(6) McDonald, R. N.; Curl, C. A. *J. Am. Chem. Soc.* **1979**, *101*, 7116–7118.
(7) Hess, H. M.; Brown, H. C. *J. Org. Chem.* **1967**, *32*, 4138–4139.
(8) Olah, G. A.; Kuhn, S. J. *J. Am. Chem. Soc.* **1960**, *82*, 2380–2382.
(9) Humski, K.; Sendijarević, V.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 7722–7728.
(10) Optical activity studies[6] suggest that some of the chiral homoallylic ions from the six-membered cyclohex-3-enyl system either leak to an achiral localized ion or undergo a racemizing ring flip. Consequently, some of the 60% of inversion material may have resulted from racemization of the homoallylic ion rather than from k_s. The 40% retention then is a lower limit for the percentage of double-bond participation. As the earlier studies were for acetolysis,[6] it is not possible to specify how much larger than 40% the actual percentage is of double-bond participation. Observation of complete retention in cyclopent-3-enyl system means that the homoallylic ion neither leaks to the localized ion nor undergoes ring flip.
(11) Mallory, T. B., Jr.; Bauman, L. E.; Carreira, L. A. *Top. Stereochem.* **1979**, *11*, 142–143.
(12) For other examples, see ref 5 and Lambert, J. B.; Mark, H. W.; Holcomb, A. G.; Magyar, E. S. *Acc. Chem. Res.* **1979**, *12*, 317–324.
(13) We thank the National Science Foundation (Grant No. CHE79-05542) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. The 360-MHz ^{1}H spectra were obtained at the Purdue University Biochemical Magnetic Resonance Laboratory, supported by National Institutes of Health Grant No. RR01077 from the Division of Research Resources. We thank Mr. Stephen M. Wharry for obtaining these spectra.
(14) National Science Foundation Undergraduate Research Participant from Barat College, Lake Forest, Ill., 1978.

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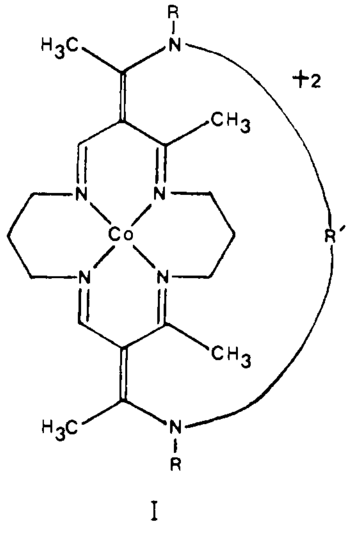
Synthesis and Structure of Totally Synthetic Coboglobin Models

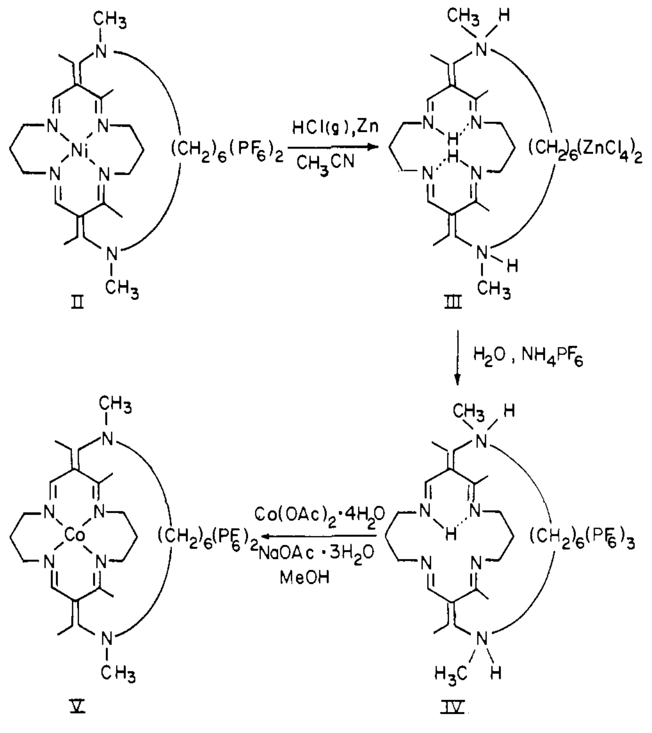
Sir:

