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Water-Soluble Macrocycles Synthesized via the Weak-Link Approach

Michael J. Wiester and Chad A. Mirkin*

Department of Chemistry and the International Institute for Nanotechnology, Northwestern University, Evanston, Illinois 60208-3113

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We report a general, high-yielding method for the synthesis of water-soluble complexes, which is based upon the weak-link approach to supramolecular coordination chemistry. Specifically, we have utilized oligomeric ethylene glycol functional groups appended to the aryl groups of the diphenylphosphine moieties to achieve solubility. Small molecules or halide ions can be used to expand these complexes into larger, more flexible macrocyclic structures. The realization of this approach should allow for the preparation of allosteric biomimetic structures which can be used in aqueous media.

For decades, chemists have been attempting to mimic the sophisticated structures and exquisite reactivity of compounds commonly found in nature. To effectively realize the properties of such systems, and enzymes in particular, chemists need high-yielding synthetic strategies that allow one to construct highly functional molecules (1) with tailorable recognition and catalytic properties, (2) that are dynamic and conformationally addressable, and (3) that exhibit solubility in aqueous media.[1] Coordination chemistry provides a platform for synthesizing biomimetic supramolecular structures, whereby it is possible to assemble structures in a convergent manner and typically in high yields and with excellent selectivity.[2,3] In this regard, structures that mimic the reactivity of enzymes have been prepared by a variety of different researchers.[4] Some of these structures are highly charged and soluble in aqueous media, creating a hydrophobic reaction pocket where, in some instances, new or unusual reactivity is observed.[5] For example, the Fujita group has shown that a cagelike complex in the shape of an octahedron can accelerate the Diels–Alder cyclization between anthracene and *N*-cyclohexylmaleimide, where the maleimide reacts at the terminal anthracene ring instead of the central one, as is typically seen.[5a] In a second example, Raymond and co-workers have demonstrated that a reaction that is normally acid-catalyzed, the hydrolysis of orthoformates, proceeds in the cavity of a tetrahedron-shaped complex in basic solutions.[5b] It should be noted that both of these examples use rigid, nonconformationally addressable structures, and there are relatively few coordination-chemistry-based synthetic strategies which allow one to construct molecules that exhibit all of the aforementioned properties.

There are many powerful methods for constructing large biomimetic systems. Two of the most popular and extensively developed are the directional-bonding approach[2] and the weak-link approach (WLA).[3,6] The former yields large rigid structures with well-defined cavities, while the latter yields two types of structures that can be chemically interconverted through small molecule reactions that occur at metal hinge sites (Figure 1). Therefore, the WLA allows one to fulfill two of the requirements for a biomimetic structure in that it yields complexes that can have tailorable pockets for both stoichiometric and catalytic reactions and structures that can be chemically toggled between active and inactive conformations, much in the way a natural allosteric system works. Indeed, this approach has been used to prepare a vast array of supramolecular structures, including mimics of single and multieffector allosteric enzymes, enzyme linked immunosorbent assay, and polymerase chain reaction.[7] However, thus far, all structures made by the WLA are only soluble in

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*To whom correspondence should be addressed. E-mail: chadnano@northwestern.edu.

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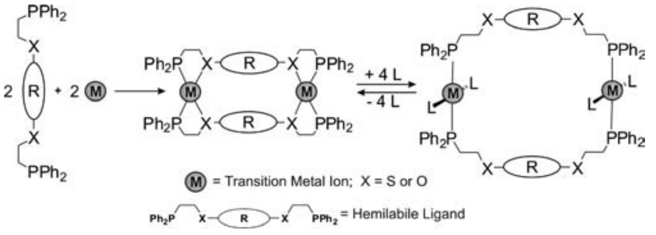


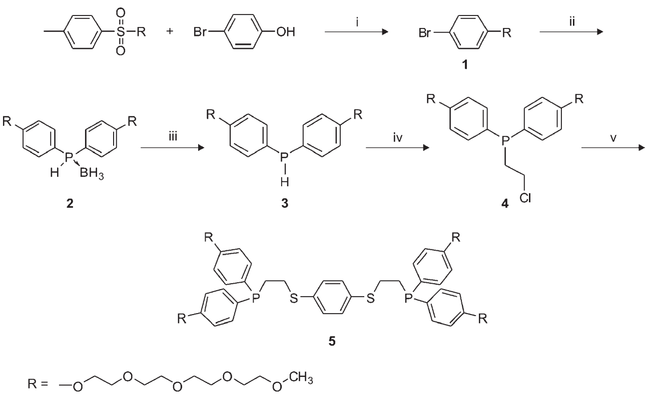
Figure 1. General strategy of the WLA.

organic solvents, limiting studies of such systems to environments that are not relevant to the structures one is trying to mimic. Herein, we present a general, high-yielding synthetic methodology for the synthesis of a new type of water-soluble hemilabile ligand that can be used in the WLA to rapidly prepare water-soluble macrocyclic coordination complexes from d^8 transition metal centers.

