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A Self-Assembling Receptor for Dicarboxylic Acids

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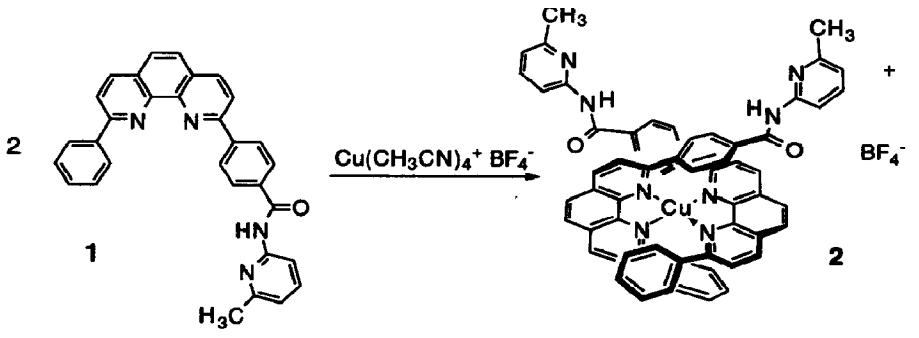
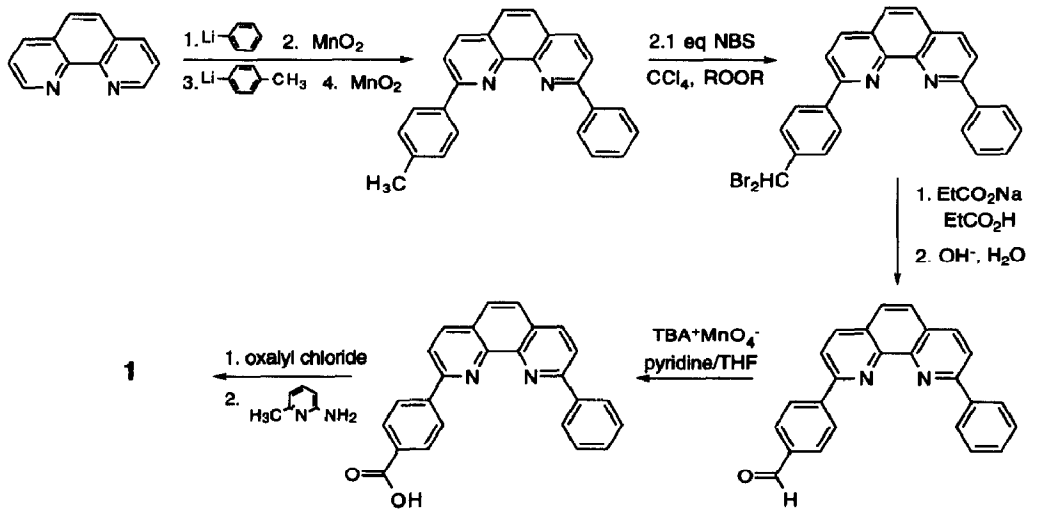
Abstract: In this paper we describe a simple binding subunit that self-assembles in the presence of metal ions to form a receptor for dicarboxylic acids. The resultant binding site is chiral and strong complexation to dicarboxylic acids in $CDCl_3$ can be detected by both NMR and UV-vis spectroscopies.

In recent years there have been many reports of synthetic receptors in which multiple binding sites are held within a covalent framework.[1,2] These often involve multi-step synthesis to achieve a proper orientation of the binding groups to complement those of the intended substrate. An alternative approach can be envisioned in which a receptor self-assembles from smaller constituents. In this way two or more *separate* molecules come together through noncovalent interactions to form the active receptor.[3,4] Such self-assembly is commonly seen in biological receptors such as HIV protease, which undergoes a dimerization to bring together the key groups in its active site.[5] Our strategy is to use the coordination environment of a transition metal to assemble and organize multiple hydrogen bonding sites. Ligand coordination to metals has been used extensively to assemble elaborate structures[6-8] or to induce an allosteric effect on binding at another site,[9-11] but has been little considered as a template for the construction of receptors.[4] In this paper we describe a phenanthroline derivative **1** that self-assembles in the presence of Cu(I) ions to a bis-(2-acylaminopyridine) receptor for dicarboxylic acids.[12] This approach has the advantage of not only bringing together two very simple halves by chelation but also exploiting the presence of the metal ion in the framework of the receptor as a spectroscopic reporter group for detecting binding.



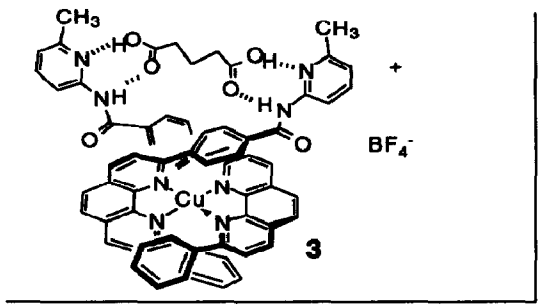
The key subunit **1** was prepared from 1,10-phenanthroline by straight-forward steps according to the route outlined in Scheme 1.[13,14] Addition of 0.5 equivalents of $Cu(CH_3CN)_4^+BF_4^-$ in CH_3CN/CH_2Cl_2 to **1** (1 equivalent) creates a distorted tetrahedral,[15] bis-phenanthroline complex **2** with two acylaminopyridine moieties properly oriented for dicarboxylic acid binding. The complex is a dark red, air stable solid, easily purified by chromatography and is very soluble in $CHCl_3$.

