Pergamon

Tetrahedron Letters 40 (1999) 7641–7644

TETRAHEDRON LETTERS

Metal control of non-polar binding shape selectivity

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Received 29 June 1999; accepted 17 August 1999

Abstract

Ligand **1** forms a hydrophobic cavity upon binding to metals, the shape of which depends on the metal. A reversal in binding preference for naphthalene or biphenyl groups is found when the metal is changed from zinc to copper, with a selectivity change of 260 fold.

Synthesis of self-assembled structures has received considerable attention in the field of molecular recognition,[1] due to the efficiency provided for the construction of well-defined large structures.[2] Self-assembly by hydrogen bonding has been extensively exploited;[1b,3] however, the ability of a metal ion to orient, as well as to gather organic fragments around its coordination sphere, is a potentially more versatile way to build specific recognition sites.[1a,4] We[5] and others[4,6] have designed and studied molecules that assemble in the presence of metal ions to form structures with hydrophobic cavities that can bind organic guests. The metals play both structural and functional roles, as substrates that bind best can simultaneously fill the cavity and interact directly with the metal. Variation of the metal causes a perturbation of the binding abilities, but relatively few metals cause the formation of good binding sites.

With the expectation that the requirements for a single metal would be less stringent than those placed upon metals that must both assemble and organize a receptor, we now report a molecule that binds a single metal ion to form a hydrophobic binding site. Schneider and DeShayes have studied related complexes.[7] We report here that flexible bis diamine **1** forms a complex with both zinc and copper (Fig. 1) and in doing so closes the macrocycle. Furthermore, the distinct coordination geometries of these metals perturb the shape of the non-polar cavity. Our studies were undertaken to investigate the effect of the metal identity on the organic binding selectivity. Here we confirm that the identity of the metal can have a profound effect on the selectivity of the derived receptor.

The desired ligand **1**, was prepared as shown in Scheme 1. *N,N*-Dimethylaniline is converted to *t*-butyl arylphosphinate **2** by heating in a sealed tube with PCl_3 and pyridine, followed by quenching with *tert*-butyl alcohol. Iodide **3** was prepared in enantiomerically pure form from phenylalanine as we have reported.[5c] Palladium catalyzed coupling[8] of phosphinate **2** with iodide **3** leads to a diastereomeric mixture of diarylphosphinates **4**. Alkylation with dibromide **5** in the presence of AgOTf, gave **6**,[9] a

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0040-4039/99/$ - see front matter
PII: S0040-4039(99)01579-8

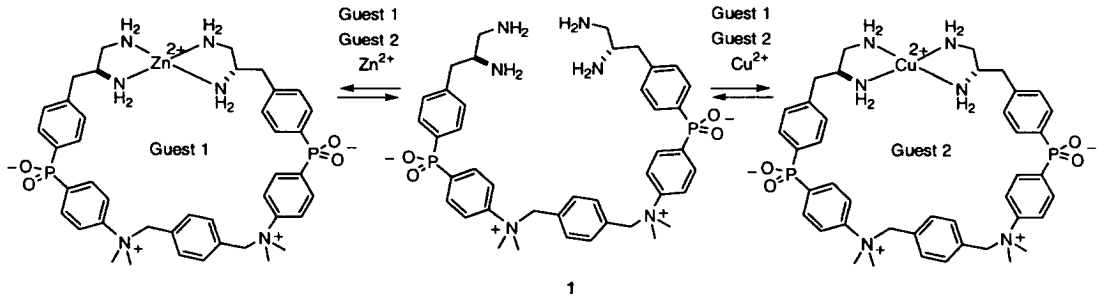
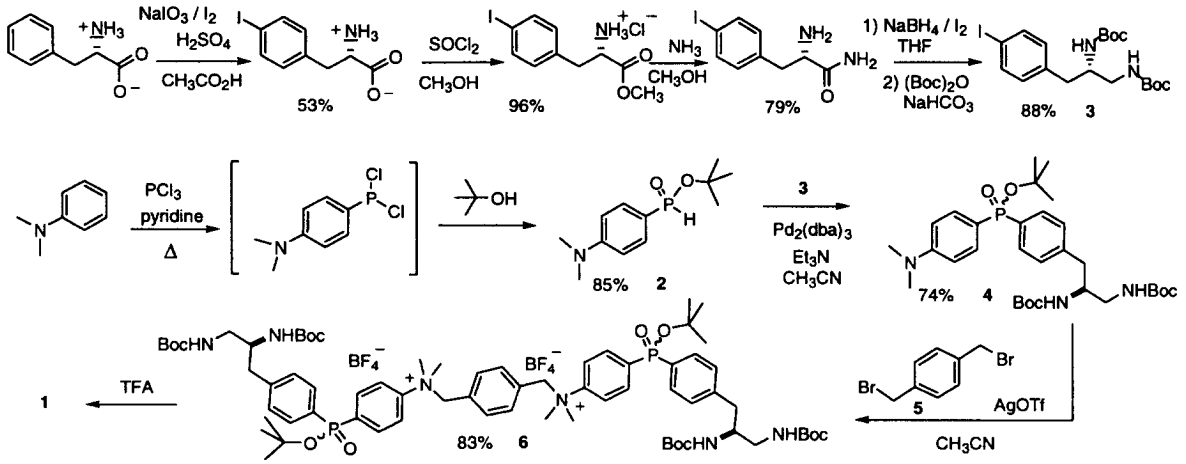


Figure 1.

protected form of **1**, as the BF_4 salt after silica gel chromatography. Deprotection with acid provided the desired ligand.[10]



Scheme 1.

