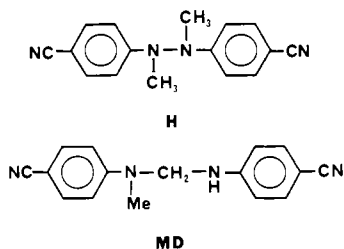


(Me₈TPP)Fe^{III}Cl there is also obtained *N,N'*-dimethyl-*N,N'*-bis-(*p*-cyanophenyl)hydrazine (H) and *N,N'*-bis(*p*-cyanophenyl)-*N*-methylmethylenediamine (MD). Both H and MD



would appear to arise by the coupling of radical species of MA. Apparently, with the more electron-deficient iron(IV)-oxo porphyrin π -cation radical species, DA becomes a better substrate for oxidation, sparing MA from 1e⁻ oxidation. In this study we find that the most electron-deficient iron(IV)-oxo porphyrin

π -cation radical ((⁺F₂₀TPP)Fe^{IV}O) is capable of hydroxylation of the aromatic ring of DA.

Acknowledgment. This work was supported by grants from the National Institutes of Health and The National Science Foundation. X-ray crystallographic studies were carried out in the Department of Chemistry and Biochemistry at UCLA by C.B.K.

Supplementary Material Available: Listing of experimental collection and reduction of X-ray data, position and vibration parameters for hydrogen, anisotropic vibration parameters for non-hydrogen atoms, position and vibration parameters for non-hydrogen atoms, bond lengths and bond angles for non-hydrogen atoms, and torsion angles (9 pages); tables of calculated and observed structure factors for 4-cyano-7-(dimethylamino)-2-benzofuranone-3-spiro-2'-cyano-5'-(dimethylamino)cyclopentadiene (9 pages). Ordering information is given on any current masthead page.

Communications to the Editor

Template and Stepwise Syntheses of a Macrocyclic Catechoylamide Ferric Ion Sequestering Agent¹

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Received November 7, 1986

The synthesis of ligands that specifically sequester a given metal ion under physiological conditions presents a challenge to the coordination chemist.²⁻⁷ A biomimetic approach to the synthesis of ferric ion specific chelators is suggested by the siderophores, low molecular weight sequestering agents which enable microorganisms to assimilate iron.⁸ We have previously reported the synthesis of siderophore analogues with linear,⁹⁻¹¹ tripodal,^{12,13} and macrocyclic¹⁴ topologies,¹⁵ some of which are promising

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[†] Deceased.

(1) Paper 16 in the series "Ferric Ion Sequestering Agents". Reference 34 is the previous paper in the series.

(2) *Development of Iron Chelators for Clinical Use*; Martell, A. E., Anderson, W. F., Badman, D. G., Eds.; Elsevier North-Holland: New York, 1981.

(3) May, P. M.; Bulman, R. A. *Prog. Med. Chem.* **1983**, *20*, 225-336.

(4) Edwards, G. L.; Hayes, R. R. *J. Nucl. Med.* **1969**, *10*, 103.

(5) Pecoraro, V. L.; Wong, G. B.; Raymond, K. N. *Inorg. Chem.* **1982**, *21*, 2209-2215.

(6) Moerlein, S. M.; Welch, M. J.; Raymond, K. N. *J. Nucl. Med.* **1981**, *22*, 710-719.

(7) Raymond, K. N.; Kappel, M. J.; Pecoraro, V. L.; Harris, W. R.; Carrano, C. J.; Weitz, F. L.; Durbin, P. W. In *Actinides in Perspective*; Edelstein, N. M., Ed.; Pergamon: Oxford and New York, 1982; pp 491-507.

(8) Raymond, K. N.; Müller, G.; Matzanke, B. F. *Top. Curr. Chem.* **1984**, *123*, 50-102.

(9) Weitz, F. L.; Raymond, K. N. *J. Org. Chem.* **1981**, *46*, 5234-5237.

(10) Weitz, F. L.; Raymond, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 1252-1255.

(11) Weitz, F. L.; Harris, W. R.; Raymond, K. N. *J. Med. Chem.* **1979**, *22*, 1281-1283.

(12) Weitz, F. L.; Raymond, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 2728-2731.

(13) Harris, W. R.; Weitz, F. L.; Raymond, K. N. *J. Chem. Soc., Chem. Commun.* **1979**, 177-178.

(14) Rodgers, S. J.; Ng, C. Y.; Raymond, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 4094-4095.

