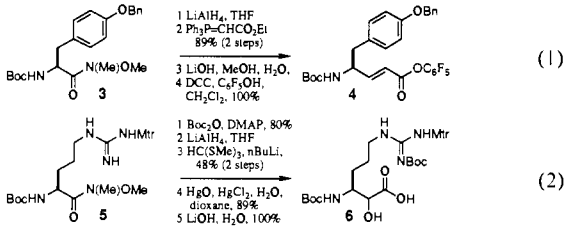
first of these involved homologation with the vinylogous tyrosine derivative **4**, which was prepared from the protected tyrosine derivative **3** by application of our standard V-amino acid synthesis[11] followed by a pentafluorophenyl ester activation protocol[15] (eq 1). Following a second homologation with D-*N*-Boc-phenylalanine,, the third coupling was achieved with the α-hydroxy acid **6**, which was prepared from the Weinreb amide[16] of a protected arginine **5** (eq 2). The guanidinium of **6** was doubly protected with Boc and 2,5,6-trimethyl-4-methoxybenzenesulfonyl (Mtr) groups to prevent nucleophilic addition to an intermediate arginine aldehyde, which was homologated to the α-hydroxy acid **6** by Seebach's procedure.[17]



Macrolactamization was achieved by a four-step process. Removal of the phenacyl group (Zn, AcOH) was followed by pentafluorophenyl ester formation at the C-terminus. Selective removal of the N-terminal Boc group with *p*-TsOH[18] illustrates the utility of the novel guanidinium protecting group strategy used in this study. After neutralization of the ammonium tosylate with Hünig's base, treatment with DMAP resulted in smooth conversion to the cyclic peptide **10**. After oxidation of the hydroxyl, which is left unprotected during the synthesis, the entire regiment of protecting groups could be removed in a single step with TFA and thioanisole. The ^{1}H NMR spectrum of the product, synthetic CyB **2** ($[\alpha]^{23}_D = -13.5°$, $c = 0.2$, MeOH),[19,20] was the same as that obtained from the natural sample. The identity of synthetic CyB, prepared in this manner, to natural CyB is in stark contrast to the products obtained by analogous procedures using the enantiomer of **3**, which results in the originally proposed structure, and the enantiomer of **5** (the stereochemistry at the arginine-like residue was not previously defined).[21] Thus, the cyclotheonamides are represented by structures **1** and **2**. With the full stereostructue and an efficient total synthesis in hand, we are presently investigating the structural features of thrombin–CyB interactions and the potential role of a vinylogous amino acid in this context.

Acknowledgment. Support of this research by the AIDS Initiative of the National Institute of General Medical Sciences (GM-44993) is gratefully acknowledged. M.H. thanks Ube Industries, Ltd., for support as a visiting scientist. We thank Michael K. Rosen and Soroosh Shambayati for their assistance with the CyB structural analysis and their suggestions for several synthetic transformations.

Supplementary Material Available: Spectral data, ^{1}H NMR spectra, and TOCSY spectra for the compounds mentioned in the text (14 pages). Ordering information is given on any current masthead page.

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(18) This reaction required careful monitoring; attempts to achieve this transformation with TFA failed to bring about the selective unmasking of the N-terminal Boc group.

(19) Synthetic CyB was purified by HPLC (column: TOSO ODS80TM 12.5 cm; mobile phase: MeCN:H_2O = 75:25, 0.1% TFA; flow rate: 1 mL/min; detection: UV 254 nm).

(20) Natural CyA: $[\alpha]^{23}_D = -13°$, $c = 0.2$, MeOH.[10]

(21) The potent inhibition of thrombin by synthetic CyB and investigations of the influence of stereochemistry on thrombin inhibition will be reported separately.

Redox Chemistry of *meso*-Octaethylporphyrinogen: Formation and Opening of a Cyclopropane Ring[§]

Jayne Jubb,[†] Carlo Floriani,*[,†] Angiola Chiesi-Villa,[‡] and Corrado Rizzoli[‡]

Section de Chimie, Université de Lausanne Place du Château 3, CH-1005 Lausanne, Switzerland Istituto di Strutturistica Chimica, Centro di Studio per la Strutturistica Diffrattometrica del CNR, Università di Parma, I-43100 Parma, Italy

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The oxidative aromatization of the *meso*-tetraalkylhexahydroporphyrinogen to porphyrin is one of the most interesting chemical and biochemical pathways.[1-3] *meso*-Octaalkylporphyrinogen,[4] for which the oxidative aromatization is prevented by the presence of two alkyl substituents at each meso carbon, shows an unexpected redox chemistry.