There are a variety of ways to make ligands water-soluble. They include the incorporation of charged groups, such as metal ions or sulfonate, carboxylate, or ammonium salts, or functional groups that can form hydrogen bonds with water, such as ethylene glycol.[8,9] To minimize the challenge of ligand purification, we targeted hemilabile structures with nonionic oligomeric ethylene glycol functional groups appended to aryl moieties. This approach has many benefits. First, all of the intermediates en route to the target ligand can be purified by column chromatography. Second, the metal complexes formed from such ligands typically are soluble in water as well as polar organic solvents such as CH$_2$Cl$_2$, THF, and MeOH. Third, the oligomeric ethylene glycol functionality does not compete with the ligating properties of the hemilabile ligand with respect to the transition metal centers of interest.

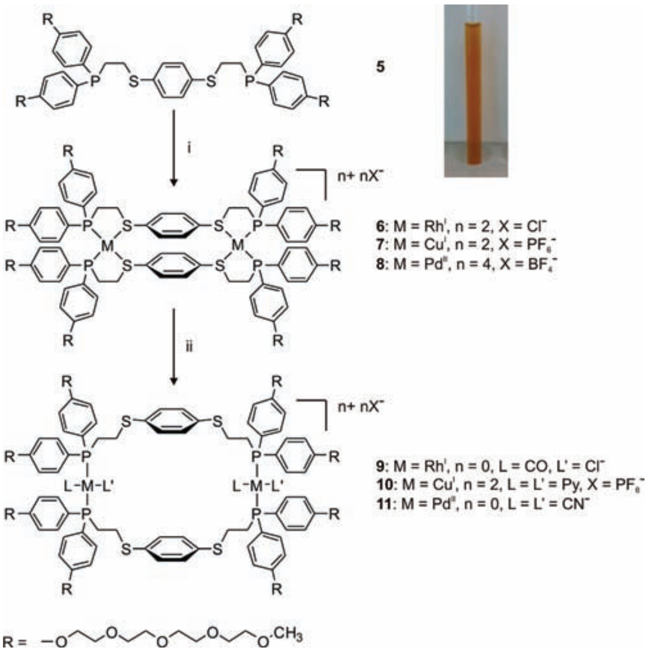
Water-soluble hemilabile ligand **5** was synthesized in five steps in 61% yield starting with commercially available p-bromophenol and p-toluene sulfonic acid 2-{2-[2-(2-methoxy−ethoxy)-ethoxy]-ethoxy}-ethyl ester (Scheme 1). These starting reagents were converted to 1-bromo-4-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-benzene, **1**, by refluxing in a DMF solution of K$_2$CO$_3$. Diethylphosphoramidous dichloride was used to prepare the Lewis acid (BH$_3$) complexed diarylphosphine with oligomeric ethylene glycol groups, **2**, in a one-pot procedure. The borane protecting group allows for purification under ambient conditions without the formation of phosphine oxide. The protecting group can be removed under mild conditions using piperazine.[10] To achieve this deprotection, we used polymer-bound piperazine, which can be readily removed from the reaction mixture, after the reaction, using filtration. The deprotection reaction can be followed using ^{31}P{^{1}H} NMR spectroscopy, with the resonance corresponding to **2** at −2.8 ppm decreasing with a concomitant increase in the intensity of the resonance for BH$_3$-free **3** at −44.4 ppm.[10] Compound **3** was converted into the chloroethyl diarylphosphine **4** by lithiation followed by reaction with 1,2-dichloroethane. Like 1-chloro-2-diphenylphosphinoethane, compound **4** will react with benzenedithiol to form the targeted ligand **5**. Compounds **1**−**5** have been characterized by ^{1}H, ^{31}P{^{1}H}, ^{13}C{^{1}H}, and ^{11}B{^{1}H} NMR spectroscopy and high-resolution mass spectrometry (see the Supporting Information).

Scheme 1. Synthesis of Water-Soluble Ligand **5**[a]



[a] (i) K$_2$CO$_3$, DMF, reflux, 90%. (ii) (a) *n*-BuLi, Cl$_2$P(NEt$_2$), THF, −78 °C; (b) HCl, THF, −78 °C; (c) LiBH$_4$, THF, 0 °C, 77%. (iii) Polymer-bound piperazine, THF, 60 °C, >99%. (iv) *n*-BuLi, ClCH$_2$CH$_2$Cl, THF, −78 °C, 95%. (v) 1,4-Benzenedithiol, K$_2$CO$_3$, CH$_3$CN, reflux, 95%.

