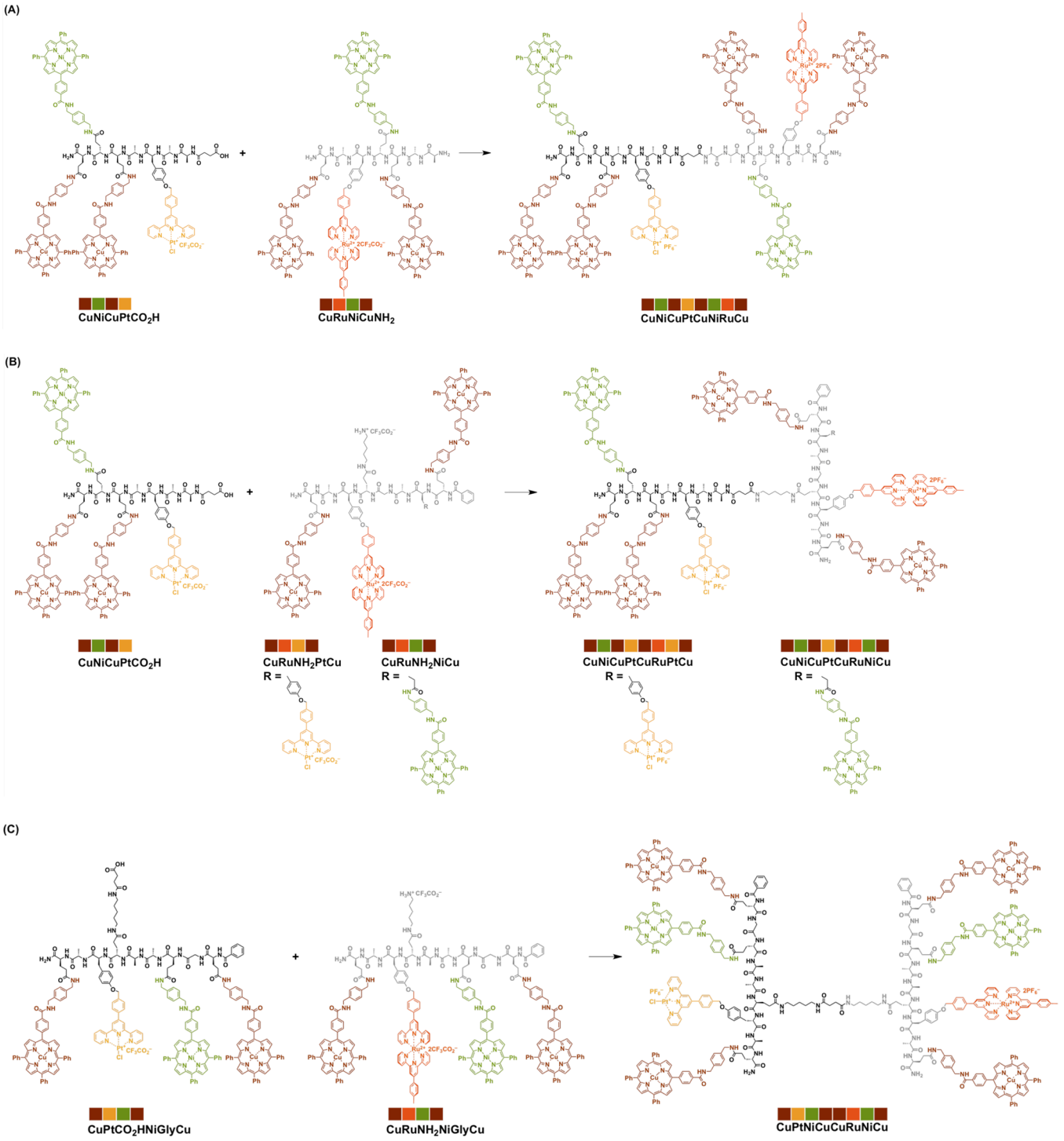
**Scheme 2. Synthetic Schemes for (A) Linear, (B) T-Branched, and (C) H-Branched Octads**




served as the branching point to another module (Schemes 1C,D and 2B,C). Moreover, glycine and alanine units were inserted in the peptide sequence to lower the steric bulk around these functionalities for the connection of modules (Scheme 2). On the basis of such a design principle, six different MOCA modules bearing either of a carboxylic acid or amine functionality were prepared (Schemes 1 and 2) by applying our reported solid-phase synthesis procedures alone,[1,3] followed by combining the resulting MOCAs cleaved from the resin with successive solution-phase functionalization.[4] By linking the appropriate pair of modules among these six through an amide bond, four octanuclear MOCAs containing four different metals in linear, T-branched, and H-branched forms were obtained (Scheme 2).

