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Macrocyclic catechol-containing ligands

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Abstract - Tri-catechol ligands form selective and strong complexes with the ferric ion, making them attractive candidates for use as iron decorporation pharmaceuticals. Recent work in our group has concentrated on the synthesis of macrocyclic and macrobicyclic ligands incorporating the 2,3-dihydroxyterephthalamide binding subunit, which has been shown to be the most efficient bidentate iron chelator known (pM's ranging from 21.1 to 22.7). Macrocyclic polycatechol ligands with endocyclic binding subunits were synthesized using high dilution techniques in yields of up to 24%. A series of macrobicyclic tri-catechol ligands in which the ligand properties were varied by incorporating TREN, mesitylene triamine, and TPT backbones, were synthesized in 10-15% yield via a stepwise approach employing high dilution conditions for the tripod-tripod coupling cyclization. In addition, a template synthesis was developed which allowed the preparation of $(Et_3NH)_3$[Fe(bicapped TRENCAM)] in 50% overall yield. Reversible electrochemical behavior was observed above pH 11.5 for Na_3[Fe(bicapped TRENCAM)] (E1/2 =-.95V vs. NHE) and above pH 8.3 for Na_3[Fe(bicapped TRENMECAM)] (E1/2 =-.92 V. vs. NHE). The crystal structure of Na_3[Fe(bicapped TRENCAM)] was determined and showed the coordination geometry about the metal center to be trigonal prismatic, an unprecedented geometry for Fe(III).

Organisms have evolved sophisticated iron solubilization and transport mechanisms to assure a supply of this essential element.[1] For example, microorganisms produce low molecular weight chelating agents, known as siderophores, whose function is to solubilize the ferric ion at physiological pH ($K_{sp}=10^{-39}$).[2] The siderophore enterobactin[3] (Figure 1), which forms the strongest complex with iron ($K_f=10^{52}$)[4] of any known ligand, perhaps best typifies the stability and selectivity which is characteristic of these natural products. This remarkable chelating agent has engendered the synthesis of other tri-catechol ligands as potential iron decorporation pharmaceuticals.[5]

The first synthetic analog, MECAM (Figure 1), was independently synthesized by Rastetter[6] and by us[7]. MECAM incorporates three 2,3-dihydroxybenzamide binding subunits attached to a mesitylene backbone, and, like enterobactin, forms a strong Fe(III) complex ($K_f=10^{46}$)[8] and mediates iron transport in E.Coli.[9] Subsequently, tri-catechol ligands with linear[10], tripodal[11], and exocyclic[7] topologies were prepared.

Macrocyclic and macrobicyclic ligands may enhance the stability of their metal complexes due to the inherent entropic and kinetic properties of a ligand ring or cage-type structure. Previous work[12] has shown that, in general, as the binding site becomes more encapsulated or preformed the reorganization entropy decreases, leading to a relatively higher formation constant for metal binding. Thus it would be expected that the formation constants should be greatest for the macrobicyclic > macrocyclic > exocyclic (Figure 2).

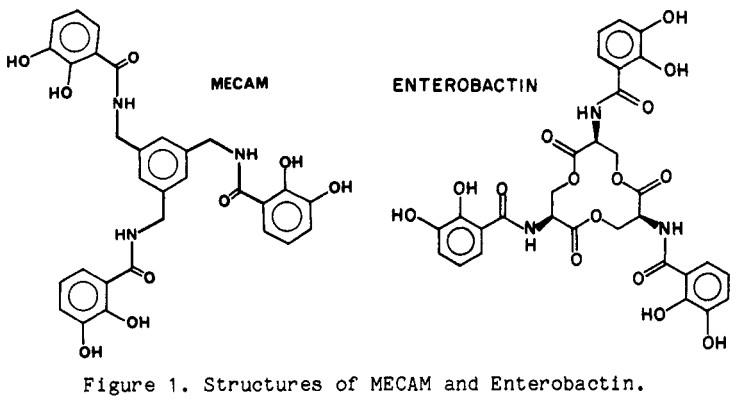


Figure 1. Structures of MECAM and Enterobactin.

