

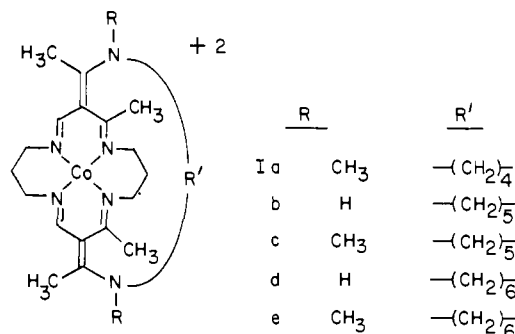
- (3) The nickel complex (structure II) (10.2 g, 12.9 mmol) was dissolved in acetonitrile (500 mL) and anhydrous HCl(g) was bubbled through the solution for 30 min during which time the color changed from orange to blue-green. A solution containing tetrachlorozincate anion is prepared by reaction of 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 $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.61 g, 2.5 mmol) and $\text{Na}(\text{OAc}) \cdot 3\text{H}_2\text{O}$ (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, $Z = 4$; $\lambda_{\text{Mo K}\alpha} = 0.71069$ Å; $\rho_{\text{obsd}} = 1.58$, $\rho_{\text{calcd}} = 1.56$; $\omega-2\theta$ scan technique for all reflections of positive hkl having $2\theta < 60^\circ$; 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 $R = 0.127$, $R_w = 0.155$, 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; $\beta = 65.98$ (4)°; $Z = 2$; $\lambda_{\text{Mo K}\alpha} = 0.71079$ Å; $\rho_{\text{obsd}} = 1.36$, $\rho_{\text{calcd}} = 1.36$; the $\omega-2\theta$ 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).
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- (12) The support of the National Science Foundation is gratefully acknowledged.

James C. Stevens, Patricia J. Jackson
Wayne P. Schammel, Gary G. Christoph,* Daryle H. Busch*¹²
Chemistry Department, The Ohio State University
Columbus, Ohio 43210
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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 ligands⁶ 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}

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 -peroxy 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_{\perp} 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

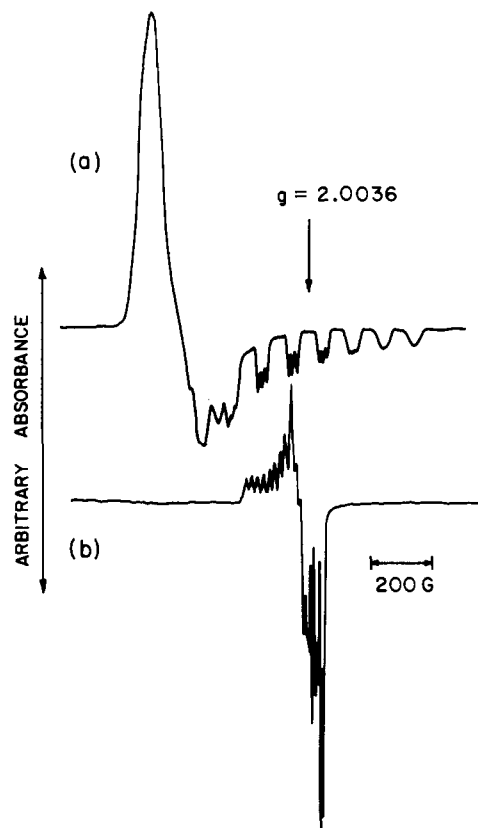


Figure 1. The EPR spectra of (a) the *N*-methyl (CH₂)₆-bridged cobalt(II) complex (structure Ie) and (b) the O₂ adduct of that complex, in frozen water containing excess *N*-methylimidazole (2.5 M) at -196 °C.

original signal is replaced by one characteristic of 1:1 cobalt-oxygen adducts (Figure 1b) with $g_1 \approx g_2 \approx 2.01$ and $g_3 \approx 2.08$.