Details of the experimental procedures and methods are described in the Supporting Information (SI).[4] Here we describe the particulars of the linear CuNiCuPtCuNiRuCu octad as an illustrative example (Schemes 1B and 2A). Coupling of copper, nickel, copper, and platinum monomers and a dialanine unit in this order on the resin and cleavage of the resultant species from the resin afforded N-terminal Fmoc-protected MOCA tetrad CuNiCuPtNHFmoc as a precursor of a module (section S2.2 in the SI and Figure 1a). The tetrad was then subjected to the



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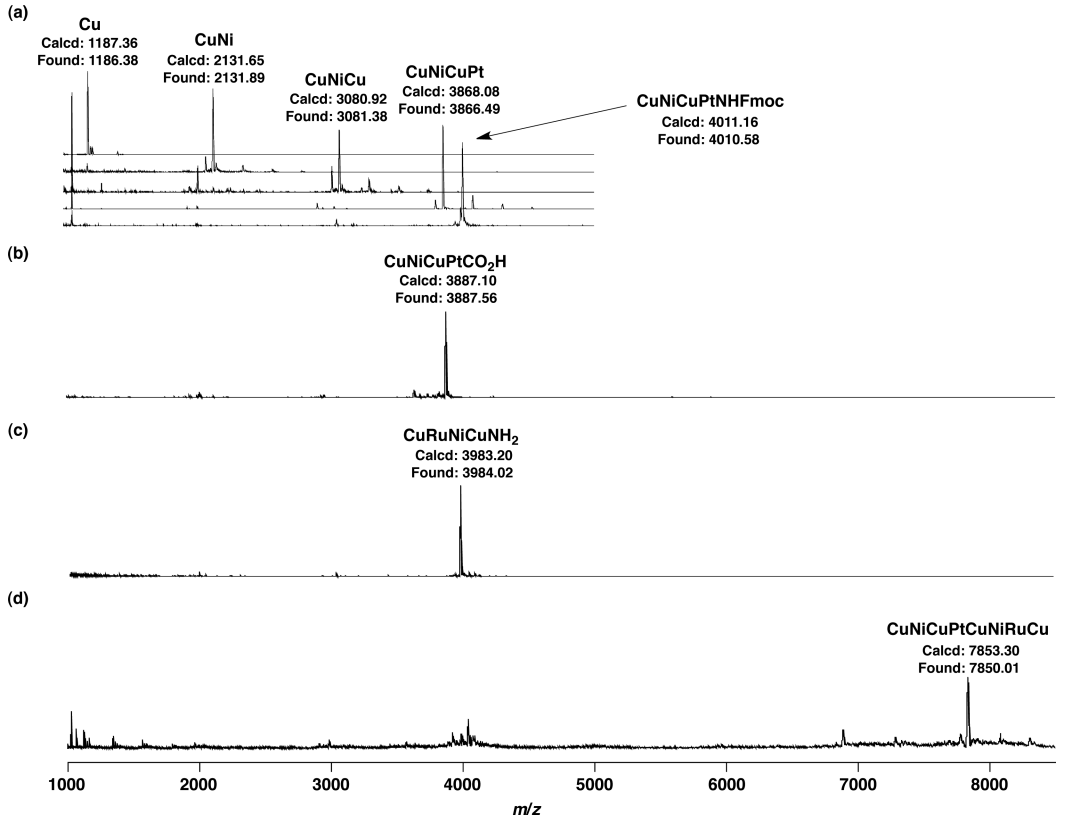


**Figure 1.** MALDI-TOF mass spectra of samples containing (a) copper monomer, CuNi dyad, CuNiCu triad, CuNiCuPt tetrad, and CuNiCuPtNHFmoc tetrad, (b) $CuNiCuPtCO_2H$ tetrad, (c) $CuRuNiCuNH_2$ tetrad, and (d) CuNiCuPtCuNiRuCu octad.

solution-phase Fmoc deprotection reaction, followed by coupling with mono-*tert*-butylsuccinic acid and $^t$Bu deprotection to give $CuNiCuPtCO_2H$ as a module (Scheme 2A and Figure 1b).[4] The other module $CuRuNiCuNH_2$ for the linear octad (Scheme 2A) was prepared and analyzed in a similar way (Figure 1c).[4] Condensation reaction between these two modules in *N*,*N*-dimethylformamide with HBTU/$^i$Pr$_2$NEt afforded a mixture (Scheme 2A),[4] which, after reprecipitation from ethyl acetate, gave a mass signal assignable to the linear CuNiCuPtCuNiRuCu octad. Chromatography of the mixture containing the linear octad on octadecyl-modified silica gel allowed us to obtain a fraction enriched in the targeted sequence, which was further confirmed by mass spectrometry (Figure 1d; the expected and found *m*/*z* values are 7853.30 and 7850.01, respectively).[4]

The molecular weights of the synthesized MOCA octads are close or even exceed those of small proteins such as Ubiquitin (~8500).[5] Given that the modularized approach allows us to access a diverse set of such elaborate sequences of metals in well-defined topologies (Figures S16−19 in the SI), we anticipate the design of sequences that may eventually be used to code for specific properties such as extraordinarily high catalytic activities for tandem-type reactions.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Synthesis and characterization of MOCAs. 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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(2) Although examples of heteronuclear multimetallic species containing up to seven different metals have been reported, the wide applicability of their synthetic processes and their amenability to design are hampered by the trial-and-error nature of their synthesis or the arduous synthetic approaches employed. For examples with more than three different metals, see: (a) Takanashi, K.; Fujii, A.; Nakajima, R.; Chiba, H.; Higuchi, M.; Einaga, Y.; Yamamoto, K. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1563−1572. (b) Packheiser, R.; Jakob, A.; Ecorchard, P.; Walfort, B.; Lang, H. *Organometallics* **2008**, *27*, 1214−1226. (c) Packheiser, R.; Ecorchard, P.; Rüffer, T.; Lang, H. *Organometallics* **2008**, *27*, 3534−3536.

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(4) See the SI.

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