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A Metal-Assembled, pH-Dependent, Resorcinarene-Based Cage Molecule

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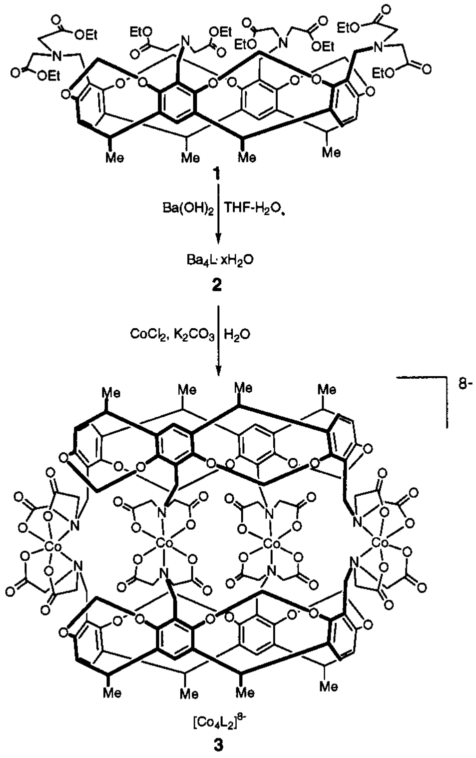
The creation of protected hydrophobic pockets that house molecules is of great interest due to the ability of the pocket to protect a molecule from external reactants, to transport a molecule between phases, or to provide a molecular reaction domain.[1] Members of the calixarene family have been used successfully to form cage complexes held together by covalent linkages[2,3] and hydrogen bonds.[4] This has facilitated the creation of a molecule with a particularly large cavity volume, 1375 Å^3.[5]

Although there are a number of reports of metal-bound calixarenes,[6] the use of metal ions to create calixarene cage molecules has been only briefly reported, and until now, an example of such a molecule has not been structurally characterized.[7] Metal ions have been used extensively to assemble a variety of supramolecular structures and architectures: e.g., chains, rings, squares, and cages.[8] Also, metal ions have been used to assist in the assembly of supramolecular host molecules that bind guests by the creation of suitably sized and charged cavities and/or by guest interaction with vacant coordination sites on the metal center.[9,10] Like hydrogen-bonded cage molecules, metal-assembled molecules could exhibit solvent and pH dependence but should be considerably more robust due to the greater strength of the metal−ligand bonds. The metal-assembled molecules may be ionic and thus suited to attract charged guest molecules. Furthermore, alteration of cage stability and binding properties may be possible by simply changing the metal oxidation state.[10] In this paper, we report the synthesis of a metal-containing, resorcinarene-based cage molecule, **3**, whose assembly is pH dependent. The X-ray crystal structure of **3** confirms the successful synthesis of this water-soluble cage molecule, whose two identical halves are bound together by four divalent cobalt ions.

Scheme 1



Formation of **3** entails the synthesis of resorcinarene **1** by the reaction of a tetra(bromomethyl)resorcinarene with diethyl iminodiacetate (Scheme 1).[11] The hydrolysis of **1**, achieved with barium hydroxide, gives the barium complex **2**. Dissolving **2** in water with dilute hydrochloric acid, followed by adding cobalt(II) chloride and potassium carbonate (approximately pH 6), gives **3**.[12] Crystals suitable for X-ray diffraction are grown by the addition of a small quantity of calcium or magnesium acetate to an aqueous solution of **3**.[13]

Complex **3** consists of two resorcinarene molecules held together by four cobalt(II) ions. The molecule possesses *pseudo-D$_{4h}$* symmetry, with the four cobalt(II) ions having a distorted octahedral geometry and positioned around the resorcinarene rim

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(1) (a) Cram, D. J.; Cram, M. J. *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1994. (b) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024−1027. (c) Kang, J.; Rebek, J., Jr. *Nature (London)* **1996**, *382*, 239.

(2) (a) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Marti, K.; Sampson, R. M.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1988**, *110*, 2554−2560. (b) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Kalleymeyn, G. *J. Am. Chem. Soc.* **1985**, *107*, 2575−2576.

(3) (a) Quan, M. L. C.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2754−2755. (b) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717−7727.