The ability of cobalt(II)-substituted hemoglobin and myoglobin to reversibly bind oxygen has provided new probes for the study of the metal atom site in these heme proteins.[1] Cobalt is similarly important in the development of totally synthetic heme protein models. Using the templating action of nickel(II), we have recently prepared and reported a new family of *superstructure* ligands (structure I) that have been designed to emulate the active sites of heme proteins.[2] We report here the synthesis and characterization of the cobalt complexes of these unusual ligands, wherein the bridge group R′ provides a protected void, or "dry cave", near the metal atom, which is intended to shelter small ligands from interactions with other cobalt centers or with solvent. Two critical questions that we faced in developing the dry cave ligand system were (1) can the ligand be removed intact from the Ni(II) template and, more importantly, can it be chelated around the more interesting (from a bioinorganic standpoint) Co(II), again without degradation or isomerization and (2) does the dry cave structure that we have designed into these ligands actually perform the desired function—is the bridging group sufficiently rigid and appropriately positioned to permit the coordination of small molecules in the cavity while restricting the entry and coordination mode of other potential ligands? We report here that the answers to both questions are unequivocally in the affirmative.



I

Scheme I



The synthesis of the cobalt(II) complexes proceeds according to Scheme I (shown for the -(CH_2)$_6$- bridged compound with CH_3 groups on the bridging nitrogens).[3] The yield of the orange microcrystalline product was 1.34 g (68%). Anal. Calcd for $CoC_{26}H_{44}N_6P_2F_{12}$; C, 39.55; H, 5.62; N, 10.64. Found: C, 39.56; H, 5.89; N, 10.61. This complex is a 2:1 electrolyte in CH_3CN (λ 282 at 25 °C) and has a magnetic moment of 2.49 β. Its ESR spectrum is reported in the following communication.[4]

The cobalt(II) complex prepared in this way was subjected to a complete X-ray structure determination.[5] While the structure is flawed by limitations associated with a disorder in the PF_6^- counterions, a number of highly significant results are nevertheless firmly established. Of primary importance, the ligand is not altered when removed from nickel and coordinated to cobalt(II) (Figures 1 and 2). The cobalt(II) is four coordinate and square planar and the dry cave is clearly evident. It is $\sim$6.65 Å wide (measured between nonbridgehead vinyl carbons) with the height varying from 4.83 (back) to 5.60 Å (front). The saddle shape of the basic macrocycle is largely responsible for formation of the cavity in the structure.

Since cobalt(III) is very nearly always six coordinate, we have chosen to form the complexes of that ion to prove that small ligands can be accommodated in the dry cave. The cobalt(II) complex can be oxidized in the presence of the small ligands $X^- = NCS^-$, N_3^-, and NCO^- to form the corresponding cobalt(III) complexes $Co^{III}(L)X_2^+$, where L = the dry cave ligand. The oxidation can be accomplished with a variety of reagents, including Ce^{4+}, $NOPF_6$, and air (24 h). These diamagnetic complexes are 1:1 electrolytes in acetonitrile solution. Also in solution, the infrared spectrum of the

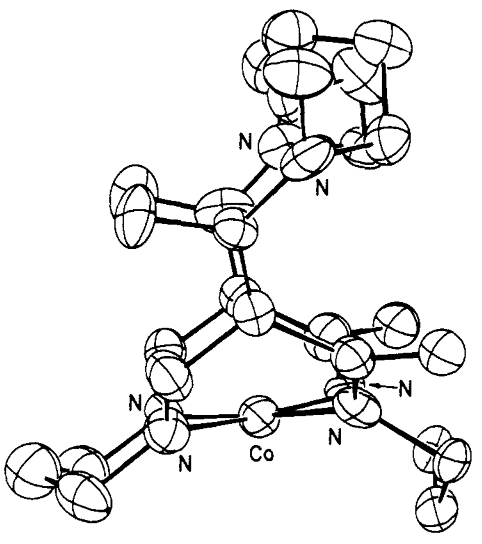


Figure 1. ORTEP drawing of the *N*-methyl $(CH_2)_6$-bridged cobalt(II) dry cave complex.