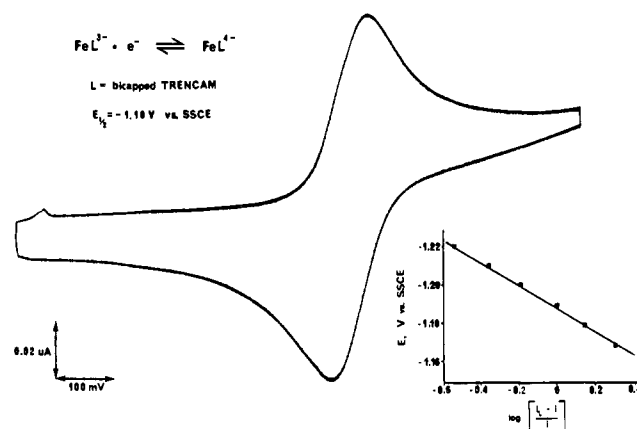


Figure 1. Cyclic voltammogram of 0.5 mM ferric(bicapped TRENCAM) in 0.4 M NaClO₄ (pH 12.0) at HMDE. Negative potentials (vs. SSCE) are plotted to the right and reduction currents are plotted upward. Scan rate, 50 mV/s; initial potential, -600 mV. The inset shows *E* vs. log [(*t*₁ - *i*)/*i*] for the normal pulse polarogram.

candidates for the in vivo removal of iron as well as the actinides.^{16,17} We describe here the synthesis of a new macrocyclic catechoylamide ligand,¹⁸ bicapped TRENCAM (**1a**), by conventional high-dilution techniques as well as the development of a high-yield template synthesis which promises to revolutionize the preparation of such ligands.

Methyl-protected bicapped TRENCAM **1b** was synthesized by two high-dilution routes (Scheme I) which resulted in cyclization yields of 3.5% and 27% after chromatography on silica gel (Chromatatron, CH₂Cl₂/5% CH₃OH). The simplicity of the ¹H and ¹³C NMR of **1b** reflects the idealized D_{3h} symmetry of the molecule.¹⁹ Elemental analysis and positive ion fast atom bombardment (FAB) mass spectroscopy confirmed the proposed

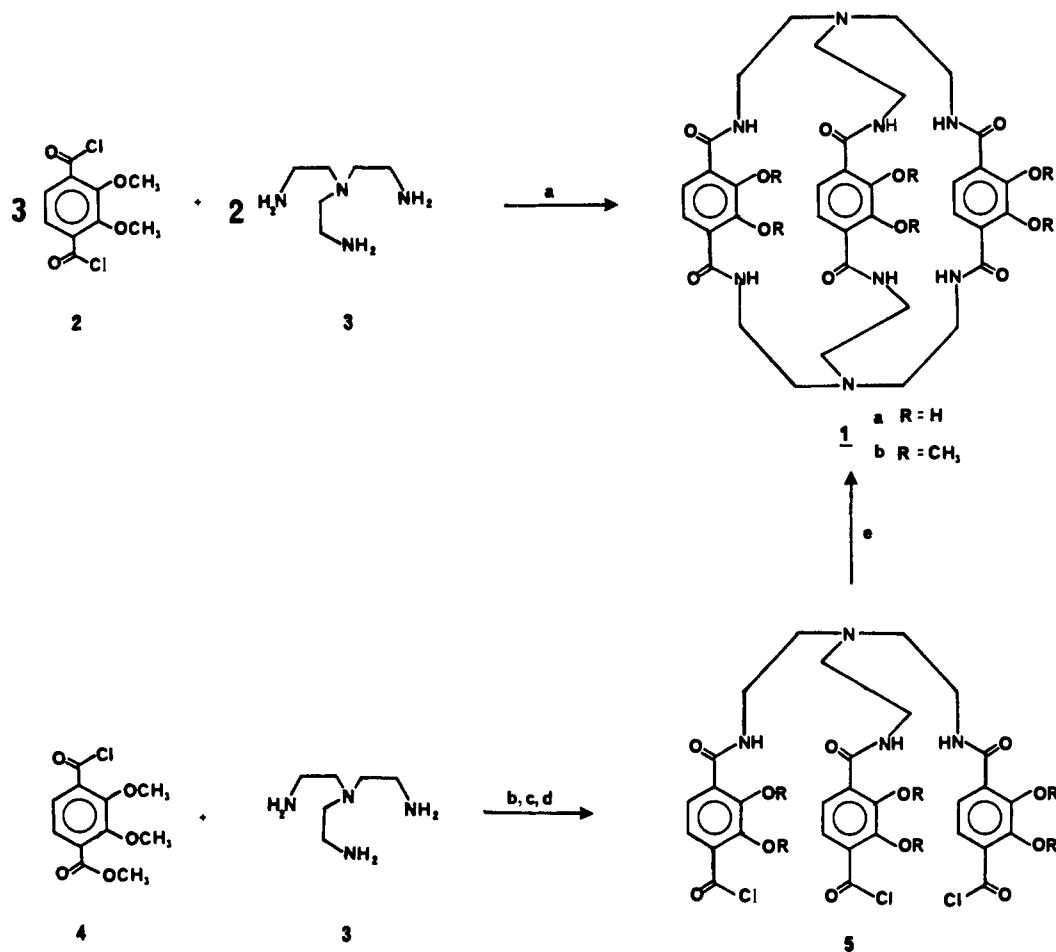
(15) Lehn, J.-M. *Science (Washington, D.C.)* **1985**, *227*, 849-856.