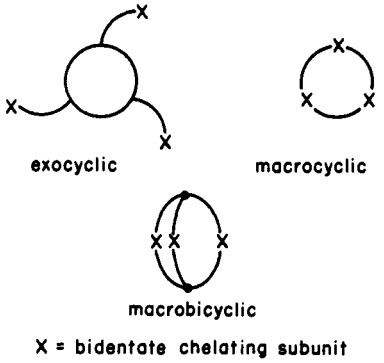
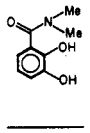
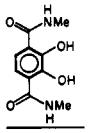
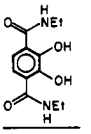
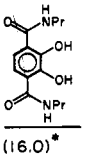


Figure 2. Possible Topologies for Macrocyclic Ligands.

				
β_{ML}	17.8	16.37(1)	16.22(1)	(16.0)*
β_{ML_2}	31.7	30.77(2)	30.54(2)	31.17(3)
β_{ML_3}	40.2	41.68(2)	42.02(2)	43.14(4)
pM	15.0	21.1	21.4	22.7
pKa_1	8.42	6.11(1)	5.95(2)	5.98(2)
pKa_2	(12.1)*	11.13(1)	11.10(1)	11.05(2)

pM = -log[Fe] at pH 7.4, $[L]_T = 10^{-5}$ M, $[Fe]_T = 10^{-6}$ M.

*Estimate.

Figure 3. Protonation Constants, Formation Constants, and pM Values for Binding Subunits Derived From Catechol.

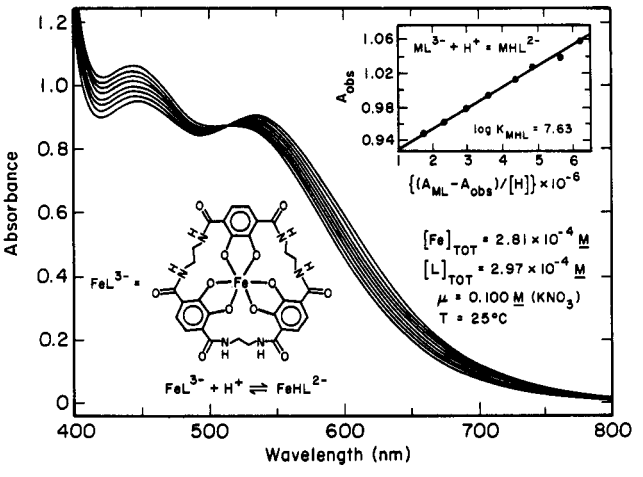


Figure 4. Spectral Changes Associated With the First Protonation of the 1:1 Ferric Ethane Trimer Complex. Top Spectrum at 450 nm: pH 8.24; Bottom Spectrum: pH 7.08.

For synthetic purposes, the idealized macrobicyclic structure in Figure 2 can be viewed as a "capped" tripod, and, encouraged by the success of Lehn[13] and Sargeson[14] on other systems, we and others began investigating macrocyclic catechol-containing ligands. Vögtle[15], Martell[16], and we[17] chose a new binding subunit for this work, 2,3 dihydoxyterephthalamide, rather than the 2,3 dihydroxybenzamide subunit used in enterobactin.

Research into simple derivatives of this new chelating moiety (the last three compounds in Figure 3) show it to be superior to the 2,3-dihydroxybenzamide group (the first structure) both in terms of formation constant and pM.[18] The difference in pM is most striking and is due primarily to the lower pKa's of the new chelating groups. In fact, at physiological pH, the terephthalamide derivatives are the most efficient bidentate iron chelators known. These results suggest that macrocyclic and macrobicyclic ligands incorporating 2,3-dihydroxyterephthalamide binding subunits should form exceptionally strong Fe(III) complexes and are therefore important synthetic targets.

Macrocyclic polycatechol ligands with endocyclic 2,3-dihydroxyterephthalamide binding subunits have been synthesized in up to 24% yield using high dilution techniques.[17] An example of this class of compounds, the ethane trimer, forms a ferric complex which protonates in two sequential one proton steps, yielding log K_{MHL}=7.63(4) (Figure 4) and $\log_{KMH_2L}$=4.8(10). Surprisingly, the pM calculated for this ligand (28.2) is only slightly higher than that obtained for TRENCAM (27.8)[11a], a tripodal ligand incorporating the 2,3-dihydroxybenzamide binding subunit. Evaluation of the series of crowns, in which the ring size is varied from 30 to 42 atoms, is expected to yield insights regarding the influence of cavity size and ligand flexibility on the strength of metal binding in macrocyclic ligands.

