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Calix[4]arenes Linked to Multiple Bidentate N-Donors: Potential Ligands for Synthetic Modeling of Multinuclear Metalloenzymes

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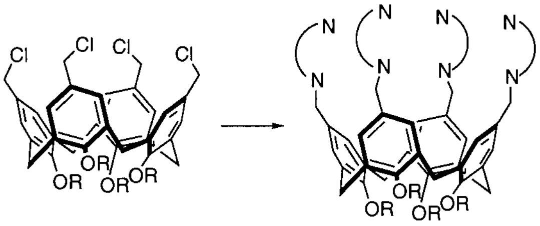
ABSTRACT



A series of calix[4]arenes incorporating three or four bidentate diamines or pyridylamines attached at the "upper rim" were synthesized via practical protocols. Proof of structure was obtained in one instance by X-ray crystallography. These molecules are designed for general use as ligands for the preparation of multinuclear active site models of metalloenzymes.

Multinuclear metal arrays are ubiquitous components of metalloprotein active sites that participate in a number of important biological reactions. For example, tricopper sites have been identified in the multicopper oxidases[1−3] and in particulate methane monooxygenase (pMMO),[4] which use O_2 to couple the four-electron reduction of O_2 to H_2O with the oxidation of substrate or to functionalize hydrocarbons, respectively. A tetracopper site ("Cu$_Z$") that features ≤ 2 N-donors per metal has been identified in an important respiratory enzyme, nitrous oxide reductase.[5] Zinc enzymes that use two or three metal ions to catalyze various hydrolytic reactions also are known.[6] Studies of suitably designed synthetic model compounds can provide new insights into the structures, spectroscopic properties, and catalytic mechanisms of these and other metalloprotein active sites.[7] For the purposes of modeling the aforementioned biological

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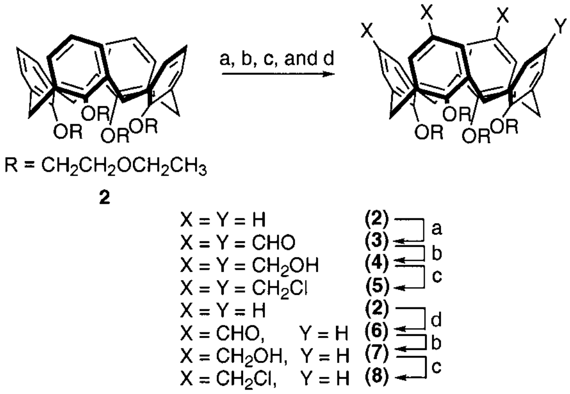
multimetal centers, it would be advantageous to use multidentate ligand systems that can accommodate ≥3 metal centers held sufficiently close to one another to enable cooperative interactions in reactions with exogeneous substrates.

Calixarenes have been found to be a useful scaffold for constructing such ligands for metalloprotein active site modeling studies, and complexes typically containing one or two Cu,[8,9] Zn,[10] or Ni[11] ions have been examined. Higher nuclearity species with three or four bound metal ions are less common,[10b] however, as are those that feature ligands comprising bidentate[9g,10a] (rather than tridentate) donors that would be expected to afford enhanced reactivity at the metal centers due to greater accessibility of lower coordination numbers. To address these deficiencies, we targeted a new class of multidentate ligands that feature three or four bidentate N-donors attached to the upper rim of a calix[4]arene scaffold, and we report their successful syntheses herein. It is our ultimate hope that the ligand framework, while providing enough flexibility to incorporate up to four metal centers, will possess enough rigidity and steric bulk to prevent intermolecular aggregation yet still bind the metal ions close enough to facilitate cooperative interactions upon small molecule activation.

