This scheme is essentially that elaborated by Abeles and Dolphin[2] but differs by terminating the role of cobalamin–substrate complexes (step v) prior to the dehydration of the geminal diol. Both enzyme[22] and model[23] studies have provided convincing evidence that a β-formyl complex, Co–CH_2CHO, cannot be a productive intermediate. In this modified scheme, formation of the geminal diol (step iv) results in a change in the substrate derivative–protein binding that promotes homolysis of the Co–$CH_2CH(OH)_2$ bond (step v) in a manner that parallels the generally accepted role of substrate binding in triggering the Co–CH_2R bond homolysis (step i).[1,2] Deconvolution of the overall process into this set of individual steps is rather artificial in that several steps could occur simultaneously in concerted transformations. As an example, formation of the substrate radical and subsequent binding with cob(II)alamin (steps ii and iii) could occur in a concerted process. The term cobalamin–substrate complex is also an exaggeration and probably should be replaced with the term cobalamin–substrate interaction, because restrictions of the protein binding sites for cobalamin and the substrate would undoubtedly produce highly strained Co–C bonds.[24,25]

The first two steps, which produce the substrate radical ($^{\bullet}CH(OH)CH_2(OH)$), and steps vi–viii, which convert the geminal diol radical ($^{\bullet}CH_2CH(OH)_2$) into acetaldehyde with regeneration of coenzyme B_{12} (Co-CH_2R), are widely accepted aspects of the enzyme mechanism.[1,2,13] The pathway that the enzyme uses in directing the isomerization of 1,2-diols to 1,1-diols has not yet been convincingly elucidated, even though the enzymatic reactions have been elegantly and exhaustively studied by isotopic labeling.[26-28] The mechanisms operative in the 1,2-rearrangements in other coenzyme B_{12} dependent enzymatic reactions also remain unresolved.[29] The primary issue is whether or not cob(II)alamin formed in the initiation step interacts with the substrate radical (step iii) and directs the isomerization (step iv). An alternate pathway is for the enzyme-bound substrate radical to rearrange through a series of intermediates to products without the influence of cob(II)alamin.[13,30] EPR studies of functioning enzymes,[31,32] radical rearrangement reactions,[33-35] and model studies[6,23] have been used to illustrate the plausibility for aspects of the radical rearrangement mechanism. The mechanistic issues and relevant enzyme and models studies have been brought into focus in a recent review.[13] In our opinion, all of the results of the enzyme studies can be accommodated by a substrate rearrangement reaction that is promoted and guided by relatively weak cobalamin–substrate organometallic interactions. The principal arguments used against invoking organometallic cobalamin–substrate derivative intermediates are the lack of direct observation of these intermediates in the enzymatic reaction and absence of a model system that illustrates the proposed reactivity for the cobalamin–substrate complex, Co–$CH(OH)CH_2(OH)$.[13] Direct observation of productive intermediates is often precluded by their efficiency in producing the desired result, and when detailed kinetic mechanistic studies are made, the observed "intermediates" often prove to be involved in only nonproductive pathways.[36] Formation of (OEP)Rh–$CH(OH)CH_2(OH)$ at equilibrium has provided the first opportunity to observe the reactivity of an α,β-dihydroxyethyl complex under controlled conditions, and this model complex does manifest the type of reactivity proposed[2] for Co–$CH(OH)CH_2(OH)$. Acid-catalyzed dehydration of **1** to produce (OEP)Rh–CH_2CHO (**2**) selectively and the dehydroxylation of (OEP)Rh–$CH_2CH_2(OH)$ to form a π-ethene complex (**5**) illustrate the potential utility of cobalamin–substrate derivative interactions in promoting and directing an enzyme-catalyzed dehydration of 1,2-diols. We presently prefer the organometallic intermediate mechanism because selective β-OH dehydroxylation of Co–$CH(OH)CH_2(OH)$ and subsequent 1,2-rearrangement that converts 1,2-diols into 1,1-diols would be a natural consequence of a vinyl alcohol π-complex intermediate, $Co(CH_2{=}CH(OH))^+$. The intermediacy of cobalamin–substrate derivative complexes in diol dehydratase catalyzed reactions remains an open question, and we hope that model studies will stimulate and focus the requisite enzyme investigations.