During our studies on the interaction of the *meso*-octaethylporphyrinogen tetraanion **2** with transition metals,[5-7] we discovered its transformation into an oxidized dianionic form **4**, which can be reduced back to the original tetraanion, as shown in Scheme I.

The attempt to complex Pd(II) with **2** led to the reduction of Pd(II) to Pd metal and the isolation of **4**,[8] whose hydrolysis led to the diprotic ligand **6**.[9] The cyclopropane form **4** can be reduced back to the tetraanion **2** by the use of lithium metal.[10] The C–C

* To whom correspondence and reprint requests should be addressed.
† University of Lausanne.
‡ University of Parma.

§ Dedicated to Professor Lamberto Malatesta on the occasion of his 80th birthday.

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(8) Preparation of 4: Palladium dichloride (1.17 g, 6.71 mmol) was added to a solution of **2** (4.66 g, 5.47 mmol) in toluene (200 mL), and the mixture was allowed to stir overnight. The filtrate, kept at −15 °C for 2 weeks, gave orange-red crystals of 4 (25%). Anal. Calcd for $C_{44}H_{64}Li_2N_4O_2$: C, 75.98; H, 9.21; N, 8.06. Found: C, 75.58; H, 9.12; N, 7.88.

(9) Preparation of 6: 4 (0.25 g, 0.42 mmol) was hydrolyzed with a few drops of aqueous HCl, followed by the addition of Et_2O. The yellow etheric phase gave, after evaporation to dryness, a pale yellow powder (88%): ^{1}H NMR (CD_2Cl_2) δ 11.6 (bs, 2 H, NH), 7.52 (d, 2 H, C_4H_2N), 6.71 (d, 2 H, C_4H_2N), 5.88 (m, 2 H, C_4H_2N), 5.78 (m, 2 H, C_4H_2N), 2.79 (q, 2 H, Et), 2.14 (m, 6 H, Et), 1.94 (m, 8 H, Et), 1.03 (m, 6 H, Et), 0.75 (m, 12 H, Et), 0.39 (t, 6 H, Et).

(10) 4 (0.50 g, 0.72 mmol) was added to THF (200 mL) under argon followed by metallic lithium sand (0.01 g, 1.44 mmol). The mixture was refluxed overnight. After concentration to dryness, **2** was isolated (89%).

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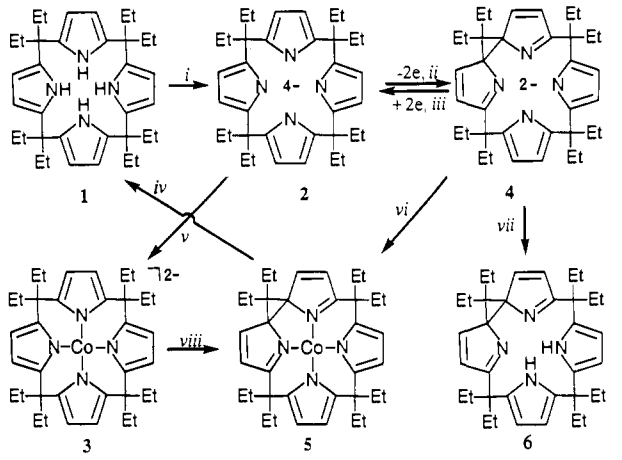
Scheme I[a]



[a] (i) LiBu; (ii) Pd(II); (iii) Li; (iv) H_2S; (v) Co(II); (vi) Co(II); (vii) hydrolysis; (viii) O_2. For **2–4**, countercations are $Li(THF)^+$ bonded to pyrroles.