The preparation of the new ligands began with calix[4]arene (**1**),[12,13] which was converted to 25,26,27,28-tetrakis-(2-ethoxyethyl)calix[4]arene (**2**, Scheme 1) via an adaption of a published procedure.[14] In contrast to the original report, we found that a vast excess of both NaH and 2-bromoethyl ether, as well as an increased temperature and reaction time, were required to obtain **2** in reasonable yield. This alkylation of the "lower rim" of the calix[4]arene was necessary to maintain the cone conformation[15] (which may be varied by binding alkali metal ions) and ensure that the chelating N-donors covalently linked to the "upper rim" all remain above the calix[4]arene frame. In all subsequent steps from **2**, retention of the cone conformation was confirmed in ^{1}H NMR spectra by the presence of two doublets in the range 2.9−3.3 and 4.3−4.6 ppm ($J = 12{-}13$ Hz).[15] We attached three or four chloromethyl groups to **2** to generate **5** and **8**, which were designed to serve as common precursors for the new target ligands (Scheme 1). Compound **5** had been reported previously via a one-pot protocol,[14] but in our hands this method proved to be unreliable, so an alternative route analogous to one reported for disubstituted calix[4]arene syntheses was developed.[16] Thus, **2** was tetraformylated by an adapted method[17] and then reduced and chlorinated to yield **5**. Compound **8** was prepared similarly, by triformylating **2**[10b] followed by reduction and chlorination.

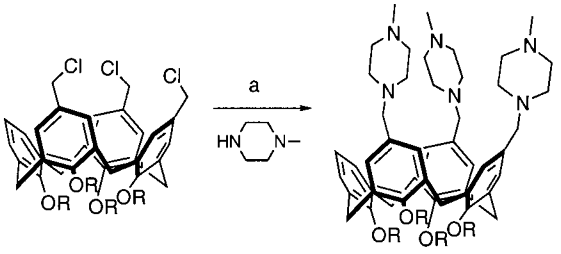
Scheme 1[a]



[a] Reagents and conditions: (a) (i) hexamethylenetetramine, trifluoroacetic acid, 125 °C; (ii) CH_2Cl_2/1 M HCl; (iii) MeOH, 47%; (b) (i) EtOH/THF, $NaBH_4$, 4 equiv; (ii) 4 M HCl, 100% (**5**) and (**8**); (c) (i) $CH_2Cl_2/SOCl_2$, xs; (ii) MeOH, 100% (**8**) and 60% (**5**); (d) ref 10b.

Attachment of secondary amines to the chloromethyl derivatives **5** and **8** led to the desired ligands (Schemes 2 and 3). The indicated amines were chosen in order to span a range of donor atom types (amine vs pyridyl), chelate ring

Scheme 2[a]



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12

[a] Reagents and conditions: (a) MeCN, xs Na_2CO_3, 100%.

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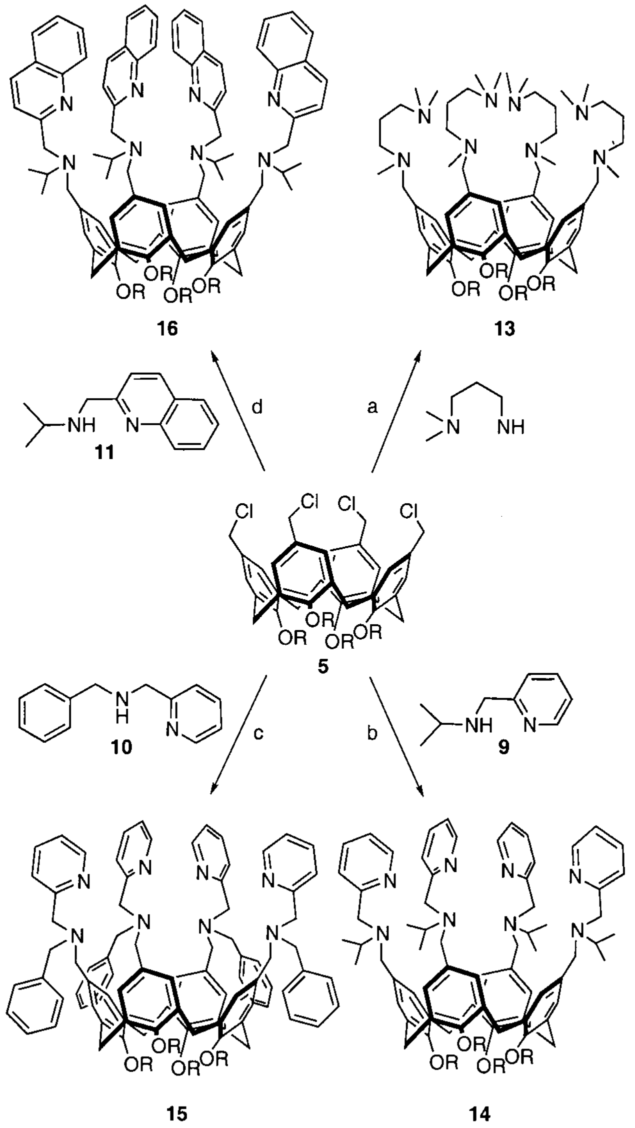
Scheme 3[a]