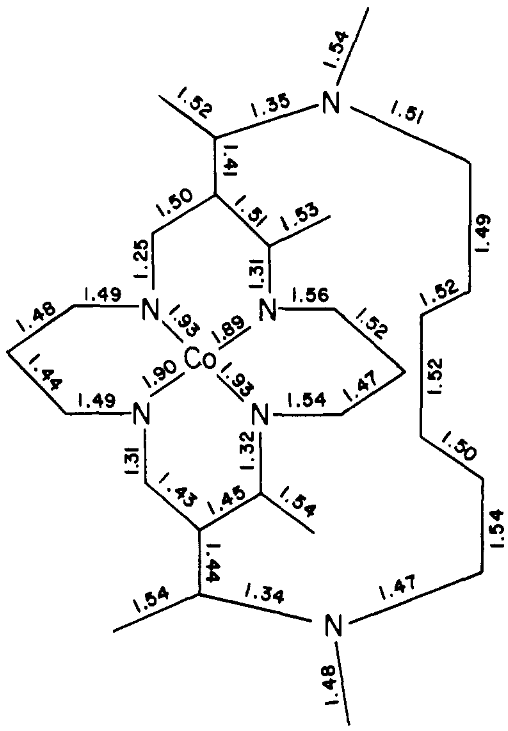


Figure 2. Structure of the cobalt(II) complex of the *N*-methyl $(CH_2)_6$-bridged dry cave ligand. Distances are given ångstroms.

bisisothiocyanato complex shows two distinct N≡C stretching modes at 2090 and 2138 cm^{-1}, indicating that the thiocyanates reside in different environments. From these results it was inferred that one NCS binds below the dry cave ligand while the second occupies the sixth-coordination site within the dry cave; this conclusion has been confirmed by single-crystal X-ray studies.[6] The essential features of the ligand remain unaltered and the two thiocyanates are indeed bound to the cobalt(III). As Figure 3 shows, this establishes the fact that small ligands, such as O_2 or CO, may enter the dry cave. The side view given in Figure 4 displays the most remarkable feature of the structure. The NCS in the dry cave is bent from the normal to the CoN_4 plane by 32°, and bond distances and electron densities reveal that it is N bonded. Steric interaction of the isothiocyanate moiety with the low roof on the dry cave has forced the normally linear Co-NCS linkage into a decidedly angular one.[7] The cavity is somewhat wider (7.09 Å) and taller (6.17 Å at front) than that of the Co(II) complex, probably as a result of the steric repulsions exerted by the thiocyanate. The N-C and C-S distances are identical for the two thiocyanates and comparable with those of other compounds.[8-11]

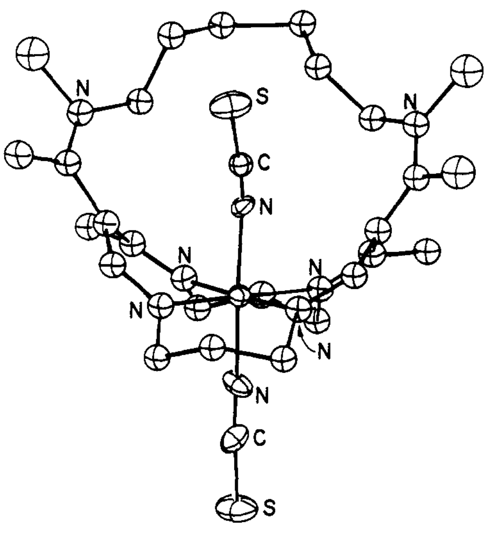


Figure 3. ORTEP drawing, looking into the cavity, for the complex $[Co^{III}(L)(NCS)_2]Cl$ where L is the *N*-methyl $(CH_2)_6$-bridged dry cave ligand.

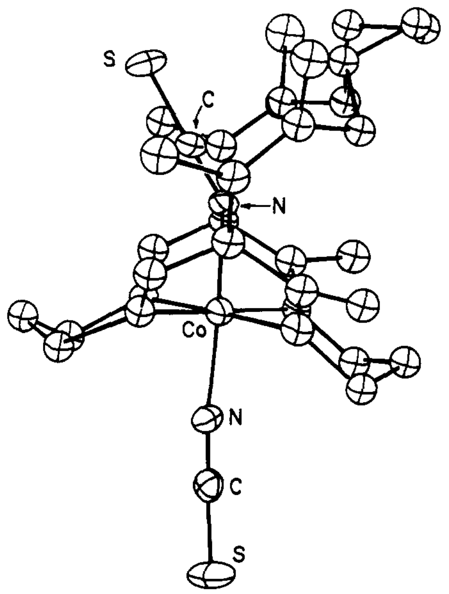


Figure 4. Side view of the complex ion $[Co^{III}(L)(NCS)_2]^+$, where L is *N*-methyl $(CH_2)_6$-bridged dry cave ligand, showing the NCS in the cavity with a bent Co-N-C linkage.

The $(CH_2)_6$ bridge is fairly flexible, within the limits of its terminal atoms being relatively rigidly fixed by the macrocycle. The conformation found in the Co(II) structure is considerably altered by the steric requirements of the isothiocyanate ligands in the Co(III) structure. However, the effects are not sufficient to force the bridge from over the cavity, and merely lead to the several alternative conformations of the hexamethylene chain.[6]

The dioxygen adducts of these new cobalt(II) complexes are the subject of the following paper.[4]

References and Notes

(1) (a) B. M. Hoffman and D. H. Petering, *Proc. Natl. Acad. Sci. U.S.A.*, **67**, 637 (1970); (b) T. Yonetani, H. Yamamoto, and G. V. Woodrow, *J. Biol. Chem.*, **249**, 682 (1974).