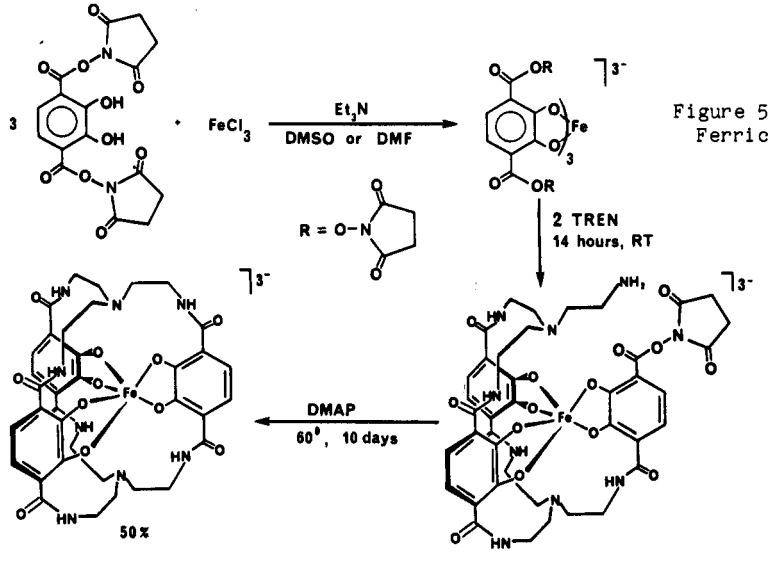


Figure 5. Template Synthesis of Ferric(bicapped TRENCAM).

A macrobicyclic tricatechol ligand, bicapped TRENCAM (1), has been prepared by both traditional high dilution techniques and by template methodology.[19] In a one step reaction, cyclization under high dilution conditions afforded a 3.5% yield of methyl protected bicapped TRENCAM, while a stepwise approach culminating in a high dilution tripod-tripod coupling gave a 27% yield. By comparison, utilizing a ferric ion template in the reaction of disuccinimido-2,3-dihydroxyterephthalate with TREN resulted in the formation of a partially cyclized intermediate (Figure 5) which could be converted to Fe(bicapped TRENCAM) in a remarkable 50% overall yield.

A thorough investigation of how macrobicyclic topology affects the stability and chemistry of Fe(III) complexes requires a series of compounds in which the ligand cavity size, flexibility and charge are varied. The macrobicyclic tris catechoylamides, in which the ligand properties are varied by incorporating TREN, mesitylene, and TPT backbones (Figure 6), satisfy this requirement.[20] The methyl protected compounds were synthesized in 10-15% yield via a stepwise route employing high dilution conditions for the tripod-tripod coupling cyclization. Deprotection (BBr_3, $CHCl_3$) typically proceeds in 75% yield to give the 2,3-dihydroxyterephthalamide derivatives.

