

Synthesis of Metal–Organic Complex Arrays

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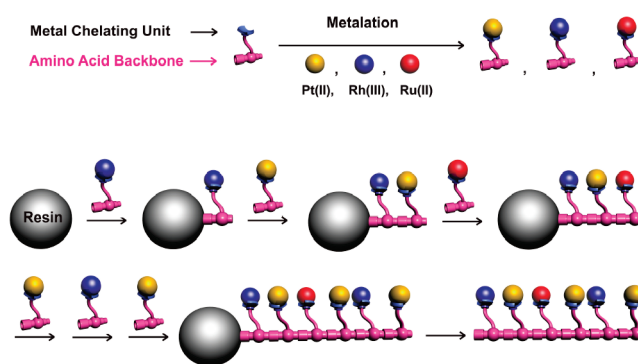
S Supporting Information

ABSTRACT: The Merrifield solid-phase peptide synthesis technique has been adapted to the synthesis of homo- and heterometallic metal–organic complex arrays (MOCAs). A terpyridine-appended and Fmoc-protected *L*-tyrosine derivative was metalated with Pt(II), Rh(III), or Ru(II) ions in solution and sequentially coupled at the surface of functionalized polymeric resin to give a metal complex triad (Rh–Pt–Ru), tetrad (Ru–Rh–Pt–Pt), pentad (Rh–Pt–Ru–Pt–Rh), and hexad (Rh–Pt–Ru–Pt–Rh–Pt) with specific metal sequence arrangements. These were cleaved from the resin, and their character was confirmed by mass spectrometry.

The synthesis of mono- and dinuclear metal complexes by design is a well-developed process, as one is able to successfully make a target complex by judicious choice of metal ions and ligands. However, in attempts to apply this process to the synthesis of multinuclear heterometallic complexes, two major difficulties are encountered: the escalating number of possible structure outcomes (e.g., for six metals with n positions, there are 6^n possibilities) and the tendency to make mixtures of different complexes rather than a complex containing different metals. Both of these factors preclude the synthesis of multinuclear heterometallic complexes and impede the ability to do so in a designable fashion. Access to such materials may lead to highly selective catalysts, cascading reactions, and molecules containing sequences of metal complexes that code for specific chemical transformations. Here we report a protocol for the synthesis of metal–organic complex arrays (MOCAs) containing multiple heterometallic units wherein the metals [Pt(II), Rh(III), and Ru(II)] are arranged in a specific sequence. Our strategy is based on the Merrifield solid-phase peptide synthesis,¹ and we used this established technique to produce heterometallic dyad, triad, tetrad, pentad, and hexad complexes. We also present details of how specific sequences of metals can be achieved.

Our synthetic approach takes advantage of the consecutive nature of polypeptide synthesis, where the order in which the amino acids are added determines their sequence in the product (Scheme 1). To implement this plan, we functionalized tyrosine with a multidentate ligand, allowed the ligand to bind a metal, and then proceeded to link this unit through the tyrosine peptide bond in the usual manner. Consequently, a specific multimetallic unit of the desired length, nuclearity, and sequence could be

Scheme 1



obtained simply by controlling the number of tyrosine units and the order in which they were added.

Examples of complexes containing up to three or four different metals have been made by “self-assembly”.² More recently, a string of metatheses, dehydrohalogenations, and carbon–carbon cross-coupling reactions yielded complexes containing up to seven different metal ions.³ The wide applicability of these processes and their amenability to design are hampered by the trial-and-error nature of their synthesis or the arduous synthetic approaches employed. The present report describes a general method for producing multinuclear heterometallic complexes with controlled length, nuclearity, and sequence.

Our synthetic protocol (Scheme 2) began with a known ^tBu- and (fluoren-9-yl)methoxycarbonyl (Fmoc)-protected *L*-tyrosine (A) that was reacted with a terpyridine chelating unit (TPy) to give protected Tyr–TPy (B). Deprotection of the ^tBu group followed by metalation using a choice of metals afforded metal complex monomers (C). In the case of the Ru(II) complex, metalation and successive ligation with another TPy preceded the deprotection. The metal complex monomer was then coupled with amino functionalities on the resin (D). For elongation of the polypeptide backbone, the Fmoc group at the N-terminal of the polypeptide backbone was deprotected (D') and another metal complex monomer was coupled (D). D' and D were alternately repeated in that order until the targeted metal complex sequence was obtained on the resin, and then the sequence was cleaved from the resin (E). With these procedures, heterometallic dyad, triad,