Acknowledgment. We acknowledge the National Science Foundation for support of this research.

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Novel Organocobalt(III) Porphyrins with an Etheno Bridge between the Cobalt and a Pyrrolic Nitrogen or a Meso Carbon

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Metalloporphyrins with a bridged structure between the central metal and one of the four pyrrole nitrogens have drawn much attention as it was proposed that the highly oxidized form of some hemoproteins may contain a ferric porphyrin with an oxygen atom inserted into an N–Fe bond.[1] Bridged metalloporphyrins with an M–O–N linkage (M = Cu,[2] Ni,[3] Fe[4]), an M–N–N linkage (M = Zn,[5] Fe[6]), an M–C–N linkage (M = Ni,[7] Fe,[1] Co[8]), and

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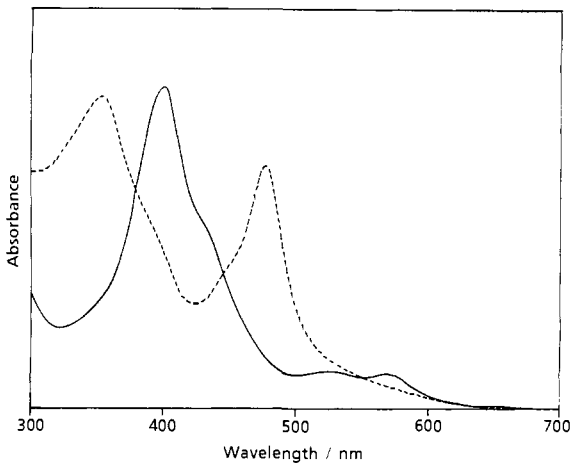
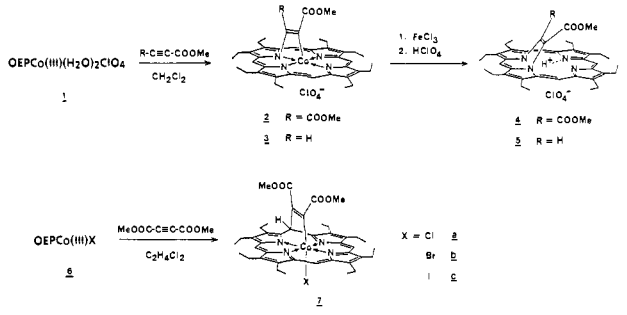


Figure 1. Visible absorption spectra of *N,Co*-bridged complex **2** (—) and C^5,*Co*-bridged complex **7b** (---) in CH_2Cl_2.

Scheme I



an Fe–O–C–C–N linkage[9] have so far been prepared. Here, we report on the first isolation of bridged metalloporphyrins with a Co–C–C–N linkage and bridged metallo-5*H*,21*H*-porphyrins[10] with a Co–C–C–C_{meso} linkage through the reaction of dimethyl acetylenedicarboxylate (DMADC) and cobalt(III) porphyrins with a variety of axial ligands in CH_2Cl_2.

When (OEP)$Co^{III}(H_2O)_2ClO_4$ (**1**) was allowed to react with DMADC (5 equiv) in CH_2Cl_2 for 2 h, [(1,2-bis(carbomethoxy)etheno)-*N,Co*](octaethylporphyrinato)cobalt(III) perchlorate (**2**)[11] was obtained in 83% yield after chromatographic purification on silica gel (CH_2Cl_2–acetone (10:1)) and recrystallization from CH_2Cl_2–*n*-hexane. The reaction of **1** with methyl acetylenecarboxylate was completed within 1 min to give *N,Co*-etheno-bridged (OEP)Co^{III} complex **3**;[12] however, an analytically very pure sample of **3** could not be obtained due to decomposition during chromatography. The visible spectra of **2** and **3** are similar to those of *N,Co*-methano-bridged (OEP)Co^{III} complexes[8] (Figure 1). Their ^1H and ^{13}C NMR spectra show C_s symmetry with an *N,Co*-etheno-bridged structure which carries the carbomethoxy group on the cobalt side, especially in the case of **3**. That is, the carbomethoxy absorption of **3** (δ 1.72) appears at the same magnetic field as the upper field carbomethoxy signal of **2** that is associated with the one on the cobalt side because of the greater ring current effect of porphyrin. Furthermore, the ^1H–^{13}C correlation NMR experiment shows that the bridge vinyl proton (δ −0.81) is connected to the bridge carbon on the N side (122.5 ppm), the assignment of which was made on the basis of the fact that signals of Co-bound carbons are broadened and frequently unobservable due to spin–spin coupling with the ^{59}Co nucleus ($I = {}^7/_2$), which undergoes moderately rapid quadrupole-induced relaxation.[13]