[a] Reagents and conditions: (a) MeCN, xs Na_2CO_3, 81%; (b) (i) MeCN, xs Na_2CO_3; (ii) Sephadex G-10 (MeOH), 60%; (c) (i) MeCN, xs Na_2CO_3; (ii) Sephadex G-10 (MeOH), 50%; (d) (i) MeCN, xs Na_2CO_3; (ii) Sephadex G-10 (MeOH), 62%.

sizes when bound to a metal ion (5 vs 6), and steric bulk. The pyridylamines *N*-isopropyl-*N*-(2-methylpyridine)[18] (**9**), *N*-benzyl-*N*-(2-methylpyridine)[19] (**10**), and *N*-isopropyl-*N*-(2-methylquinoline)[20] (**11**) had been reported previously, but we developed more convenient one-pot reductive amination procedures for their syntheses. In general, the alkylation reactions leading to ligands **12**−**16** were found to proceed best when a large excess of the amine and Na_2CO_3 as base were heated with **5** or **8** in refluxing MeCN for 3−7 days. Compounds **12**−**16** were isolated as brown oils and identified by high-resolution fast-atom bombardment mass spectrometry (FAB-MS), NMR spectroscopy, and in one instance (**15**), X-ray crystallography. X-ray quality crystals of (**15**) were grown by slow diffusion of Et_2O into a MeCN solution. The structure shows that the calix[4]arene framework is in the "cone" conformation, tetrasubstituted on the upper rim with *N*-benzyl-*N*-(2-methylpyridine) (Figure 1). The ligand preorganization can clearly be seen, as the covalently linked amine donors are positioned above the calix[4]arene framework in preparation for metal ion complexation.

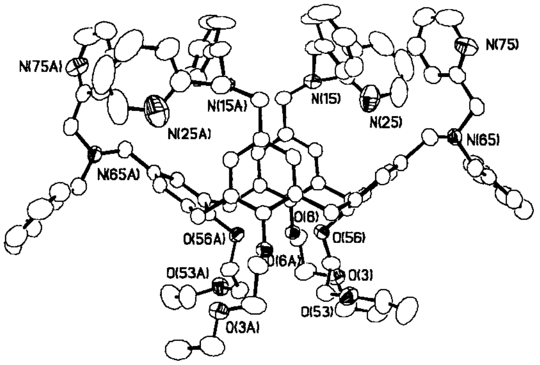


Figure 1. X-ray crystal structure representation of **15**, shown at 50% thermal ellipsoids with only heteroatoms labeled and hydrogen atoms omitted for clarity.

In summary, we have developed straightforward, dependable syntheses of a new set of multidentate ligands **12**−**16**. Each incorporates ≥3 bidentate N-donors that are covalently linked to and preorganized by the calix[4]arene framework for metal complexation. These ligands will enable future investigations aimed at binding metal ions and exploring the chemistry of the resulting complexes, with the ultimate objective being to understand the reactivity, structures, and spectroscopic properties of multinuclear metal arrays found in Nature.

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Supporting Information Available: Experimental procedures and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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