Scheme 2. Synthesis of Water-Soluble Complexes[a]



[a] (i) For **6**, [Rh(cyclooctene)$_2$Cl]$_2$, CH$_2$Cl$_2$; for **7**, Cu(CH$_3$CN)$_4$PF$_6$, CH$_2$Cl$_2$; for **8**, Pd(CH$_3$CN)$_4$(BF$_4$)$_2$, acetone, CH$_2$Cl$_2$. (ii) For **9**, CO (1 atm), D$_2$O; for **10**, pyridine, D$_2$O; for **11**, KCN, D$_2$O. Inset: A photograph of a solution of **11** in D$_2$O.

To probe the reactivity of ligand **5**, we synthesized a series of transition metal complexes, **6**, **7**, and **8**, from it and a variety of metal ions (Rh^I, Cu^I, and Pd^{II}, respectively; Scheme 2). These complexes were formed by adding 1 equiv of **5** in CH$_2$Cl$_2$ to a CH$_2$Cl$_2$ solution of the appropriate metal

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ion precursor. All of the resulting binuclear complexes were isolated as viscous oils and were characterized by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy and high-resolution mass spectrometry. The ^{31}P{^{1}H} NMR spectrum of each complex in CD_2Cl_2 exhibits a single highly diagnostic resonance in the δ 61−64 range for **6** and **8** and near δ 0 for **7**, assigned to the corresponding highly symmetric rigid condensed macrocycle with a *cis*-phosphine coordination environment. Each of these resonances are within 2 ppm of model complexes without oligomeric ethylene glycol groups.[11,12] All other data are fully consistent with the proposed structures **6**−**8**.

The most extensively characterized macrocycles made via the WLA are Rh^I complexes, and ^{31}P{^{1}H} NMR spectroscopy is one of the most utilized tools for the characterization of these complexes. For example, complex **6** contains a doublet at δ 63.7 with a diagnostic J_{Rh-P} coupling constant of 161 Hz, which is indicative of a phosphine−thioether ligand chelated to the rhodium with the phosphines bound in a cis fashion.[11] The high-resolution mass spectrum of **6** exhibits the expected M^{2+} ion peak at *m*/*z* 1494.6748. When CO is added to a solution of complex **6**, complex **9** is formed immediately and in quantitative yield, as seen in the ^{31}P{^{1}H} NMR spectrum. Complex **9** exhibits the expected upfield shift in its ^{31}P{^{1}H} NMR spectrum,[11] a doublet at 23.3 ppm with a J_{Rh-P} coupling constant of 110 Hz, which indicates that the thioether ligand is no longer chelated to the rhodium and the complex contains a *trans*-P−Rh−P coordination environment.[11] Significantly, the opened macrocycle **9** is also soluble in aqueous media, despite its neutral charge, because of the presence of the oligomeric ethylene glycol moieties. All of the synthesized complexes exhibit ^{31}P{^{1}H} NMR resonances that correspond well with analogous complexes without oligomeric ethylene glycol units (see the Supporting Information).[11,12]

Interestingly, complexes **6**−**8** exhibit solubility in water where small molecules or halide ions can be used to expand them into larger, more flexible macrocyclic structures such as **9**−**11**. The type of small molecules and halide used for this ring expansion depend upon the transition metal center. The Pd^{II} complex **8** can be opened by the addition of CN^-, the Cu^I complex **7** by the addition of a nitrogen donor such as pyridine, and the Rh^I complex **6** by the addition of Cl^- and CO (1 atm).[6] All of the open complexes, except **10**, are uncharged yet highly soluble in water (e.g., **11** in Scheme 2, inset).

In conclusion, we have described the synthesis of a new water-soluble hemilabile ligand **5**, suitable for use in the WLA. Using a variety of transition metal precursors, we have synthesized a series of condensed macrocyclic structures, which can be opened into flexible water-soluble macrocycles through ligand displacement reactions. These are the first water-soluble complexes made by the WLA, and their realization points toward routes to biomimetic structures that can function as novel catalysts and amplified chemical detection systems.[7] Significantly, this strategy of appending oligomeric ethylene glycol groups to hemilabile phosphine-containing ligands should be general enough to confer water solubility to many ligands previously used in the WLA.

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Supporting Information Available: Experimental procedures for compounds **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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