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Scheme 2

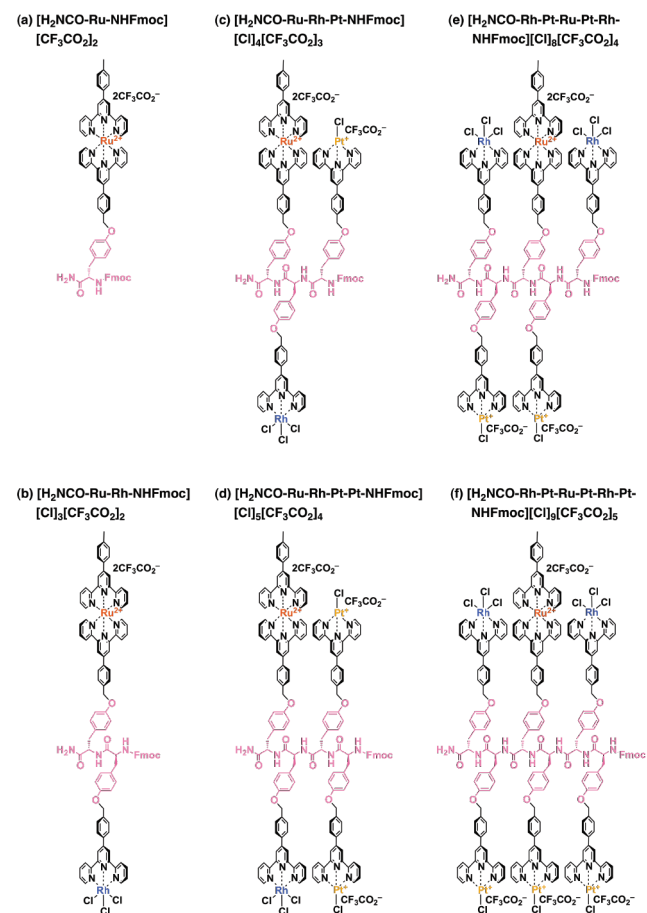
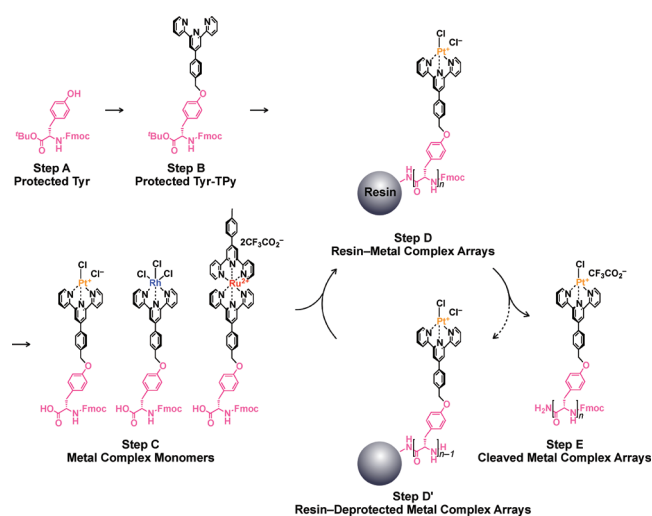


Figure 1. Molecular structures of selected metal–organic complex arrays.

tetrad, pentad, and hexad complexes were obtained (Figure 1 and Figure S13 in the Supporting Information). Details of the experimental procedures and methods are described in the Supporting Information.⁴ Here we describe the particulars of the heterometallic tetrad $[\text{H}_2\text{NCO-Ru-Rh-Pt-Pt-NHFmoc}][\text{Cl}]_5[\text{CF}_3\text{CO}_2]_4$