Reversible UV-visible spectral changes were observed for aqueous solutions of Ie containing *N*-methylimidazole upon oxygenation (Figure 2). The presence of five isobestic points, coupled with the EPR data, clearly demonstrates a simple equilibrium between the five-coordinate cobalt(II) complex and the 1:1 oxygen adduct. A solution equilibrium apparatus similar to Collman's¹³ was used to obtain the equilibrium constants for reversible oxygen binding. P_{50} for Ie as an *N*-methylimidazole adduct in aqueous solution is 0.63 ± 0.04 Torr at 20 °C. To our knowledge this is the most thermodynamically stable 1:1 adduct reported for a cobalt(II) species. For comparison, at 20 °C, P_{50} for cobalt myoglobin (sperm whale) is 33 Torr, while P_{50} for iron myoglobin (sperm whale) is 0.5 Torr.

We have obtained extensive equilibrium data for the series of compounds Ia-e in acetonitrile solution containing 1.5 M *N*-methylimidazole (Table I). It can be seen that the nature of bridging group has a profound effect on the oxygen binding ability of the cobalt complexes. For example, Ia has a value of P_{50} at -40.1 °C more than five orders of magnitude larger than that for Ie (calculated from ΔH and ΔS). Since electrochemical data on three metal ions¹¹ (Co, Ni, Fe) indicate that the electron density at the metal ion does not change in the series Ia, Ic, Ie, this change is attributable to the alteration in the dimensions of the cavity.

The fact that the steric constraints of the dry cave greatly affect the magnitude of the O₂ binding constant provides a precedent for the role of steric effects in the cooperativity of O₂ binding in hemoglobin. According to Perutz,⁵ the two basic questions are "how does combination of ligands (i.e., O₂) with the heme irons change the quaternary structure of the globin from *T* to *R*?" and, conversely, "how does the change from *R*

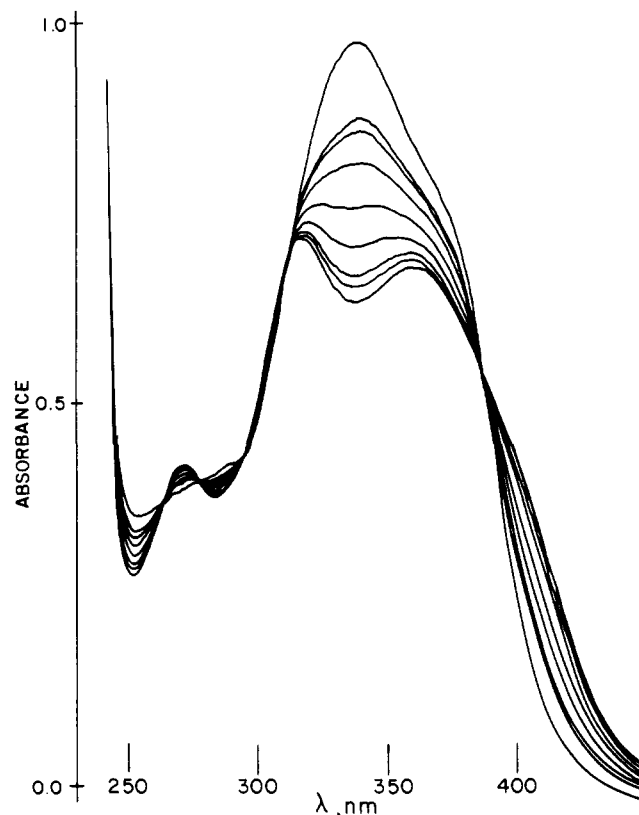


Figure 2. The electronic spectral changes accompanying formation of the O₂ adduct by the *N*-methyl (CH₂)₆-bridged cobalt(II) complex (structure Ie) in aqueous solution, containing excess *N*-methylimidazole (2.5 M) at 6 °C. Absorption maximum at 338 nm is due to O₂ adduct.

Table I. Equilibrium Constants for O₂ Adduct Formation by the Cobalt-Dry Cave Complexes in CH₃CN in the Presence of 2.5 M *N*-Methylimidazole

compd ^a	bridge	<i>T</i> , °C	<i>P</i> ₅₀ , Torr
Ia	$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ -\text{N}-(\text{CH}_2)_4-\text{N}- \\ \quad \end{array}$	-40.1	500 ± 50
Ib	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ -\text{N}-(\text{CH}_2)_5-\text{N}- \\ \quad \end{array}$	-10.1	52 ± 1
Ic	$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ -\text{N}-(\text{CH}_2)_7-\text{N}- \\ \quad \end{array}$	-10.1	3.98 ± 0.08
Id	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ -\text{N}-(\text{CH}_2)_8-\text{N}- \\ \quad \end{array}$	-10.1	2.03 ± 0.03
		2.1	8.2 ± 0.3
Ie	$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ -\text{N}-(\text{CH}_2)_6-\text{N}- \\ \quad \end{array}$	-40.1	0.003 ^b
		-10.1	0.22 ± 0.05
		1.0	0.75 ± 0.02
		20.0	6.5 ± 0.2
Co myoglobin (sperm whale)		2.1	9.1 ^c