It has been reported that *N,Fe*- and *N,Co*-methano-bridged porphyrins are oxidatively transformed into the corresponding N^{21},N^{22}-methano-bridged porphyrins.[1c,8a] **2** and **3** were similarly converted into N^{21},N^{22}-etheno-bridged OEP·$HClO_4$, **4** and **5**,[14] in 82% (based on **2**) and 45% (based on **1** without isolation of **3**) yield, respectively, by treatment with $FeCl_3$ (ca. 20 equiv suspended in CH_2Cl_2) and then 10% $HClO_4$ aqueous solution.[15]

In contrast, treatment of (OEP)Co^{III}Br (**6b**) with DMADC (5 equiv) at reflux in 1,2-dichloroethane for 5 h gave [(1,2-bis(carbomethoxy)etheno)-C^5,*Co*](octaethyl-5*H*,21*H*-porphyrinato)cobalt(III) bromide (**7b**)[16] in 69% yield after purification according to the procedure for **2**. The UV–vis spectrum of **7b** is quite different from those of normal porphyrins (Figure 1). The 5*H*,21*H*-porphyrinato[17] structure of **7b** is best proved by the ^1H and ^{13}C NMR spectra, which show C_s symmetry with a mirror plane containing a C^5–Co–C^{15} axis and are indicative of the interruption of the π-conjugation of porphyrin. The ^{13}C signal at 141.1 ppm is solely assignable to the carbon derived from the acetylenic carbons of DMADC since the other carbon is σ-bonded to the Co(III) and thus difficult to observe just like the Co-bound carbons of **2** and **3**.[13] Whereas (OEP)Co^{III}Cl (**6a**) and (OEP)Co^{III}I (**6c**) gave similar chloro (**7a**) and iodo (**7c**) complexes in 49% (80 °C, 1 h) and 51% (80 °C, 48 h) yield, respectively, both (OEP)$Co^{III}CH_3$ and (TPP)Co^{III}Cl failed to react with DMADC.

The electronic structure of cobalt(III) porphyrins is strongly dependent on the nature of their axial ligation. It has been shown that **1** loses axial ligands and takes a form of d^7 Co(II) porphyrin π-cation radical in CH_2Cl_2 while it is a diamagnetic d^6 Co(III)

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(10) 5*H*,21*H*-porphyrin is also referred to as isoporphyrin. Hereafter, OEP denotes the dianion of octaethylporphyrin.

(11) **2**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 10.53 (s), 10.18 (s); CH_2 4.2–3.9 (m); OCH_3 2.39 (s), 1.72 (s); CH_3 1.83 (t), 1.90 (t), 1.94 (t), 1.99 (t) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) CO 163.0, 148.5; py-$C_{\alpha,\beta}$ 147.9, 146.8, 146.7, 146.5, 146.2, 146.1, 146.1, 142.7; N-C_{bridge} 114.6; C_{meso} 101.7, 101.2; OCH_3 50.3, 49.8; CH_2 20.9, 20.2, 19.9, 19.8; CH_3 18.3, 18.2, 17.9, 15.9 ppm. Anal. Satisfactory C, H, N for $C_{42}H_{50}N_4O_8ClCo$. UV–vis (CH_2Cl_2) λ_{max} (log ϵ) 394 (4.72), 431 (sh) (4.52), 515 (3.50) 565 (3.40) nm. IR (KBr) ClO_4^- 1100, 621 cm^{-1}.

(12) **3**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 10.54 (s), 10.21 (s); CH_2 4.4–4.1 (m); CH_3 1.98 (t), 1.94 (t) (×2), 1.85 (t); OCH_3 1.72 (s); H_{vinyl} −0.81 (s) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) CO 160.4; py-$C_{\alpha,\beta}$ 147.8, 146.9, 146.7, 146.4, 145.9 (×2), 144.4, 144.0; N-C_{bridge} 122.5; C_{meso} 102.2, 101.1; OCH_3 49.5; CH_2 20.9, 20.2, 20.0, 19.9; CH_3 18.6, 18.2, 18.1, 16.5 ppm. UV–vis (CH_2Cl_2) λ_{max} 394, 431, 523, 565 nm.