(16) Durbin, P. W.; Jeung, N.; Jones, E.; Weitz, F. L.; Raymond, K. N. *Radiat. Res.* **1984**, *99*, 106-128.

(17) Weitz, F. W.; Raymond, K. N.; Durbin, P. W. *J. Med. Chem.* **1981**, *26*, 439.

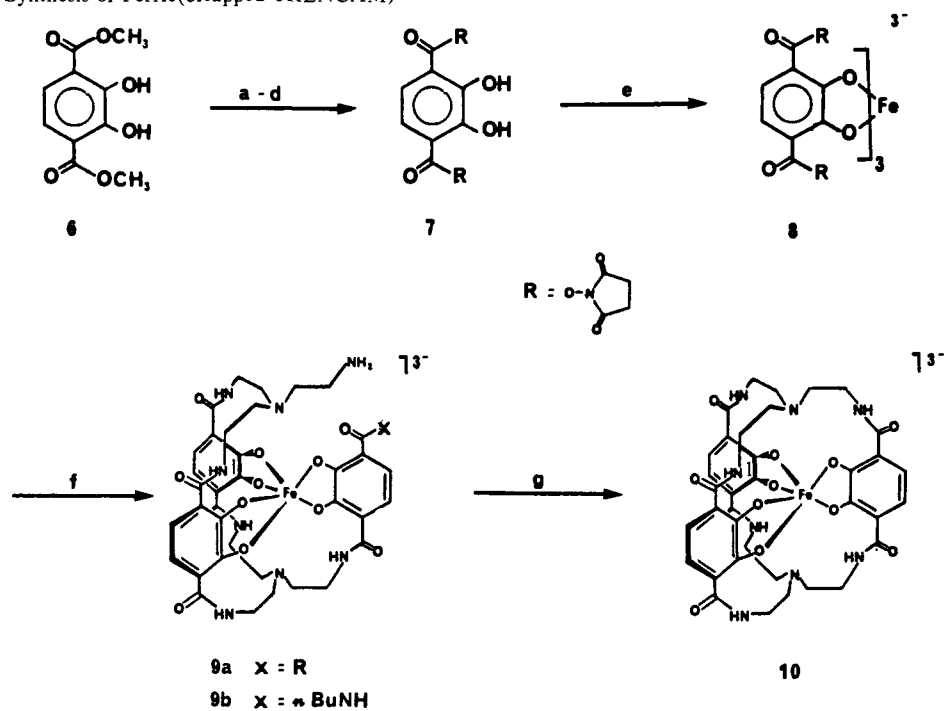
(18) Wolfgang, K.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 714.

(19) ¹H NMR (200 MHz, CDCl₃) δ 2.74 (br m, 12 H), 3.61 (br m, 12 H), 3.80 (s, 18 H), 6.72 (s, 6 H), 7.61 (t, 6 H, *J* = 4.6 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 36.68, 52.25, 61.57, 124.12, 131.45, 151.27, 166.28.

Scheme I.^a High-Dilution Synthesis of Bicapped TREN CAM

^a (a) THF, Et₃N, high dilution, 3.5%; (b) Schotten-Baumann, CH₂Cl₂, aqueous KOH, not isolated; (c) MeOH, aqueous NaOH, 2 h, 89%; (d) SOCl₂, THF, catalytic DMF; (e) TREN (1 equiv), THF, Et₃N, high dilution, 27%.