^a (PF₆)₂ salts. ^b Calculated from Vant-Hoff plot, ln *K* vs. *T*⁻¹. ^c Calculated from $\Delta H = -11.9$ kcal/mol; $\Delta S = -47.6$ eu/mol.

to *T* lower the ligand (O₂) affinity of the heme iron?" The first change (first question) is assumed to be controlled by the displacement of the iron atoms and the proximal histidines from the plane of the porphyrins. However, in the case of the β -protein subunits, the change in O₂ affinity has been ascribed to a steric effect exerted by certain valine groups. We have clearly shown that steric effects can easily alter P_{50} by the amounts associated with the change between the *T* and *R* states of hemoglobin.

Substitution at the bridgehead nitrogen also influences the stability of the 1:1 adduct. The O_2 affinities of the *N*-methyl complexes **1c** and **1e** are some 9–13 times greater than those of the corresponding *N*-H complexes **1b** and **1d**. This is consistent with the observation that oxygen affinity is related to the electron density at the metal atom.^{4,12} The increased binding constants correlate with preliminary electrochemical results.¹¹ The NH compounds are 80–90 mV more difficult to oxidize than the *N*-methyl compounds. By careful selection of structural parameters it is possible to obtain P_{50} values strikingly similar to those of the cobalt-substituted natural system (cf. structure **1d** at 2.1 °C).

References and Notes

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James C. Stevens, Daryle H. Busch*

Chemistry Department, The Ohio State University
Columbus, Ohio 43210

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Synthesis and Absolute Configuration of Optically Active *trans*-1,2-Disubstituted Cycloalkenes

Sir:

In connection with a projected synthesis of configurationally defined betweenanenes^{1,2} (Scheme I) we had need of optically stable *trans*-cycloalkenes (**1**) of known configuration.³ Cope and co-workers^{4a} resolved *trans*-cyclooctene (**1**, R = H; *a* = 6) and found it to be optically stable ($t_{1/2} \sim 10^5$ years at room temperature). In contrast, *trans*-cyclononene (**1**, R = H; *a* = 7) rapidly racemizes ($t_{1/2} \sim 10$ s at room temperature).^{4b} Alkyl substituents on the double bond would expectedly increase the rotational (jump rope) energy barrier of the *trans*-cycloalkene [(*R*)-**1** \rightleftharpoons (*S*)-**1**] thereby retarding racemization, but little is known regarding the magnitude of this effect. To establish the range of ring sizes available to us in our quest for optically active betweenanenes via routes involving cyclization (Scheme I, **I** \rightarrow **II**),⁵ we undertook the studies described herewith (Chart I).

We have previously shown that the bicyclic diol **1a** (X = OH), available from 2-carbomethoxycyclooctanone via Mi-

Scheme I

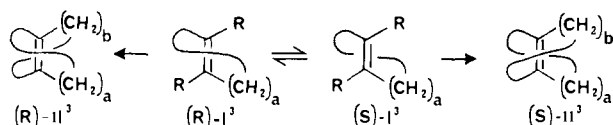
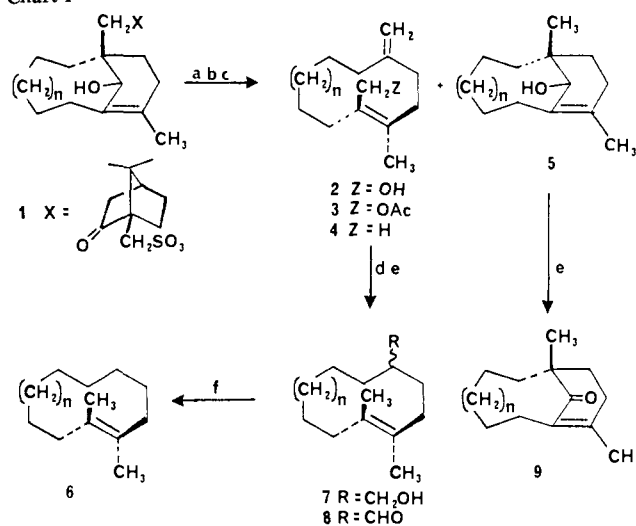