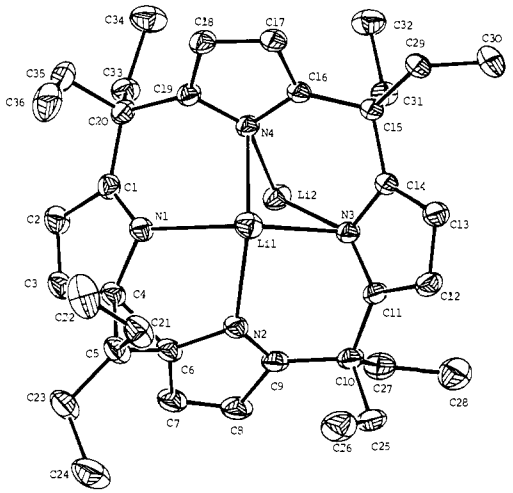


Figure 1. ORTEP view of **4**. Ethyls at C5, C10, C15, and C20 and one THF per lithium are omitted for clarity. Selected bond distances (Å): Li1–N1, 2.221 (4); Li1–N2, 2.164 (4); Li1–N3, 2.327 (4); Li1–N4, 2.274 (4); Li2–N3, 1.967 (4); Li2–N4, 1.981 (4); N1–C1, 1.303 (3); N1–C4, 1.442 (3); N2–C6, 1.433 (3); N2–C9, 1.304 (3); C4–C5, 1.522 (3); C4–C6, 1.577 (3); C5–C6, 1.529 (3); C14···C16, 2.533 (3); C14–C15, 1.530 (3); C15–C16, 1.529 (3).

bond across the two pyrroles functions as a two-electron reservoir. The oxidation of **2** can be achieved by dioxygen when it is bonded to cobalt(II), complex **3**.[7] Such a reaction led to a high yield of **5**.[11] The same complex is obtained by reacting cobalt(II) chloride with **4**.[12] The demetalation of **5** was achieved, along with the two-electron reduction of the cyclopropane, by the use of S^{2-} leading to the formation of the free porphyrinogen **1**, which was isolated almost quantitatively, and CoS_n.[13] The proposals in Scheme I are supported by the isolation and structural identification of all compounds.[6,7] The X-ray structures of **4**[14] and **5**[15]

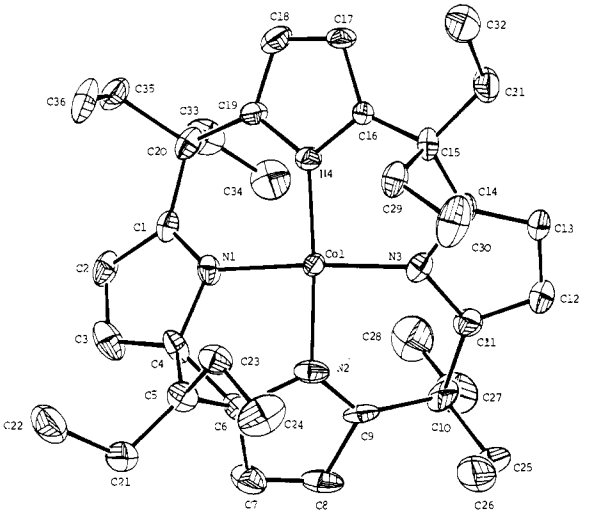


Figure 2. ORTEP view of **5**. Ethyls at C5, C10, C15, and C20 are omitted for clarity. Selected bond distances (Å): Co1–N1, 1.885 (8); Co1–N2, 1.893 (7); Co1–N3, 1.864 (8); Co1–N4, 1.871 (7); N1–C1, 1.269 (12); N1–C4, 1.460 (12); N2–C6, 1.450 (12); N2–C9, 1.278 (13); C4–C5, 1.537 (14); C4–C6, 1.517 (14); C5–C6, 1.516 (14); C14···C16, 2.465 (11); C14–C15, 1.538 (13); C15–C16, 1.503 (13).

reported in this paper serve to support the presence of a cyclopropane unit (Figures 1 and 2) in the free ligand and in the cobalt complex. The X-ray analysis of **4** supports the bonding sequence shown in Scheme I. Li1 is five-coordinated, while Li2 is in a trigonal planar coordination. The N_4 unit is planar with Li1 and Li2 displaced by 0.920 (4) and 1.279 (1) Å, respectively, from it. The pairs of pyrrole rings bridged by a cyclopropane unit are tilted down and the other two are up, referenced to the N_4 plane. The dihedral angle between the cyclopropane ring and the N_4 plane is 102.3 (2)°. When the dianionic ligand is bonded to cobalt rather than two lithium cations, **5** has a saddle-shaped conformation with the four pyrrole rings tilted on the same side with respect to the N_4 plane, as shown in Figure 2.