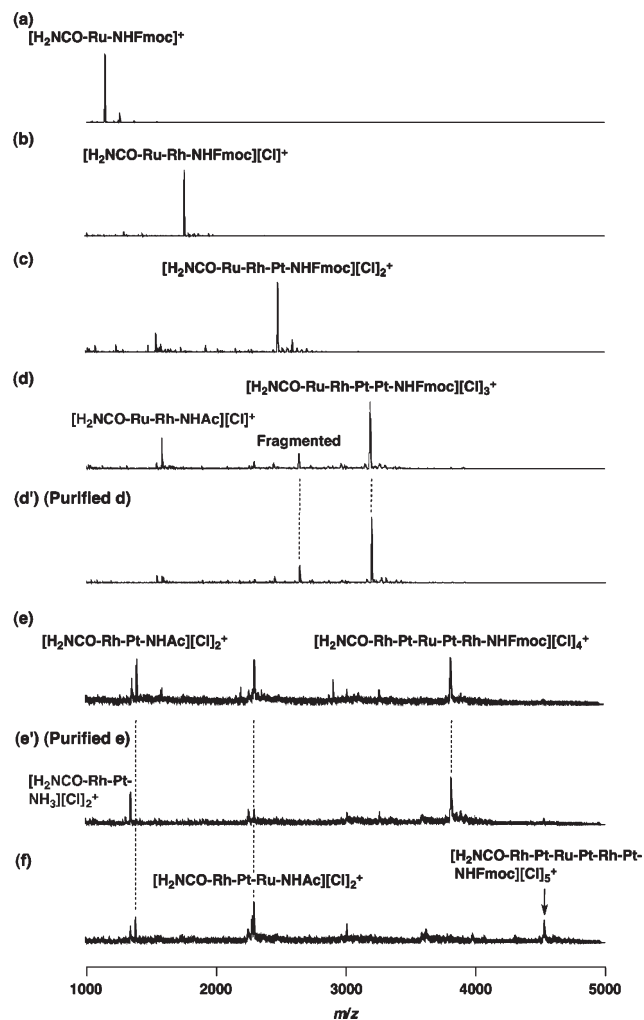


Figure 2. MALDI-TOF mass spectra of as-cleaved from the resin samples containing the (a) Ru monomer, (b) Ru–Rh dyad, (c) Ru–Rh–Pt triad, (d) Ru–Rh–Pt–Pt tetrad, (e) Rh–Pt–Ru–Pt–Rh pentad, and (f) Rh–Pt–Ru–Pt–Rh–Pt hexad.

(Figure 1d) as an illustrative example. MALDI-TOF mass spectrometry confirmed the loading of the monomer and that it was cleaved from the resin (Figures 1a and 2a). After coupling of the Rh complex monomer (Scheme 2) with the previously loaded and Fmoc-deprotected Ru complex on the resin, the cleaved mixture exclusively gave a signal at m/z 1769.15, which is close to the calculated value of m/z 1770.40 for the Ru–Rh heterometallic dyad (Figures 1b and 2b). When the cycle of Fmoc-deprotection/coupling with Pt complex monomer was repeated on the resultant resin two times, signals at m/z 2483.25 (Figure 2c) and then 3197.28 (Figure 2d) were clearly observed. Again, the observed values were in agreement with those calculated for the Ru–Rh–Pt triad (Figure 1c; m/z 2485.52) and the Ru–Rh–Pt–Pt tetrad (Figure 1d; m/z 3201.65), respectively. Chromatography of the cleaved mixture containing the tetrad on Bio-Rad Bio-Beads S-XI allowed us to obtain a fraction enriched in the targeted sequence, which was further confirmed by mass spectrometry to be the same as the tetrad (Figure 2d'). The same procedure was followed to obtain another tetrad sequence Rh–Pt–Ru–Pt, which was further extended into the corresponding pentad (Figures 1e and 2e) and hexad (Figures 1f and 2f). For these longer arrays, again the expected and found m/z values matched well (3822.70 and

3824.36 for the pentad and 4538.83 and 4537.71 for the hexad, respectively).

In solid-phase polypeptide synthesis, products on the resin at every synthetic step are easily separated from unreacted amino acids and other reagents in solution by washing the resin with proper solvents.⁵ This is one of the general important advantages of solid-phase synthesis in comparison with solution-phase synthesis. This advantage is especially attractive for the synthesis of multimetallic complexes, as a limited number of versatile methods are available for their separation. On the other hand, since the conventional protocols of solid-phase polypeptide synthesis have been optimized for pure organic amino acids, we learned that there are a number of requisites for the application of the same methodology for metal–organic complex arrays: large amounts of metal complex monomers to allow full coverage of the resin, efficient peptide bond formation/Fmoc deprotection on the resin under the conditions necessary to produce the sequence, quantification of the reaction conversion efficiency, removal of unreacted metal complex monomers and other reagents from the resin, suppression of the production of undesired sequences due to the nonquantitative peptide bond formation, and cleavage of the products on the resin under mild conditions without their decomposition and sequestering into the cross-linked polymer network of the resin. In Sections S10–S18,⁴ we outline the full reaction workup procedures that allowed us to successfully deal with these issues in the synthesis of MOCAs.

It was critical to confirm that no metal exchange took place during the full reaction workup procedures. Any metal exchange would give unexpected sequences with disproportionate relative metal-to-metal content. We confirmed the absence of metal exchange activity in the metal complex monomers on the basis of the fact that ¹H NMR spectra of mixtures containing one of the monomers and another terpyridine ligand that were kept standing for 2 days at 25 °C showed no resonances to the nonmetalated Tyr-based ligand (singlet peaks assignable to metalated terpyridine benzyl protons appear at δ 5.22, 5.22, and 5.26 in Figure S1a–c, respectively, while that for nonmetalated terpyridine appears at δ 5.14 in Figure S1d). Furthermore, the absence of metal exchange was supported by the fact that no other sequences with unexpected metal content were detected by mass spectroscopy. Specifically, the as-cleaved products (Scheme 2E) did not display molecular weight signals attributable to any unexpected metal sequences (Figure 2).

Given the diversity of metal complex monomers that could be made with various amino acids, chelating units, and metal ions and the simple methodology we have developed for making MOCAs, it should be possible to achieve a large number of sequences with wide-ranging applications.

■ ASSOCIATED CONTENT

S **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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- (5) *Synthetic Notes in Peptide Synthesis 2008/2009*; White, P., Dörner, B., Eds.; Merck: Darmstadt, Germany, 2008.