(4) (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (b) Hamann, B. C.; Shimizu, K. D., Rebek, J. Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1328.

(5) MacGillivray, L. R.; Atwood, J. L. *Nature (London)* **1997**, *389*, 469−472.

(6) For a few recent references, see: (a) Roundhill, D. M. *Prog. Inorg. Chem.* **1995**, *43*, 533. (b) Schmitt, P.; Beer, P. D.; Drew, M. G. B.; Sheen, P. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1840−1842. (c) Cameron, B. R.; Loeb, S. J.; Yap, G. P. A. *Inorg. Chem.* **1997**, *36*, 5498−5504. (d) Giannini, L.; Caselli, A.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C.; Re, N.; Sgamellotti, A. *J. Am. Chem. Soc.* **1997**, *119*, 9709−9719. (e) Staffilani, M.; Hancock, K. S. B.; Steed, J. W.; Holman, K. T.; Atwood, J. L.; Juneja, R. K.; Burkhalter, R. S. *J. Am. Chem. Soc.* **1997**, *119*, 6324−6335. (f) Hampton, P. D.; Daitch, C. E.; Shachter, A. M. *Inorg. Chem.* **1997**, *36*, 2956−2959. (g) Xu, W.; Vittal, J. J.; Puddephatt, R. J. *Inorg. Chem.* **1997**, *36*, 86−94.

(7) (a) Dalcanale, E.; Jacopozzi, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613−615. (b) Fujimoto, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 2915−2918. (c) Stang, P. J.; Cao, D. H.; Chen, K.; Gray, G. M.; Muddiman, D. C.; Smith, R. D. *J. Am. Chem. Soc.* **1997**, *119*, 5163−5168.

(8) (a) Baxter, P. N. W. In *Comprehensive Supramolecular Chemistry;* Sauvage, J. P., Hosseini, M. W., Eds.; Pergamon: Oxford, 1996; Vol. 9, pp 165−211. (b) Linton, B.; Hamilton, A. D. *Chem. Rev.* **1997**, *97*, 1669−1680. (c) Manna, J.; Whiteford, J. A.; Stang, P. J.; Muddiman, D. C.; Smith, R. D. *J. Am. Chem. Soc.* **1996**, *118*, 8731−8732. (d) Baxter, P.; Lehn, J. M.; DeCian, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 69−72. (e) Fuchs, R.; Habermann, N.; Klufers, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 852−854. (f) Livoreil, A.; Sauvage, J.-P.; Armaroli, N.; Balzani, V.; Flamigni, L.; Ventura, B. *J. Am. Chem. Soc.* **1997**, *119*, 12114−12124.

(9) (a) Fujita, M.; Nagao, S.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 1649−1650. (b) Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. *Nature (London)* **1995**, *378*, 469−471. (c) Maverick, A. W.; Buckingham, S. C.; Yao, Q.; Bradbury, J. R.; Stanley, G. G. *J. Am. Chem. Soc.* **1986**, *108*, 7430−7431. (d) Cole, K. L.; Farran, M. A.; Deshayes, K. *Tetrahedron Lett.* **1992**, *33*, 599−602.

(10) (a) Schwabacher, A. W.; Lee, J.; Lei, H. *J. Am. Chem. Soc.* **1992**, *114*, 7597−7598. (b) Schwabacher, A. W.; Lee, J. *J. Am. Chem. Soc.* **1994**, *116*, 8382−8383. (c) Saalfrank, R. W.; Horner, B.; Stalke, D.; Salbeck, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1179−1182. (d) Saalfrank, R. W.; Burak, R.; Breit, A.; Stalke, D.; Herbst-Irmer, R.; Daub, J.; Porsch, M.; Bill, E.; Muther, M.; Trautwein, A. X. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1621−1623.

(11) Compound **1** was synthesized by the reaction of the brominated resorcinarene (Sorrell, T. N.; Pigge, F. C. *J. Org. Chem.* **1993**, *58*, 784−785) with diethyl iminodiacetate. Tetrafunctionalized compound **1** has been characterized by single-crystal X-ray diffraction; the synthesis and structural details of **1** will be published elsewhere.

(12) Complete synthetic and characterization details of compound **3** are found in Supporting Information.