Scheme II. Template Synthesis of Ferric(bicapped TREN CAM)



^a (a) PhCH₂Cl₂, KI, K₂CO₃, acetone reflux, 72 h, 85%; (b) NaOH, DME/H₂O, reflux, 9 h, 94%; (c) *N*-hydroxysuccinimide, DCC, dioxane, 72%; (d) H₂/5% Pd-C, EtOAc, room temperature, 1 h, 100%; (e) FeCl₃, Et₃N, DMF or Me₂SO, not isolated; (f) TREN (2 equiv), room temperature, 14 h; (g) DMAP, 65 °C, 5 days, 70%.

structure.²⁰ Removal of the methyl protecting groups (BBR₃, CH₂Cl₂) gave the hexahydroxy ligand **1a** which exhibited a parent ion at 779 [M + H]⁺ in the positive ion FAB mass spectrum. However, the ¹H NMR of this material in Me₂SO-*d*₆ is quite complex,²¹ and variable-temperature experiments indicate a fluxional process is occurring.²² A simplified spectrum of the ligand was observed upon coordination of gallium(III),²³ indicating that the metal complex is the D₃ symmetry complex, while cis-trans isomerization leads to a mixture of conformers for the free ligand.²⁴

A conceptually simple synthetic approach which circumvents the high-dilution reaction involves the use of a transition-metal template.^{25,26} Elegant examples of the use of metal ions as templates can be found in the synthesis of macrobicyclic cobalt amine sepulchrate complexes by Sargeson and co-workers^{27,28} and the preparation of catenands by Dietrich-Buchecker, Sauvage, and Kern.^{29,30} In the present case, preorganizing three suitably functionalized catechol ligands about a metal ion enables the macrobicyclic complex to be formed by combining with 2 equiv of TREN³¹ (Scheme II).

The template reaction proceeded to give a 90% yield, estimated by HPLC, of the intermediate **9a** identified on the basis of its IR (1734 cm⁻¹) and the properties of its monobutyl amide derivative **9b**.³² When heated in the presence of 4-(dimethylamino)pyridine, **9a** was slowly converted to Fe(bicapped TRENCAM) (**10**), remarkably in 70% yield! Demetalation (Na₂S₂O₄/HCl) of the ferric complex obtained from the template reaction provided bicapped TRENCAM, as ascertained by positive ion FAB mass spectrometry (*m/e* 779 [M + H]⁺), NMR, and HPLC.

Ferric(bicapped TRENCAM) was characterized by cyclic voltammetry (Figure 1) in 0.4 M NaClO₄ at pH 12.00 by using a hanging drop mercury electrode. The peak-to-peak separation was 60 mV and the ratio of the cathodic to anodic peak currents was 1.0. Normal pulse polarography indicated an *E*_{1/2} = -1.19 V vs. SCE and a plot of *E* vs. log [*i*_L - *i*]/*i* was linear with a slope of 60 mV, indicating reversible electron transfer was occurring. The negative reduction potential, characteristic of other ferric tris catecholate complexes we have studied,^{33,34} demonstrates that the strong preference for coordination of the ferric ion over the ferrous ion (*K*_{Fe(III)}/*K*_{Fe(II)} = 10²⁹) is retained in the cage complex.

The syntheses of bicapped TRENCAM illustrate the benefits derived from utilizing the coordination template effect for the synthesis of macrobicyclic catechoylamide ligands. We intend

to investigate the scope of the approach, including the synthesis of unsymmetrical macrobicycles via a "half-cage" template reaction. In addition, quantitative determination of the formation constant for ferric bicapped TRENCAM is in progress in our laboratory.

Acknowledgment. We thank Dr. Chiu Ng for his experimental assistance. This research is supported by NIH Grant AM 32999. An NIH postdoctoral fellowship to T.J.M. is gratefully acknowledged.

Registry No. **1a**, 107712-27-6; **1b**, 107742-32-5; **2**, 7169-12-2; **3**, 4097-89-6; **4**, 7168-94-7; **5b**, 107712-28-7; **6**, 75956-62-6; **7**, 107712-29-8; **8**, 107712-30-1; **9a**, 107712-31-2; **9b**, 107712-32-3; **10**, 107712-33-4; Ga(TRENCAM)³⁺, 107712-34-5; *N*-hydroxysuccinamide, 6066-82-6.

Torsional Motion in Aromatic Molecules. Conformational Analysis of Methyl-, Ethyl-, and *n*-Propylbenzenes[†]

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Received November 24, 1986

To an ever increasing extent, information regarding torsional vibrations of organic molecules is being provided by theoretical treatments rather than by experimental observation.¹ When experimental data are available, all too frequently they pertain to mole fraction weighted averages of the individual contributing conformations rather than the individual conformations themselves.² We now demonstrate that supersonic molecular jet spectroscopy can provide a novel means (a) to determine experimental values for torsional potential barriers in S₀ and S₁, (b) to "freeze out" molecular conformations which have very low (ca. 1-5 kcal mol⁻¹) free energy barriers between themselves, (c) to "count" the number of stable ground state conformations and, by doing so, establish their molecular geometries, and (d) to observe spectroscopic properties of these individual conformations.