Association of this ligand with metals is readily discerned: changes in CD and NMR spectra are consistent with 1:1 complexes (Fig. 2) with Zn^{2+} and Cu^{2+}, as well as a 2:1 complex in the presence of excess Cu^{2+}. The shape of the hydrophobic cavity, as well as the relative orientation of the nearby metal center, should be distinctly different for these two complexes since Cu^{2+} should lead to square planar coordination, while Zn^{2+} is probably octahedral. Simple model-building exercises lead to the prediction that square planar coordination by bis diamine **1** provides a macrocyclic metal complex **1**·Cu that has a distinctly different cavity shape from **1**·Zn formed upon octahedral coordination. Naphthalene guests have been much more extensively studied[11] than biphenyls, but little selectivity has been observed in the few cases investigated.[12]

NMR titrations of diamagnetic zinc complex **1**·Zn with naphthoxyacetate **7** and with 2-phenylphenoxyacetate **8** provided strong evidence for a two-state binding event. In each titration, resonances of host–metal complexes were fitted by multidimensional non-linear least squares to a single K_d. Titration of paramagnetic copper complex **1**·Cu was monitored by changes in circular dichroism (CD), and fitted in the same manner. No evidence for binding of **1** to substrates in the absence of metals was observed by NMR, CD or fluorescence[13] titrations at the concentrations studied ($\leq 10^{-3}$ M).

As shown in Table 1, a modest 2.3 fold stronger binding of naphthalene **7** by copper complex **1**·Cu compared to zinc complex **1**·Zn becomes a ≥600 fold stronger binding by the Cu complex on replacement of the aromatic portion of the guest with biphenyl **8**. Phosphate **9** rather than carboxylate

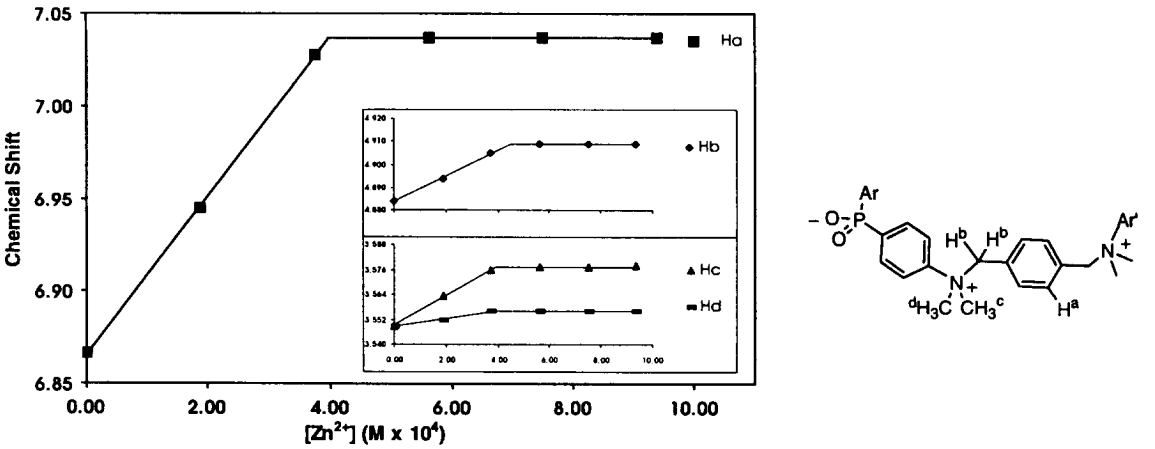


Figure 2. NMR titration of 4×10^{-4} M **1** with Zn^{2+} in borate. Linear changes until saturation indicates high Zn affinity and a 1:1 stoichiometry. H^a, H^b, H^c and H^d are defined as above

Table 1

Guest		1·Zn Kd (M)[a]	1·Cu Kd (M)[b]
7	2-(1-naphthoxy)acetate	$(1.69 \pm 0.11) \times 10^{-4}$ M	$(7.25 \pm 1.42) \times 10^{-5}$ M
8	2-(2-phenylphenoxy)acetate	$(6.00 \pm 0.43) \times 10^{-3}$ M	$\leq (9.73 \pm 2.50) \times 10^{-6}$ M [c]
9	1-naphthyl phosphate	$(5.04 \pm 0.18) \times 10^{-4}$ M	$(1.66 \pm 0.54) \times 10^{-4}$ M

[a]Measured by NMR titration. [b] Measured by CD titration. [c][Host]=10^{-5} M, so this value is an upper limit. Error bars reflect only random error

slightly decreases the affinity, which highlights the non-polar component to the binding. This corresponds to a reversal in aromatic group preference for these two metal complexes. Approximately a 35-fold preference for the naphthalene **7** over the biphenyl **8** is found for complex **1**·Zn, in contrast **1**·Cu prefers the biphenyl substrate by at least a factor of 7.4. Metal causes a very substantial non-polar shape selectivity with a 260-fold change.