(2) W. P. Schammel, K. S. B. Mertes, G. G. Christoph, and D. H. Busch, *J. Am. Chem. Soc.*, **101**, 1622 (1979).

(3) The nickel complex (structure II) (10.2 g, 12.9 mmol) was dissolved in acetonitrile (500 mL) and anhydrous HCl(g) was bubbled through the solution for 30 min during which time the color changed from orange to blue-green. A solution containing tetrachlorozincate anion is prepared by reaction of granular zinc (5 g, 76.5 mmol) in 500 mL of acetonitrile saturated with anhydrous HCl(g). Upon addition of this solution to the blue-green solution, the ligand precipitated as the tetrachlorozincate(II) salt (structure III): yield, 9.7 g (87%). This salt (III) was dissolved in 100 mL of water and reprecipitated as the hexafluorophosphate salt by the addition of aqueous NH_4PF_6. Cobalt(II) was inserted into IV by slurrying the ligand salt(IV) (2.17 g, 2.5 mmol) in 25 mL of methanol and adding a solution of $Co(OAc)_2 \cdot 4H_2O$ (0.61 g, 2.5 mmol) and $Na(OAc) \cdot 3H_2O$ (0.34 g, 2.5 mmol) in 25 mL of methanol. After the solution was heated to boiling and then cooled, the orange microcrystalline product precipitated and was isolated by filtration.

(4) J. C. Stevens and D. H. Busch, *J. Am. Chem. Soc.*, following paper in this issue.

(5) Space group $P2_12_12_1$; a = 15.442 (3), b = 11.016 (2), c = 19.708 (3) Å, Z = 4; $\lambda_{Mo\ K\bar{\alpha}}$ = 0.71069 Å; ρ_{obsd} = 1.58, ρ_{calcd} = 1.56; ω-2θ scan technique for all reflections of positive *hkl* having $2\theta < 60°$; 4772 independent reflections of which 2098 had intensities $>3\sigma(F^2)$ above background. The structure was solved by the heavy-atom Patterson technique and refined using standard Fourier and least-squares methods. Both PF_6^- ions were found to be disordered and this was treated by refining the coordinates, orientation, and occupancy factors of six rigid, partial-occupancy PF_6^- groups. The final disagreement indices for 4772 reflections are R = 0.127, R_ω = 0.155, and GOF = 5.5. Although these indices are somewhat high by current standards, we believe that this is a result of the PF_6^- disorder and the high proportion of weak data and that the general features of the structure are basically correct.

(6) A crystal of bis(isothiocyanato)cobalt(III) complex of the ligand having structure IV, with a chloride counterion, was subjected to complete X-ray analysis. Space group $P2_1$; a = 11.526 (4), b = 14.362 (7), c = 11.986 (4) Å; β = 65.98 (4)°; Z = 2; $\lambda_{Mo\ K\alpha}$ = 0.71079 Å; ρ_{obsd} = 1.36, ρ_{calcd} = 1.36; the ω-2θ scan technique gave 6456 independent reflections of which 4513 were $\geq 3\sigma(F^2)$. The structure was solved by the heavy-atom Patterson technique and refined in the usual way. The middle carbons of the hexamethylene bridge were found to be disordered and this was treated by refining the position and occupancy factors of carbon atoms at eleven possible sites. The final discrepancy indices for 6456 reflections were R = 0.101, R_w = 0.136 and GOF = 2.4.

(7) The possible implications of this in treating the hypothesis on the detoxification of CO by the distal imidazole of hemoglobin is a matter of on-going research. See J. P. Collman, J. I. Brauman, T. R. Halbert, and K. S. Suslick, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 3333 (1976).

(8) A. B. Orlandini, C. Calebresi, C. A. Ghilandi, P. L. Orioli, L. Sacconi, *J. Chem. Soc., Dalton Trans.*, 1383 (1973).

(9) S. Baggio and L. N. Becka, *Acta Crystallogr., Sect. B*, **25**, 946 (1969).

(10) B. W. Brown and E. C. Lingafelter, *Acta Chrystallogr.*, **16**, 753 (1963).

(11) P. Jain and E. Lingafelter, *J. Am. Chem. Soc.*, **89**, 6131 (1967).

