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COMMUNICATION

Encapsulating zinc(II) within a hydrophobic cavity

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A new macrobicyclic ligand has been prepared, and it is shown to bind Zn^{2+} on the inside. The ligand consists of a triamido(amine) motif to coordinate the metal ion and a narrow, hydrophobic channel above the metal binding site.

Biomimetic models of metalloenzymes seek to recreate the active site, from the metal-binding pocket to the second coordination sphere.¹ Sterically bulky ligands are often used to protect the metal site, and may even impart size selectivity in reactions with substrates. The ideal extent of steric bulk, however, is often empirical. Too much steric bulk may inhibit reactivity of the metal center, or worse, interfere with the coordination of the ligand to the metal.

A complementary strategy is to protect the metal through an encapsulating ligand. Macrobicyclic ligands bind and protect metal centers without needing steric bulk. They provide a well-defined cavity and have the potential to gate substrates in and out of the cavity. However, the coordination chemistry of macrobicyclic ligands is not well developed, primarily because such ligands can be challenging to prepare.² Representatives of two encapsulating ligand families are shown in Fig. 1.³

The coordination chemistry of these two families is significantly restricted by the limited ligand variants in each family. For instance, only Zn^{2+} and $Cu^{1+/2+}$ ions have been shown to be



Fig. 1 Representatives of two ligand families that successfully bind transition metals and create well-defined cavities.

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encapsulated by the calix[6]cryptand family.⁴ To achieve a wider breadth of coordination compounds, we targeted a new triamido (amine) proligand, or compound **5** in Scheme 1, because this motif has been demonstrated to support mid-to-late transition metals and their reactivity with small molecules, *e.g.* O_2 .⁵ Of note, the hydrocarbon cap in **5** is the first example, to our knowledge, of a hydrophobic cavity that avoids the use of carbon-heteroatom linkages in its construction.

The synthesis of the proligand begins with the previously reported 1,3,5-tri(3-butenyl)benzene 1,⁶ and builds complexity in a linear sequence as shown in Scheme 1. Hydroboration of 1 with 9-BBN generates 2, which is subjected to Suzuki–Miyaura coupling with 4-methyl iodobenzoate in the next step to form the tricarboxylic ester 3. Hydrolysis of 3 under basic conditions, followed by an acidic workup, provides the tricarboxylic acid 4. The last step of the proligand synthesis is the selective one-to-one coupling of 4 with tren, or tris(2-aminoethyl)amine. This key transformation was achieved by using 2,2'-dipyridyl disulfide and triphenylphosphine to create the amide linkages of proligand 5.⁷ From commercially available starting materials, 5 was isolated in 5 steps with an overall yield of ~30%.

To demonstrate that proligand **5** can chelate transition metal ions, we began the metallation studies with zinc(II) because of its redox inertness and diamagnetism. The metallation conditions were directly adapted from Borovik *et al.* as shown in Fig. 2 to yield the anionic zinc coordination complex, $[K(DMA)_n][Zn(L)]$ **6**, in 90% yield.⁵ The aryl region of the proton NMR spectra is distinctly different for proligand **5** and complex **6**, which provided good evidence that the metallation reaction was successful. Notably, the amide protons of the proligand (triplet at 7.7 ppm) are missing in the proton NMR spectrum of **6**. Definitive proof was obtained in the form of an X-ray crystal structure of **6** (*vide infra*).

To obtain crystals of **6** suitable for an X-ray diffraction study, the potassium countercation was swapped with $[PPh_4]^+$. The structure of $[PPh_4][Zn(L)]$ (**6'**) revealed a trigonal monopyramidal coordination geometry for zinc (Fig. 3a).[‡] The molecular symmetry is nearly C_3 (Fig. 3b) with a dramatic twisting of the ligand arms by 40 to 43°. The bond distances between the zinc center and the N-donors are for Zn–N_{ap}, 2.128(2) Å, and for Zn–N_{eq}, 1.985(2) Å, on average. These distances are quite similar to those reported by Cummins and Nocera for the two zinc ions in their dizinc-cryptand complex (ave Zn–N_{ap} 2.162 Å, ave Zn–N_{eq} 1.973 Å), which has a similar first coordination sphere to our complex.⁸

Compound **6** may be considered a rudimentary model for active sites of metalloenzymes containing hydrophobic channels.