These results can be rationalized using models. The octahedral **1**·Zn complex appears capable of forming many unstrained box-like conformations that readily accommodate naphthalenes. In contrast, the square planar **1**·Cu stretches the cavity lengthwise. A favorable conformation places an inward-pointing methyl group toward the center of one side. This conformation would be compatible with biphenyl binding, as the central twist prevents steric interference. However, the methyl group could interfere with naphthalene binding, so a different conformation would be anticipated. That different conformations of Zn and Cu species are present is indicated by the difference between the CD spectra of **1**·Zn and **1**·Cu. The complex **1**·Zn shows little if any CD, while **1**·Cu exhibits a distinct negative extremum at 234 nm. We believe that the metal centers interact with the anionic portions of the guest molecules.[5] While both naphthalene and biphenyl guests bear the same anionic groups, the polar groups will be presented differently to the metal upon binding of the non-polar aromatic group into the cavity.

We have presented an effective synthesis of the new ligand **1** which forms a metal complex of 1:1 stoichiometry. The hydrophobic cavity shape upon binding to metal depends on the metal with the selectivity as hoped: the octahedral complex **1**·Zn prefers naphthalene, while the square planar **1**·Cu preferably binds biphenyl. The convergent synthesis of **1** allows ready structural variation.

Acknowledgements

This work was supported by NIH grant GM 47736-02.

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9. NMR data of **6**: ^{1}H NMR ($CDCl_3$) δ 7.90 (br dd, 4H), 7.86 (br dd, 4H), 7.62 (br dd, 4H), 7.30 (br dd, 4H), 6.97 (s, 4H), 5.29 (br m, 4H), 4.87 (s, 4H), 3.87 (br m, 2H), 3.48 (s, 12H), 2.99 (br m, 4H), 2.80 (br m, 4H), 1.45 (s, 18H), 1.40 (s, 18H), 1.33 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 155.83, 154.93, 146.11, 141.96, 136.98 (d, J=136.2 Hz), 132.40, 132.03, 130.48 (d, J=9.7 Hz), 129.87 (d, J=142.4 Hz), 128.73 (d, J=7.5 Hz), 128.68, 120.43 (d, J=12.5 Hz), 84.01 (d, J=8.2 Hz), 78.37, 78.18, 71.17, 51.66, 42.76, 38.00, 29.84 (d, J=3.9 Hz), 27.37, 27.33; ^{31}P NMR ($CDCl_3$) δ 26.02; FAB-MS: calcd for $[C_{70}H_{104}N_6O_{12}P_2BF_4]^+$: 1370; found: 1370. Anal. calcd for $C_{70}H_{104}N_6O_{12}P_2B_2F_8 \cdot 2CH_2Cl_2$: C, 53.15; H, 6.69; N, 5.17; found: C, 53.21; H, 6.63; N, 5.56.
10. NMR data of **1**: ^{1}H NMR (D_2O) δ 7.79 (dd, J=10.9, 8.9 Hz, 4H), 7.67 (dd, J=11.7, 8.0 Hz, 4H), 7.54 (dd, J=7.4, 1.6 Hz, 4H), 7.43 (dd, J=8.0, 2.4 Hz, 4H), 6.89 (s, 4H), 4.91 (s, 4H), 3.97 (ddd, J=10.4, 10.4, 6.4 Hz, 2H), 3.57 (s, 12H), 3.42 (dd, J=13.7, 5.7 Hz, 2H), 3.36 (d, J=13.0, 4.7 Hz, 2H), 3.23 (dd, J=14.3, 6.2 Hz, 2H), 3.06 (dd, J=14.3, 8.6 Hz, 2H); ^{13}C NMR (D_2O) δ 146.14 (d, J=3.1 Hz), 138.75 (d, J=2.8 Hz), 137.31 (d, J=140.0 Hz), 133.03 (d, J=138.2 Hz), 133.27 (d, J=11.1 Hz), 132.91, 132.05 (d, J=10.7 Hz), 130.15 (d, J=13.4 Hz), 129.85, 121.95 (d, J=13.1 Hz), 73.25, 53.35, 50.86, 41.04, 36.46; ^{31}P NMR (D_2O) δ 22.82. FAB-MS: calcd for $[C_{42}H_{56}N_6O_4P_2BF_4]^+$: 857; found: 857.
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