Much current interest exists in the conformational analysis of alkyl-substituted benzene substrates, and herein we focus specific attention on the first three members of this class of compounds: methyl, ethyl, and *n*-propyl. Both time of flight mass spectra (TOFMS) and dispersed emission (DE) spectra are determined for the systems studied.³ Figure 1 presents the TOFMS of *m*-xylene (**1**) for the 0₀⁰ region of the S₁ ← S₀ transition. The various features of this spectrum are attributed to transitions between internal rotor states of the two methyl groups. A double one-dimensional rigid rotor model can be employed to fit these data.⁴⁻⁶ Parameters of this quantum mechanical model can be

(20) Elemental anal. Calcd for C₂₄H₃₄N₆O₁₂·2H₂O: C, 57.26; H, 6.41; N, 12.72. Found: C, 57.52; H, 6.34; N, 12.43. + FAB-MS *m/e* 863 (M + H)⁺.

(21) NMR (200 MHz, Me₂SO-*d*₆) δ 12.666 (s, 3 H), 11.84 (s, 2 H), 10.0 (br s, 1 H), 9.00 (br s, 3 H), 8.29 (br s, 3 H), 6.80 (q, 6 H, *J* = 8 Hz) 3.78 (br s, 6 H), 3.59 3.52 (br s, 12 H plus H₂O), 2.821 (s, 6 H).

(22) *T*_c (Ar H) = 70.1 °C; the *T*_c (amide H) is < 100 °C, at 200 MHz.

(23) Other catechol ligands readily complex the diamagnetic gallium(III) ion; see ref 3-5.

(24) ¹H NMR (200 MHz, D₂O, pH 10.5) δ 6.962 (s, 6 H); 3.690 (br s, 12 H), 2.833 (br s, 12 H).

(25) Thompson, M. C.; Busch, D. H. *J. Am. Chem. Soc.* **1964**, *86*, 3651-3656.

(26) Melson, G. A. *Coordination Chemistry of Macrocyclic Compounds*; Plenum: New York, 1979.

(27) Creaser, I. I.; Geue, R. J.; Harrowfield, J. McB.; Hertl, A. J.; Sargeson, A. M.; Snow, M. R.; Springborg, J. *J. Am. Chem. Soc.* **1982**, *104*, 6016.

(28) Geue, R. J.; Mabley, T. W.; Harrowfield, J. M.; Sargeson, A. M.; Snow, M. R. *J. Am. Chem. Soc.* **1985**, *107*, 899-901.

(29) Dietrich-Buchecker, C. D.; Sauvage, J.-P.; Kern, J. M. *J. Am. Chem. Soc.* **1984**, *106*, 3043-3045.

(30) Dietrich-Buchecker, C. O.; Kern, J. M.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1985**, 760-762.

(31) Abbreviations used in the text: TREN, tris(2-aminoethyl)amine; DMAP, 4-(dimethylamino)pyridine; DCC, dicyclohexylcarbodiimide; SSCE, standard saturated calomel electrode; HMDE, hanging mercury drop electrode.

(32) IR 1609 cm⁻¹; - FAB MS 903 [M + 2H]⁺.

(33) Lee, C.-W.; Ecker, D. J.; Raymond, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 6920-6923.

(34) Rodgers, S. J.; Lee, C.-W.; Ng, C. Y.; Raymond, K. N. *Inorg. Chem.* **1987**, *27*, 1622-1625.

[†]Dedicated to Professor Ernest L. Eliel, to commemorate his 65th birthday and to honor his commitments to science, education, society, and professionalism.

(1) (a) Ōsawa, E.; Musso, H. *Top. Stereochem.* **1982**, *13*, 117. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982. (c) Clark, T. *A Handbook of Computational Chemistry*; Wiley: New York, 1985. (d) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(2) (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (b) Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH Publishers: Deerfield Beach, FL, 1985. (c) Jackman, L. M.; Cotton, F. A. *Dynamic NMR Spectroscopy*; Wiley: New York, 1975. (d) Chen, J.-S.; Shirts, R. B.; Lin, W.-C. *J. Phys. Chem.* **1986**, *90*, 4970. (e) Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* **1985**, *18*, 80.

(3) Bernstein, E. R.; Law, K.; Schauer, M. *J. Chem. Phys.* **1984**, *80*, 207.

(4) Okuyama, K.; Mikami, N.; Ito, M. *J. Phys. Chem.* **1985**, *89*, 5617.