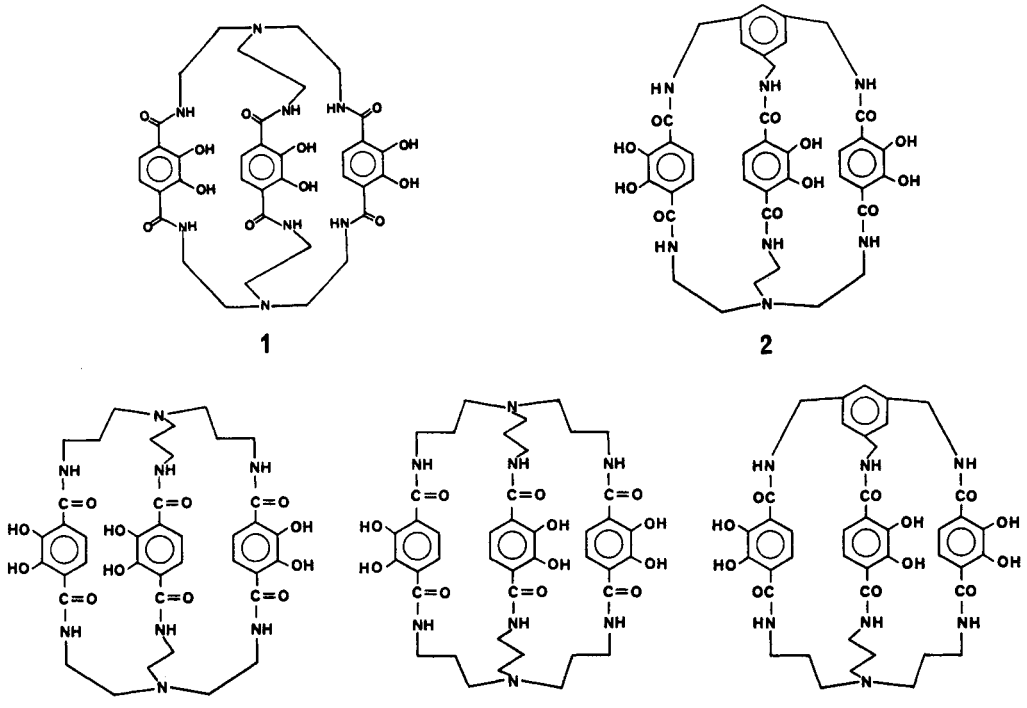


Figure 6. Macrobicyclic Tri-Catechol Ligands.

Cyclic voltammetry of Na_3[Fe(bicapped TRENCAM)], performed in 0.4 M $NaClO_4$ at pH 12.0 using a hanging mercury drop electrode, showed a peak separation (E_{pc} - E_{ac}) of 60 mV, while the ratio of cathodic to anodic currents was 1.0.[19] Normal and differential pulse polarography indicated $E_{1/2}$=-0.95V vs. NHE, and a plot of potential vs. $\log[i_l - i/i]$ was linear with a slope of 60 mV, as expected for a reversible, one electron transfer. While 1 exhibits complicated pH dependence below pH 11.5, the $E_{1/2}$ for bicapped TRENMECAM 2 is invariant between pH 8.3 and 12.0 (-0.92 V vs. NHE). The large, negative reduction potential observed for these compounds is characteristic of other tri-catechol ligands we have studied[21], and indicates that the selectivity for coordination of the ferric over the ferrous ion is retained in the cage complexes, giving a ratio of the formation constants K_f Fe(III)/Fe(II) $\simeq 10^{29}$.

Crystals of Na_3[Fe(bicapped TRENCAM)]·17.5 H_2O suitable for X-ray diffraction were obtained by evaporation from methanol/H_2O. The structure is the first to be determined for any ferric tris-catechoylamide complex. Remarkably, the coordination geometry around the metal center is trigonal prismatic, an unprecedented structure for Fe(III).[20] As shown in Figure 7, the entire catechoylamide group is planar, with the trans configuration of the amide allowing for a strong hydrogen bond between the amide proton and the coordinated catechol oxygen. To accommodate this stable ligand structure, the metal ion lies 0.81 A away from the ligand so that there is a 31° dihedral angle between the plane defined by the iron and two oxygen atoms and the catechol plane. The resultant triskelion is shown clearly in Figure 8.

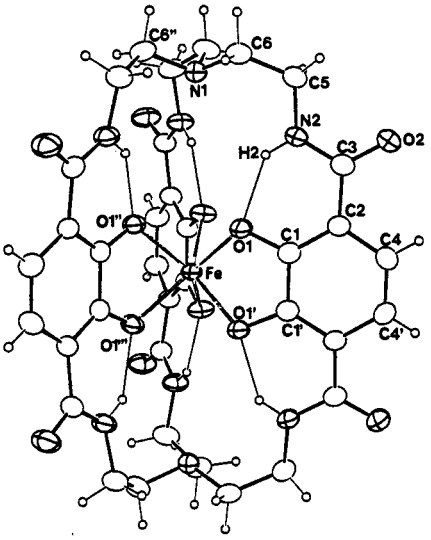


Figure 7. ORTEP showing a side view of Fe(bicapped TRENCAM). The ellipsoids are scaled to represent the 50% probability surface.

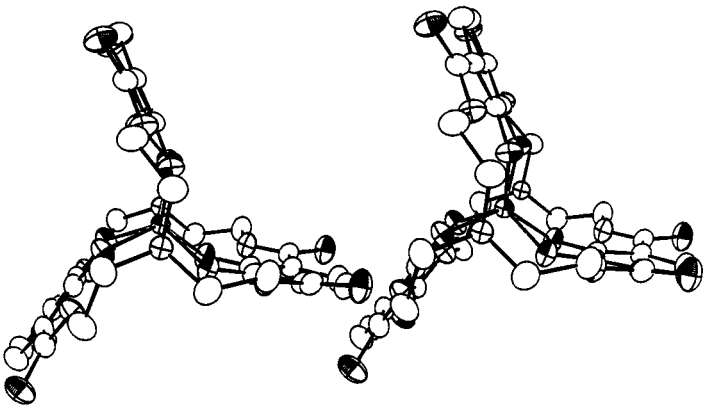


Figure 8. Stereoview showing a top view of Fe(bicapped TRENCAM). The ellipsoids are scaled to represent the 50% probability surface.