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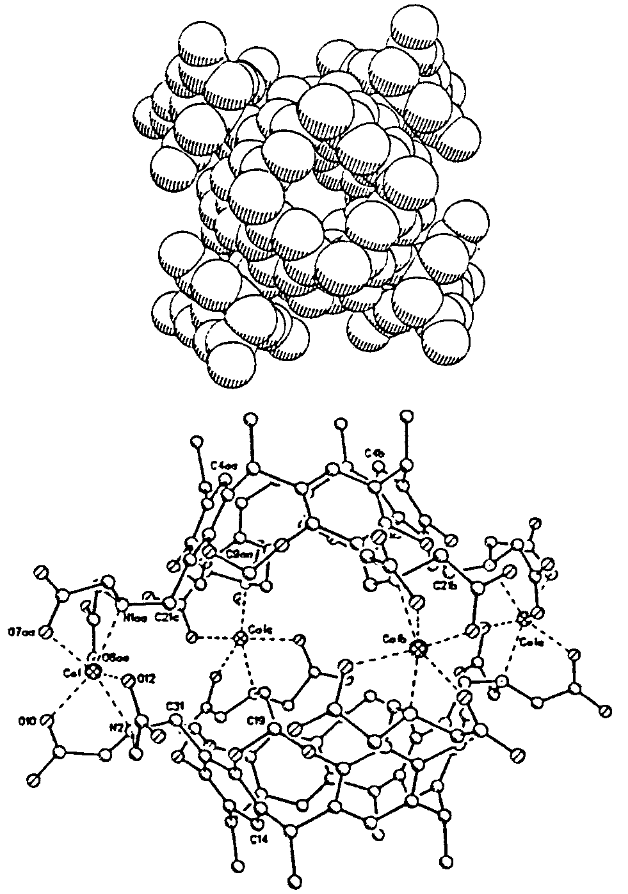

Figure 1. Molecular structure of **3**. The top view is a space-filling picture showing the four cobalts ligated on the periphery of the resorcinarenes. The bottom diagram illustrates the distance between the two resorcinarenes and shows the cobalt coordination environment. Selected bond distances (Å): Co−N2, 2.192(13); Co−N1aa, 2.245(13); Co−O7aa, 2.095(12); Co−O6aa, 2.084(11); Co−O10, 2.068(11); Co−O12, 2.080(13). Hydrogen atoms, countercations (barium and cobalt), and solvent molecules in the structure are omitted for clarity.

(Figure 1). Each cobalt(II) ion is coordinated to two doubly deprotonated iminodiacetate moieties, resulting in an octaanionic complex. Barium and cobalt ions act as countercations to the complex and are positioned between cage molecules. The cavity created by the pairing of the two cup-shaped resorcinarene halves is essentially an oblate sphere, with diameters of 10.9 Å (distance between the lower rims, C4aa to C14) and 9.76 Å (distance across, C21c to C21b). CPK models demonstrate the cavity of **3** to be large enough to accommodate a variety of small molecules including acetone, benzene, dioxane, and dichloromethane. It is interesting that the gap between resorcinarenes is smaller (4.76 Å, C9aa to C19) than the opening in the lower rim (5.25 Å, C4aa to C4b). The closest contact distance between the two resorcinarene halves comes between the hydrogens of the benzyl carbons (C21c to C31). These carbons are 3.65 Å apart. Although **3** was synthesized in the aqueous phase, solvent molecules were not observed within the cavity. This is not surprising, given the hydrophobic nature of the cavity.[14]

Three geometric isomers are possible for a bis(iminodiacetato) mononuclear metal complex, *N,N-trans mer*,[15] *N,N-trans fac*,[16] and *N,N-cis fac*.[17] The cobalt ions in **3** form the *N,N-cis fac* isomer and are significantly distorted from octahedral toward a trigonal prismatic geometry. The distortion is illustrated by the ligand−cobalt bond angles; atoms from different resorcinarenes form angles larger than 90° (N−Co−N, 123° and O−Co−O, 112°) while atoms from the same resorcinarene form angles less than 90° (N−Co−O, 75.9°, 77.5°, 77.4°, 76.5°) and those atoms nearly trans to each other form angles less than 180° (N−Co−O, 156°, 157° and O−Co−O, 149°). The ability of cobalt(II) ions to adopt the *N,N-cis fac* geometry is fundamental to the self-assembly process that creates the cage molecule.[18,19] The only form of coordination that could result in cage formation and hence generation of a discrete supramolecular species is the *N,N-cis fac* arrangement. Consequently, the formation of the cage is expected to be highly metal-dependent.