Scheme 1



The interaction of **2** with dicarboxylic acids in $CHCl_3$ was followed by ^1H NMR titrations. Addition of small aliquots of glutaric acid to a 1.00 mM $CDCl_3$ solution of **2** resulted in chemical shift changes in all the protons of the receptor. The most pronounced changes occurred in the NH protons of the receptor, which shifted downfield by 2.4 ppm, indicative of hydrogen bond formation. Analysis of the titration curve[16] gave an association constant ($K_a \sim 4.3 \times 10^4\ M^{-1}$) that was too high to be measured accurately by NMR methods. However, a 1:1 stoichiometry for the glutaric acid/**2** complex was confirmed by a Job's plot, which showed a maximum at a mole fraction of 0.5. In the absence of Cu(I), phenanthroline **1** and glutaric acid form a 1:1 complex with $K_a = 2.7 \times 10^3\ M^{-1}$. This is somewhat higher than expected for one carboxylic acid-aminopyridine interaction (normally $\sim 2 \times 10^2\ M^{-1}$), suggesting that an additional hydrogen bond between the second carboxylic acid and phenanthroline-N is present. In support of this, propionic acid and **1** were shown to form a 1:1 complex[17] with an association constant of $1.9 \times 10^2\ M^{-1}$. Nonetheless, these results clearly show that the binding of glutaric acid to **2** in $CDCl_3$ is much stronger than for receptor **1** alone, indicating the involvement of a four hydrogen bonded complex of the type shown in **3**.

A slight color change (red-orange→orange-red) was observed in solutions of **2** upon addition of dicarboxylic acids. Figure 1 shows the effect of glutaric acid on the UV-visible spectrum of **2**. A slight blue shift occurs in λ_{max} in addition to an increase in the intensity of the long wavelength shoulder. The lower concentrations necessary for UV-vis spectroscopy allowed these changes to be used in a more accurate determination of the value of K_a for a variety of dicarboxylic acids. The results are tabulated in Table I and are in good agreement with the NMR result for glutaric acid.



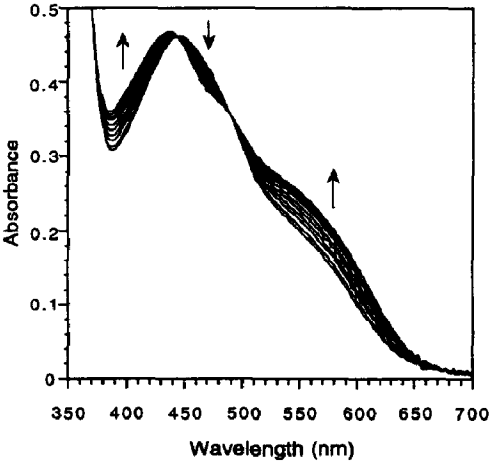


Figure 1. Change in UV-vis of **2** upon addition of glutaric acid in $CDCl_3$.
[**2**] = 0.125 mM.
[glutaric acid] = 0 - 0.40 mM.

Table I also shows λ_{max} and the change in relative absorptivity at 550 nm for each substrate/receptor combination. These changes are substrate dependent with, for example, pimelic acid giving a less pronounced increase in the long wavelength shoulder and a smaller blue shift in λ_{max} (for **2**, λ_{max} = 445 nm) than complexation of the 5-carbon acids, glutaric and *N*-Cbz-L-glutamic. A lengthening of the dicarboxylic acid by only two carbon atoms thus results in half the change in absorptivity upon complexation.

Table I. UV-vis Binding Constants for **2** with Dicarboxylic Acids

Dicarboxylic Acid	Binding Constant (K_a)	λ_{max} (nm)	% Increase (λ=550 nm)
glutaric acid	$4.9 \times 10^4\ M^{-1}$	436	30
pimelic acid	$1.5 \times 10^4\ M^{-1}$	440	15
1,3-phenylenediacetic acid	$3.4 \times 10^4\ M^{-1}$	434	31
N-Cbz-L-glutamic acid	$7.0 \times 10^4\ M^{-1}$	436	31

Cu(I) complex **2** is a chiral receptor, reminiscent of other C_2-symmetrical receptors investigated by ourselves[18] and others.[19] Binding of an optically pure dicarboxylic acid to a racemic mixture of **2** should result in the formation of two diastereomeric complexes. Indeed, addition of *N*-Cbz-L-glutamic acid to a $CDCl_3$ solution of racemic **2** resulted in the splitting of the receptor peaks into two distinct sets of signals. It is not yet possible to assign the NMR peaks to a specific stereoisomer of the receptor.

In summary, we have shown that simple components can be designed to self-assemble into functional receptors by the addition of a template metal ion. The resulting receptors shows strong binding, an internal spectroscopic reporter group, and chirality. We are currently extending this strategy to other metal complex types as well as other classes of substrate.

Acknowledgments

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