

Chiral, Metallomacrocycles

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One of the challenging problems to chemists is the creation of synthetic receptors having the remarkable binding properties seen in biological receptors such as enzymes and antibodies.¹ To construct such receptors, chemists use the multi-step synthetic methodology to make macrocyclic structures that have the shape and functionalities to complement to those of a given substrate. However, the macrocyclization reactions required much synthetic effort and the general applicability of these reactions still is limited because these are good for certain types of substrate only.

Recently, an alternative method in which a metallo-macrocyclic receptor self-assembles from a flexible ligand by exploiting metal-ligand coordinate bond is recognized as an efficient method to construct molecular receptors.² In metallo-macrocyclic receptors, metal acts to maintain macrocyclic structure and thus makes the receptor to be preorganized for the effective complexation with the corresponding substrates. Besides, certain metals can offer the following advantages: (1) changes in the coordination number and geometry of different metals can allow a modification of the shape of templated receptor sites, (2) certain metals can act both to organize receptor site formation, and as catalytic center for subsequent reaction on a bound substrate as seen in metalloenzyme, (3) upon complexation with a substrate, certain metals can act chromogenic center and thus have the potential applicability for chemical sensors.

Over past few years, a variety of metal templated self-assembling metallo-macrocycles have been reported.³ Of great challenge yet importance is to construct more biologically relevant, self-assembling receptors with chirality and functionalities as seen in biological receptors such as enzymes and antibodies. Here, we describe Zn(II), Cu(II) and Ni(II) templated self-assembling, chiral metallo-macrocyclic receptors with binding sites having convergent hydrogen bonding donor/acceptor functionalities, as well as hydrophobic surface.

Syntheses of receptor **1**, **2** and **3** began with the preparation of the flexible ligand. DIC-promoted amide coupling reaction between bis-carboxylic acid⁴ and mono-Boc-(1R,2R)-1,2-diaminocyclohexane and the subsequent reaction with Boc-4-aminobenzoyl pentafluorophenyl ester provide

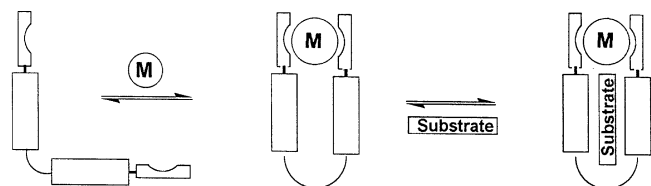
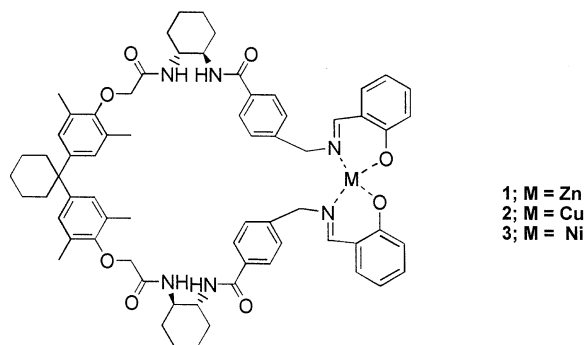


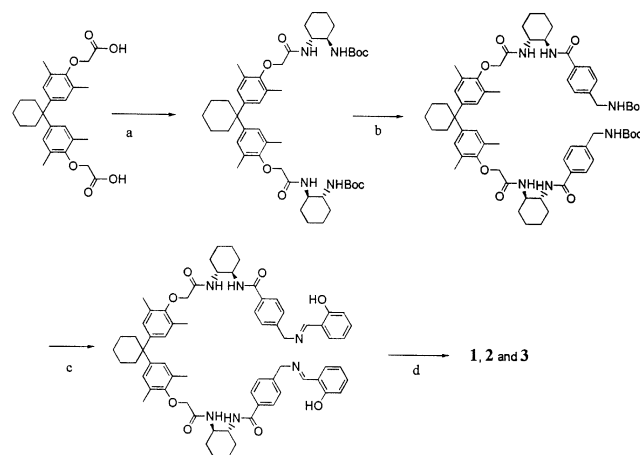
Figure 1. Schematic representation of metallomacrocyclic receptors.



Scheme 1. Structure of Metallomacrocyclic Receptors (1-3).

bis-amine intermediate. Bis-salicylidene imine ligand was prepared by heating the mixture of bis-amine intermediate and salicylaldehyde in ethanol.⁶ Metallomacrocycles were prepared by exploiting Zn(II), Cu(II), Ni(II)-salicylidene imine coordinate bond.⁵ The Zn(II) complex **1** was prepared as white solids with 55% yield by mixing 0.5 eq. of Zn(OAc)₂ and the corresponding ligand in ethanol, stirring for 3 hrs under reflux condition, then adding diethyl ether. The Cu(II), Ni(II) complexes **2** and **3** were prepared as dark green solids with 45% and 41% yield under the similar condition. The products, M(II) complexes **1**, **2** and **3**⁷⁻⁹ are air-stable, moisture-insensitive, and soluble in various organic solvents including dichloromethane, chloroform, acetone, and dimethyl sulfoxide.