The pH dependence of cobalt(II) coordination to the resorcinarene ligand can be monitored using proton NMR. An NMR spectrum of the ligand, generated by dissolving **2** in D_2O with trifluoroacetic acid, precipitating the barium with sodium sulfate, and adding 2 equiv of cobalt(II) chloride at pD 1.0, exhibits the expected resonances for the ligand without adverse broadening or isotropic shifting due to the paramagnetic cobalt(II) ions. Gradually raising the pD causes spectral changes such that at pD 6, the observed spectrum is that of a paramagnetic compound exhibiting significant broadening and shifting of resonances with no signals which can be attributable to noncomplexed diamagnetic ligand. Addition of trifluoroacetic acid to the solution affords the NMR signals for the free ligand again. Thus, a change in pH results in a change from unbound to metal-bound resorcinarene. Further studies to probe the conditions of cage formation and the solution behavior of complex **3** are in progress.[20]

Complex **3** is an initial example of a water-soluble, metal-assembled resorcinarene cage complex that can be formed by manipulation of pH. The necessity for carcerands that operate in this manner has previously been noted.[21]

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Supporting Information Available: Experimental procedures for **1**−**3**, details of the structure determination, the atomic positional and thermal parameters of all atoms in the crystal structure, and bond lengths and angles of **3** (11 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[13] Crystallographic data for $\mathbf{3}\cdot 2CH_3OH\cdot 31H_2O$: red color, dimensions 0.4 × 0.6 × 0.6 mm, tetragonal, space group $I4_1/a$ (no. 88), $Z = 4$, $a = 20.129(4)$ Å, $c = 54.40(2)$ Å, $V = 22041(10)$ Å^3, $D_{calcd} = 1.065$ g/cm^3; Mo Kα radiation ($\lambda = 0.71073$ Å); 7447 total data, 3241 ($F > 4\sigma(F)$) observed independent reflections with $2.25° < \theta < 23°$ collected: $R = 0.1113$, $wR^2 = 0.2869$.

[14] Water molecules found in the X-ray crystal structure of a polar octaamide hemicarcerand were located within the cavity. See refs 1 (pp 179), 2a, and: Choi, H.-J.; Buhring, D.; Quan, M. L. C.; Knobler, C. B.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1733−1735.

[15] Koine, N.; Tanigaki, T.; Hidaka, J.; Shimura, Y. *Chem. Lett.* **1980**, 871−874.

[16] (a) Mammano, N. J.; Templeton, D. H.; Zalkin A. *Acta Crystallogr.* **1977**, *B33*, 1251. (b) Mori, M.; Shibata, M.; Kyuno, E.; Maruyama, F. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 75−77.

[17] (a) Mootz, D.; Wunderlich, H. *Acta Crystallogr.* **1980**, *B36*, 445−447. (b) Reference 16b.

[18] Cobalt(II) and cobalt(III) bis(iminodiacetato) complexes show the *N,N-cis fac* geometry: (a) Lukes, I.; Smidova, I. *Inorg. Chim. Acta* **1982**, *58*, 95−100. (b) Cooke, D. W. *Inorg. Chem.* **1966**, *5*, 1141−1145. (c) Smith, B. B.; Sawyer D. T. *Inorg. Chem.* **1968**, *7*, 922−928. (d) Corradi, A. B.; Palmieri C. G.; Nardelli, M.; Pellinghelli, M. A.; Tani, M. E. V. *J. Chem. Soc., Dalton Trans.* **1973**, 655−658.

[19] Co(II)−EDTA complex. McCandlish, E. F. K.; Michael, T. K.; Neal, J. A.; Ligafelter, E. C.; Rose, N. J. *Inorg. Chem.* **1978**, *17*, 1383−1394.

[20] We are pursuing mass spectrometric evidence (FAB or ESI-MS) for the existence of the octaanionic complex in the solution phase.

[21] Yoon, J.; Cram, D. J. *J. Chem. Soc. Chem. Commun.* **1997**, 497−498.