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(14) **4**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 10.96 (s), 10.73 (s) (×2), 10.38 (s); CH_2 4.4–4.1 (m); CH_3 1.97 (t), 1.92 (t), 1.84 (t), 1.73 (t); OCH_3 1.92 (s); NH −3.95 (br) ppm. Anal. Satisfactory C, H, N for $C_{42}H_{51}N_4O_8Cl$. UV–vis (CH_2Cl_2) λ_{max} (log ϵ) 401 (5.13), 535 (3.94), 569 (4.06), 614 (3.63) nm. **5**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 10.95 (s), 10.74 (s), 10.71 (s), 10.29 (s); CH_2 4.4–4.0 (m); CH_3 2.03 (t), 1.97 (t), 1.93 (t), 1.92 (t), 1.88 (t), 1.85 (t), 1.76 (t) (×2); OCH_3 1.48 (s); H_{vinyl} −1.67 (s); NH −4.02 (br) ppm. Anal. Satisfactory C, H, N for $C_{40}H_{49}N_4O_6Cl$. UV–vis (CH_2Cl_2) λ_{max} (log ϵ) 402 (5.05), 537 (3.92), 573 (4.03), 620 (3.21) nm.

(15) Although the reaction of **1** with alkynes in the presence of $FeCl_3$ affords various N^{21},N^{22}-etheno-OEPs (Setsune, J.-i.; Ikeda, M.; Kishimoto, Y.; Kitao, T. *J. Am. Chem. Soc.* **1986**, *108*, 1309), *N,Co*-etheno-(OEP)Co^{III} complexes could not be obtained unless alkynes were substituted with electron-withdrawing groups.

(16) **7b**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 6.44 (s), 6.16 (s) (×2), 6.14 (s); OCH_3 3.79 (s), 3.76 (s); CH_2 2.5–2.2 (m); CH_3 1.13 (t), 1.10 (t), 1.06 (t), 0.99 (t) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) CO 174.6, 159.9; py-$C_{\alpha,\beta}$ 152.5, 151.5, 149.7, 146.1, 145.1, 144.7, 144.2, 140.5; C_{bridge} 141.1; C_{meso} 121.9, 118.3 (×2), 45.8; OCH_3 52.4, 51.4; CH_2 18.4, 17.7, 17.6, 17.5; CH_3 16.7, 16.0, 15.8, 14.4 ppm. Anal. Satisfactory C, H, N for $C_{42}H_{50}N_4O_4CoBr$. UV–vis (CH_2Cl_2) λ_{max} (log ϵ) 355 (4.37), 477 (4.25) nm.

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species in methanol.[18] On the other hand, **6a-c** are diamagnetic d^6 Co(III) complexes both in methanol and in CH_2Cl_2. The reactivity of (OEP)Co^{III} toward DMADC increases with decreasing electron donation from the axial ligand (Me > I > Br > Cl > H_2O), and consequently with increasing charge transfer interaction of the porphyrin ligand with Co(III). However, **1** is no longer a d^6 Co(III) complex in noncoordinating solvents, and thus the direction of attack of DMADC is changed. As a Co(III) complex of dibenzo[*b*,*i*]-5,7,12,14-tetramethyl-1,4,8,11-tetraaza[14]annulene reportedly[19] reacts analogously to **6**, the present reaction is remarkable since the metalloporphyrin is completely planar and rigid and biologically significant in relation to heme catabolism.[20] That is, a *C*^{5},*Fe*-peroxo-bridged iron 5*H*,21*H*-porphyrin structurally similar to **7** may be formed from Fe(II) porphyrin with dioxygen and converted into oxophlorins and eventually into biliverdins in vivo.

In summary, the reaction behaviors of Co(III) porphyrins are strongly dependent on the nature of their axial ligands to give novel organocobalt(III) porphyrins of biological interest.