The structures of **1**, **2** and **3** were established by mass spectrum, ¹H NMR spectroscopy, IR and UV spectroscopy. In ¹H NMR spectrum of **1**, upon complexation with Zn the



Scheme 2. Syntheses of Metallomacrocyclic Receptors (1-3); (a) DIC, HOBT, mono-Boc-(1R,2R)-1,2-diaminocyclohexane. (b) TFA, then Et₃N, Boc-4-aminobenzoyl pentafluorophenyl ester. (c) TFA, then Et₃N, Salicylaldehyde. (d) M(OAc)₂.

resonance peak of arising from the benzylic protons changes from singlet at 4.84 ppm to AB quartet ($J = 13.5$ Hz) at 4.11 and 4.32 ppm. Also the resonance peak of arising from the imine protons shows upfield-shift from 7.82 to 7.37 ppm due to the effect of aromatic groups. Furthermore, upon complexation the disappearance of resonance peak of arising from the phenolic protons of the ligand at 13.3 ppm is compatible with the proposed structure. In IR spectrum of **1**, **2** and **3**, upon complexation the absorption band arising from the imine stretching shift from 1632 to 1618, 1622 and 1613 cm^{-1} , respectively. Also, in UV/VIS spectrum of **1**, **2** and **3**, upon complexation the absorption peak of ligand show the red shift from 318 to 376, 370 and 420 nm, respectively. These observations are well compatible with the proposed structures. In mass spectrum of **1**, **2** and **3**, the detection of peaks arising from $M+1$ at m/z 1170, 1169 and 1164 confirm the proposed structures.

In conclusion, Zn(II), Cu(II), Ni(II) templated macrocyclic, chiral receptors with the well-defined binding cavity were successfully prepared from the flexible bis-salicylidene imine ligand. The binding properties of these receptors using NMR titration method and solid phase color assay¹⁰ are investigated in this laboratory and will be reported in due course.

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6. Spectroscopic data of ligand: ^1H NMR (DMSO- d_6) δ 1.26-1.50 (m, 10H), 1.71-2.07 (m, 16H), 3.77 (m, 2H), 3.92 (m, 2H), 4.02 (dd, 4H, $J = 14.5, 8.5$ Hz), 4.84 (s, 4H), 6.81 (s, 4H), 6.87 (d, 2H, $J = 8.0$ Hz), 6.91 (t, 2H, $J = 7.5$ Hz), 7.33 (t, 2H, $J = 7.5$ Hz), 7.38 (d, 2H, $J = 8.0$ Hz), 7.48 (dd, 2H, $J = 6.0, 1.5$ Hz), 7.55 (d, 2H, $J = 7.5$ Hz), 7.76 (d, 4H, $J = 8.5$ Hz), 8.22 (d, 2H, $J = 8.5$ Hz), 8.72 (s, 2H), 13.34 (s, 2H); IR (KBr) 3309, 2934, 1632, 1536, 1501, 1455 cm^{-1} ; UV/Vis (CH_2Cl_2 soln) 240, 253, 318 nm.
7. Spectroscopic data of **1**: ^1H NMR (DMSO- d_6) δ 1.28-1.53 (m, 10H), 1.73-2.08 (m, 16H), 3.72 (m, 2H), 3.93 (m, 2H), 3.96 (dd, 4H, $J = 13.5, 8.0$ Hz), 4.32 (dd, 4H, $J = 13.5, 8.0$ Hz), 6.52 (t, 2H, $J = 8.5$ Hz), 6.54 (d, 2H, $J = 7.0$ Hz), 6.74 (s, 4H), 7.13 (d, 4H, $J = 8.5$ Hz), 7.20 (t, 2H, $J = 7.5$ Hz), 7.22 (d, 2H, $J = 7.5$ Hz), 7.52 (d, 4H, $J = 8.5$ Hz), 7.81 (d, 2H, $J = 7.5$ Hz), 8.10 (d, 2H, $J = 8.0$ Hz), 8.37 (s, 2H); ^{13}C NMR (CDCl_3) δ 14.81, 17.16, 23.34, 25.34, 25.69, 32.87, 37.86, 45.50, 53.12, 53.36, 64.11, 71.28, 115.64, 117.76, 118.72, 119.41, 128.25, 129.49, 130.09, 130.59, 134.08, 136.14, 136.55, 139.85, 145.40, 152.78, 166.83, 170.96, 171.88; IR (KBr) 3328, 2934, 1644, 1618, 1536, 1503, 1447 cm^{-1} ; UV/Vis (CH_2Cl_2 soln) 239, 273, 376 nm; MS (FAB) $m/z = 1170$ (MH^+).
8. Spectroscopic data of **2**: IR (KBr) 3325, 2934, 1622, 1536, 1503, 1450 cm^{-1} ; UV/Vis (CH_2Cl_2 soln) 237, 269, 304, 370 nm; MS (FAB) $m/z = 1169$ (MH^+).
9. Spectroscopic data of **3**: IR (KBr) 3327, 2934, 1613, 1538, 1502, 1451 cm^{-1} ; UV/Vis (CH_2Cl_2 soln) 236, 331, 420 nm; MS (FAB) $m/z = 1164$ (MH^+).
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