Chart I^a



(a series, *n* = 1; b series, *n* = 2; c series, *n* = 3)

^a (a) $LiAlH_4$, $MeOCH_2CH_2OMe$. (b) $(CH_3CO)_2O$, C_5H_5N . (c) Li , NH_3 , THF. (d) $(Siam)_2BH$, THF; H_2O_2 , $NaOH$. (e) $ClCrO_3H \cdot C_5H_5N$, CH_2Cl_2 . (f) $(Ph_3P)_3RhCl$, C_6H_6 .

chael addition of methyl vinyl ketone followed by aldol cyclization in concentrated sulfuric acid and subsequent reduction ($LiAlH_4$), undergoes both fragmentation to diene **2a** and reduction to alcohol **5a** upon treatment of its mono *p*-toluenesulfonate derivative **1** (X = *p*- $CH_3C_6H_4SO_3$) with lithium aluminum hydride.⁶ Attempts at the optical resolution of **2a** were totally unsuccessful. However, diol **1a** (X = OH) afforded the spectacularly crystalline camphorsulfonate **1a** [white needles from ethyl acetate, mp 155–157 °C, $[\alpha]_D^{22} + 18.5^\circ$ (*c* 3.23, $CHCl_3$)] in 23% yield (twice recrystallized but not optimized). Treatment of the (+)-sulfonate **1a** with lithium aluminum hydride in refluxing 1,2-dimethoxyethane for 20 h gave diene **2a** [33% yield, bp 100 °C at 0.1 Torr, $[\alpha]_D^{22} - 35^\circ$ (*c* 5.79, CH_2Cl_2)] and alcohol **5a** [60% yield, mp 69–70 °C, $[\alpha]_D^{22} - 75^\circ$ (*c* 3.61, EtOH)] with the expected spectral properties.⁶

Acetylation of alcohol **2a** and Li/NH_3 reduction of the resulting allylic acetate **3a** afforded the diene **4a** [95% yield, mp 39–40 °C, $[\alpha]_D^{22} - 135^\circ$ (*c* 4.71, CH_2Cl_2)]. Hydroboration–oxidation yielded alcohol **7a** (mixture of diastereoisomers) which was oxidized to aldehyde **8a** (diastereoisomers) with pyridinium chlorochromate (PCC).⁷ Prolonged treatment of aldehyde **8a** with tris(triphenylphosphine)rhodium(I) chloride⁸ in refluxing benzene yielded the cyclodecene **6a** [60% yield, bp 50 °C at 0.03 Torr, $[\alpha]_D^{22} - 118^\circ$ (*c* 2.18, CH_2Cl_2)]. The spectral properties of this material matched those of racemic *trans*-1,2-dimethylcyclodecene.⁹

The absolute configuration of olefin **6a** and its congeners was assigned through correlation with enone **9a** [bp 70 °C at 0.1 Torr, $[\alpha]_D^{22} + 128^\circ$ (*c* 0.72, MeOH)] secured in 94% yield via oxidation of alcohol **5a** with PCC.⁷ The ORD curve of enone **9a** showed a strong positive Cotton effect at 303 nm thus establishing the *R* configuration for the quaternary center in bicyclic alkenes **9a**, **5a**, and **1a**.¹⁰ Accordingly, the world's first optically stable *trans*-cyclodecenes¹¹ **2a–4a** and **6a–8a** have the *S* configuration.³

The bicyclic alcohol (–)-**5a** showed a sharp methyl singlet in its NMR spectrum. This signal shifted to higher field but remained intact upon addition of $Pr(facam)_3$ shift reagent.¹² Racemic **5a**, on the other hand, gave rise to two clearly distinct methyl singlets in the presence of the shift reagent. Likewise, the distinctive AB pattern of the $-CH_2OH$ grouping in alcohol (–)-**2a**⁶ was shifted downfield by $Eu(facam)_3$,¹² but no new signals were produced. These experiments indicate that the