The determination of formal stability constants and further investigation into the pH dependence of the electrochemistry are in progress. Structure determinations of ferric complexes of other macrobicycles in the series with more flexibility and larger cavity sizes may be expected to form the normal octahedral coordination geometry. In any case, complexation of transition metals with large octahedral crystal field stabilization energies (such as Cr(III)) should force the geometry away from the novel trigonal prismatic coordination demonstrated by Fe(bicapped TRENCAM).

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REFERENCES

1. The Biochemistry and Physiology of Iron, P.Saltman, J.Hegenauer, Eds. Elsevier Biomedical (1981).
2. K.N.Raymond, G.Muller, B.F.Matzanke, Top. Curr. Chem. 123, 50-102 (1984).
3. J.R.Pollack, J.B.Neilands, Biochem. Biophys. Res. Comm. 38, 989 (1970). I.G.O'Brien, F.Gibson, Biochim. Biophys. Acta. 215, 393 (1970).
4. W.R.Harris, C.J.Carrano, S.R.Cooper, S.R.Sofen, A.Avdeef, J.V.McArdle, K.N.Raymond, J. Am. Chem. Soc. 101, 6097-6104 (1979).
5. Development of Iron Chelators for Clinical Use; A.E.Martell, W.F.Anderson, D.G.Badman, Eds. Elsevier North-Holland, New York, (1981).
6. M.C.Venuti, W.H.Rastetter, J.B.Neilands, J. Med Chem. 22, 123-124 (1979).
7. F.L.Weitl, K.N.Raymond, J. Am. Chem. Soc. 101, 2728-2731 (1979).
8. W.R.Harris, K.N.Raymond, J. Am. Chem. Soc. 101, 6534-6541 (1979).
9. S.Heidinger, V.Braun, V.L.Pecoraro, K.N.Raymond, J. Bacteriol. 153, 109-115 (1983).
10. F.L.Weitl, W.R.Harris, K.N.Raymond, J. Med. Chem. 22, 1281-1283 (1979). F.L.Weitl, K.N.Raymond, P.W.Durbin, J. Med. Chem. 24, 203 (1981). R.J.Bergeron, Acc. Chem. Res. 19, 105-113 (1986).
11. (a) S.J.Rodgers, C.W.Lee, C.Y.Ng, K.N.Raymond, Inorg. Chem., in press. (b) B. Wolff, A. Weiss Angew. Chem Int. Ed. Eng. 25, 162-163 (1986).
12. A.E.Martell, "The Design and Synthesis of Chelating Agents", in Development of Iron Chelators for Clinical Use; A.E.Martell, W.F.Anderson, D.G.Badman, Eds. Elsevier North Holland, New York (1981).
13. J.-M.Lehn, Science (Washington, D.C.) 227, 849-856 (1985).
14. R.J.Geue, T.W.Mabley, J.M.Harrowfield, A.M.Sargeson, M.R.Snow, J. Am. Chem. Soc. 107, 899-901 (1985), and references therein.
15. K.Wolfgang, F.Vögtle, Angew. Chem. Int. Ed. Eng. 23, 714 (1984).
16. Y.Sun, A.E.Martell, R.J.Motekaitis, Inorg. Chem. 25, 4780 (1986).
17. S.J.Rodgers, C.Y.Ng, K.N.Raymond, J.Am. Chem. Soc. 107, 4094-4095 (1985).
18. T.M.Garrett, P.W.Miller, K.N.Raymond, manuscript in preparation.
19. T.J.McMurry, S.J.Rodgers, K.N.Raymond, J. Am. Chem. Soc., in press.
20. T.J.McMurry, M.W.Hosseini, T.M.Garrett, F.E.Hahn, Z.E.Reyes, K.N.Raymond, submitted to J. Am. Chem. Soc.
21. C.-W.Lee, D.J.Ecker, K.N.Raymond, J. Am. Chem. Soc. 107, 6920-6923 (1985).