[†]Electronic supplementary information (ESI) available: Experimental section including synthetic details and additional spectroscopic data. CCDC 870365. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2dt30529a



Scheme 1 Synthetic route to the proligand 5.



Fig. 2 (top) Scheme of the metallation reaction to form 6. (bottom) Comparison of the aryl regions of the ¹H NMR spectra (500 MHz, d_6 -DMSO) of 5 (in black) and 6 (in red) with corresponding peak assignments (labelled in blue).

The length between the zinc center and the centroid of the aryl ring is nearly one nanometer (9.58 Å), and the cylindrical cavity is narrow (Fig. 3c). Hence, substrate access to the metal site should be size selective. In Cummins' and Nocera's cryptand systems, which have a similarly narrow cavity, cyanide ligands were reported to bind the two opposing metals in the cryptand pocket.⁸ Because of the flexibility of its longer ligand arms, **6** should be able to accommodate linear diatomics and perhaps even slightly larger molecules.

The flexibility of the methylene linkers in 6 has been investigated through density functional theoretical studies (M06-L, Gaussian09). Prior to obtaining the crystal structure of 6, we performed a geometry optimization on a hypothetical structure, and



Fig. 3 (a) Molecular structure of **6'** shown at 30% probability level. Hydrogen atoms, solvent, and countercation were omitted. Top view of **6'** as (b) ball-and-stick model, or as (c) space-filling model with the aryl cap removed for better visualization of the cavity.

found convergence to a local minimum solution. This structure has a cavity height (measured from the zinc center to the centroid of the aryl ring) of 8.27 Å. A second geometry optimization was performed starting from the crystal structure coordinates. The result is a lower energy solution by 11.3 kcal mol⁻¹, wherein the cavity height of 9.29 Å is expectedly closer to that observed in the crystal structure. A comparison of these two optimized structures indicates that the cavity can readily adopt conformations with cavity height changes of at least ~1 Å at room temperature.

Host–guest chemistry of **6** was canvassed with coordinating molecules, *e.g.* CH₃CN, DMF, and DMSO, as well as nonpolar substrates, *e.g.* pentane, hexane, benzene and trifluorotoluene. In

all cases, the reactions were unproductive as determined by proton NMR spectroscopy in DMSO-d₆. The lack of reactivity can be rationalized by considering two factors: (1) the Lewis acidity of the Zn^{2+} center is significantly attenuated by the ligand's three anionic amide groups; and (2) the cavity is so narrow that it would exclude most of these substrates based on their size. Possible avenues for future research include extending the coordination chemistry to more reactive transition metals as well as expanding the cavity size by increasing the number of methylene linkers in the ligand arms.

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Notes and references

‡Crystal data for **6'**: C₇₃H₇₇N₄O₄PZn, M = 1170.73, monoclinic, a = 13.1597(8) Å, b = 34.881(2) Å, c = 14.5029(9) Å, $\alpha = 90.00^{\circ}$, $\beta = 14.5029(9)$ Å, $\alpha = 14.5029(9)$

92.8190(10)°, $\gamma = 90.00°$, V = 6649.2(7) Å³, T = 173(2) K, space group P2(1)/n, Z = 4, 9502 reflections measured, 13 959 independent reflections ($R_{int} = 0.0000$). The final R_1 values were 0.0523 ($I > 2\sigma(I)$). The final w $R(F^2)$ values were 0.1247 ($I > 2\sigma(I)$). The final R_1 values were 0.0857 (all data). The final w $R(F^2)$ values were 0.1371 (all data).

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