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Biomimetic Ferric Ion Carriers. A Chiral Analogue of Enterobactin

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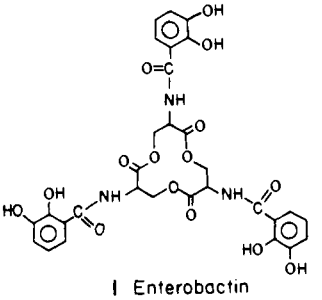
The potency of enterobactin **1**, the most powerful natural siderophore (ferric ion carrier),[1-3] has stimulated the synthesis of a large number of analogues,[2] with the triscatecholate **2** (MECAM) prepared and analyzed by Harris and Raymond[4] being the most efficient one. It has recently been shown that only the native enterobactin, but not its enantiomer, is taken up by *Escherichia coli*[5] and that the native molecule assumes a right-handed propellerlike conformation which is governed by its chirality and intramolecular hydrogen bonds (H bonds).[6] Similar arrangements stabilized by interchain H bonds have recently been obtained in C_3 symmetric molecules where three L-amino acids are attached to a mesitylene as common anchor.[7] Here we demonstrate that an extension of such amino acid derivatives by catecholates provides a binder **3b** and its protected precursor **3a** that mimic enterobactin: **3a** adopts a chiral structure circularly organized by interchain H bonds, and **3b** forms metal complexes of similar geometry and identical configuration, Δ-cis. Although still below enterobactin, the binding efficiency of **3b** is comparable and perhaps even better than that of Raymond's artificial binder **2**, the best so far prepared.[4]

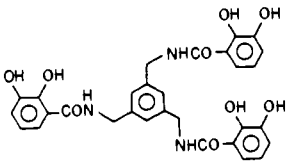
Table I. ^{1}H NMR Chemical Shift (δ) Values[a] of Ligands **1**, **3b**, and **2**[e]

proton	**1**[b]	**3b**	**2**
N*H*	9.06 (+2.66)	8.79 (+1.16)[c] 8.57 (+0.13)[d]	9.39 (+0.76)
o-catechol	7.34 (-0.50)	7.42 (-0.42)	7.29 (-0.28)
m-catechol	6.73 (-0.60)	6.67 (-0.33)	6.65 (-0.27)
p-catechol	6.98 (-0.54)	6.91 (-0.34)	6.91 (-0.32)

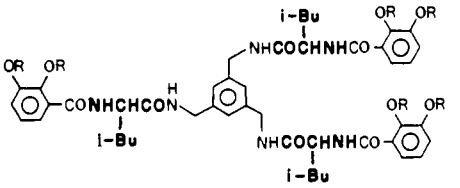
[a] In DMSO-d_6. Concentrations: **1**, ca. 0.045 M; **3b** and **2**, 0.033 M. Temperature: **1**, ca. 318 K; **3b** and **2** 298-300 K. δ values are expressed as ppm downfield from internal TMS. [b] Data taken from ref 12. [c] C*α*-N*H*. [d] CH_2NH. [e] Their induced changes (Δδ) upon Ga^{3+} binding are in parentheses.



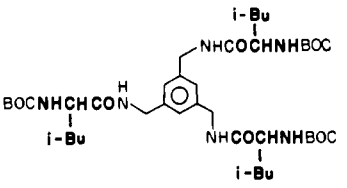
1 Enterobactin



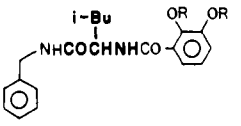
2



3a R = CH_2Ph
3b R = H



4



5 R = CH_2Ph

To prepare the catecholate ligand **3b**, 1,3,5-tris(*N*-Boc-leucylamido)benzene (**4**)[7] was deprotected, condensed with 2,3-bis(benzyloxy)benzoyl chloride,[8] and subsequently hydrogenolytically removed of the protecting groups. The IR spectrum of **3a** in dilute $CHCl_3$ (0.5 mM) showed only low-frequency NH absorptions at 3354 cm^{-1}. The NMR spectrum ($CDCl_3$, 5 mM) revealed nonequivalence of the diastereotopic $C_6H_3(CH_2NH\text{-})_3$ protons (Δδ = 0.56 ppm). The single chain reference molecule **5** shows higher NH frequencies (3437, 3361 cm^{-1}) and magnetic equivalence for the diastereotopic PhCH_2NH protons. In DMSO-d_6 the NMR pattern of **3a** becomes similar to that of **5**.

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