(12) The support of the National Science Foundation is gratefully acknowledged.

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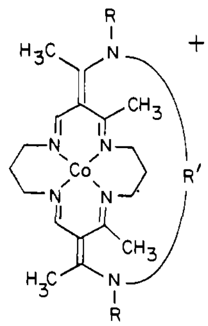
Totally Synthetic Coboglobin Models with Oxygen Binding Capabilities Equivalent to Those of Coboglobin

Sir:

The studies reported here are part of a general program which focuses on the design of greatly simplified chemical species capable of retaining certain essential functions of natural products and their derivatives. Immediate attention is directed toward a new series of cobalt(II) complexes (structure I and preceding communication) that display oxygen binding behaviors comparing favorably with those of the coboglobins.[1,2] Given that a particular set of ligands provides the metal with an appropriate ligand field, it is generally agreed that this kind of reversible O_2 binding is facilitated when two irreversible processes are impeded.[3-5] These are an oxidative dimerization reaction and proton-promoted, one-electron transfer between the metal ion and the O_2 group. In the natural iron-containing oxygen carriers, hemoglobin and myoglobin, and their cobalt derivatives, the protein forms a hydrophobic pocket in the vicinity of the binding site in order to accomplish both protective goals. Similarly, the ligands represented by structure I are designed to bind O_2 in a hydrophobic pocket, a "dry cave", created in this case by a simple bridging group. These ligands[6] are neutral (forming cationic complexes), nonplanar, and, while containing two unsaturated chelate rings, not aromatic. Thus the origins and natures of both the main ligand field and the hydrophobic pocket are distinctly different from those of the natural products. Highly successful model systems based on modified porphyrin structures are, of course, well known.[3,7,8]



	R	R'
I a	CH_3	$-(CH_2)_4-$
b	H	$-(CH_2)_5-$
c	CH_3	$-(CH_2)_5-$
d	H	$-(CH_2)_6-$
e	CH_3	$-(CH_2)_6-$

The new ligands were first synthesized by a template reaction using nickel(II), and an X-ray study on a nickel complex established their structures.[6] Subsequently, it has been shown that the intact ligand can be removed from the nickel(II) and used to prepare various cobalt complexes.[9] Most significantly, those studies have proven that small ligands can be accommodated in the dry cave binding site and that the steric constraints of the bridge group can exert striking effects on the mode of binding of the small ligands.[9]

Studies on the complex formation equilibrium between *N*-methylimidazole (*N*-mim) and the cobalt(II) complexes have shown that these equilibria can be saturated (>99% complexation) at ~1.5 M in acetonitrile solution and at ~2.5 M in aqueous solutions.[10] Saturation of these binding sites requires the O_2 molecule to bind at the dry cave site. Electrochemical studies on the Ni^{2+}, Fe^{2+}, and Co^{2+} complexes provided a preliminary indication that the cobalt derivatives might have O_2 affinities comparable with that of coboglobin.[11] These show redox processes at potentials similar to those of the metal porphyrins, suggesting comparable electron densities at the metal ion sites.

The following characteristics of O_2 binding systems are viewed as favorable for the purposes of this study: the 1:1 O_2 adducts should (a) exist at room temperature and above, (b) survive in aqueous solution, (c) approach coboglobin in stability (P_{50}), and (d) not react rapidly to form 2:1 μ-peroxo complexes. A variety of synthetic complexes satisfy most of these criteria;[4] however, no previously known synthetic species appears to satisfy all four. Particularly conspicuous is the absence of 1:1 O_2 adducts that are stable in aqueous solution. The complexes of general structure I are subject to broad structural variations. Examples in which R and R′ are chosen to maximize O_2 binding produce 1:1 O_2 adducts that are stable at and above room temperature, in aqueous solution, and with P_{50} values indicating affinities for O_2 as large as, and surpassing, those of coboglobins.

The identities of the species existing in solution were further defined by EPR studies. The EPR spectrum of the new complex Ie (Figure 1a) in frozen water or acetonitrile solutions, containing excess *N*-methylimidazole, at −196 °C is similar to those of other square pyramidal, low-spin cobalt(II) complexes,[12] showing very nearly axial symmetry with $g_\perp \approx 2.3$ and $g_\parallel \approx 2.00$. The eight bands of $g_\parallel$ are further split into equal intensity triplets by the interaction of the unpaired spin with only one axial *N*-methylimidazole. Closely similar EPR spectra were recorded for water, acetonitrile, and acetonitrile-methanol solutions, indicating that the same structures occur in all those media. Upon exposure of the solutions to oxygen, the

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