The cobalt(II) low spin (2.83 μ_B at 298 K) has a nearly planar coordination assured by the nitrogen donor atoms, the metal being only 0.109 (1) Å out of the coordination plane. The most exposed axial position of cobalt(II) is somehow filled by the hydrogen atoms of two ethyl groups [Co···H232 2.34, Co···H291 2.69 Å]. In both compounds **4** and **5**, the C_3 plane of cyclopropane is almost perpendicular to the N_4 coordination plane. Under the conditions mentioned above, a two-electron exchange process leads to the formation and cleavage of a cyclopropane ring and the consequent

(11) Preparation of **5** (Method A): **3**[7] (1.50 g, 1.68 mmol) was dissolved in toluene (75 mL) and then reacted for 30 min with dry O_2 at room temperature. The mother toluene solution, after removal of amorphous material, gave **5** as crystals suitable for X-ray analysis. Anal. Calcd for $C_{36}H_{48}CoN_4$: C, 72.58; H, 8.12; N, 9.40. Found: C, 72.60; H, 8.30; N, 9.50. μ_{eff} = 2.83 μ_B at 298 K.

(12) Preparation of **5** (Method B): 4 (0.43 g, 0.62 mmol) was suspended in toluene (50 mL). $CoCl_2 \cdot (THF)_{1.5}$ (0.17 g, 0.72 mmol) was added, and the dark mixture was then heated at 60 °C for 2 h. After filtration, the filtrate was set aside for 2 days, yielding **5** as a microcrystalline product (81%).

(13) Demetalation of **5**: H_2S was bubbled through a THF solution of **5** (0.51 g, 0.84 mmol), and after 30 min the $CoS_{1.7}$ precipitated out as a black amorphous solid. The mixture was filtered over Celite, and the pale yellow filtrate was concentrated to dryness to yield **1** as a white solid (93%).[6]

(14) Crystal data for **4**: $C_{44}H_{64}Li_2N_4O_2$, M = 694.9, monoclinic, space group $P2_1/c$; a = 11.250 (1) Å, b = 19.317 (2) Å, c = 19.080 (2) Å, β = 100.80 (1)°, V = 4073.0 (7) Å^3, Z = 4, ρ_{calcd} = 1.133 g cm^{-3}; Cu Kα radiation (λ = 1.541 78 Å), μ(Cu Kα) = 4.92 cm^{-1}; crystal dimensions 0.24 × 0.32 × 0.64 mm. The structure was solved by direct methods (SHELX 86) and anisotropically refined for all non-hydrogen atoms by full-matrix least-squares. For 5124 unique observed structure amplitudes [$I > 2\sigma(I)$, no correction for absorption] collected at room temperature on a Siemens AED diffractometer in the range $6 < 2\theta < 140°$, the R value is 0.047. All of the hydrogen atoms but those associated with the THF molecules, which were put in calculated positions, were located from a difference map and introduced as fixed contributors prior to the last stage of refinement (U_{iso} = 0.08 Å^2).

(15) Crystal data for **5**: $C_{72}H_{96}Co_2N_8$, M = 1191.5, monoclinic, space group $P2_1$; a = 15.804 (2) Å, b = 12.237 (1) Å, c = 17.026 (3) Å, β = 91.15 (2)°, V = 3292.1 (8) Å^3, Z = 2, ρ_{calcd} = 1.202 g cm^{-3}; Mo Kα radiation (λ = 0.710 69 Å), μ(Cu Kα) = 5.47 cm^{-1}; crystal dimensions 0.34 × 0.45 × 0.58 mm. The structure was solved by the heavy atom method (Patterson and Fourier synthesis) and anisotropically refined for non-hydrogen atoms by a blocked full-matrix least-squares calculation. For 4967 unique observed structure amplitudes [$I > 2\sigma(I)$], collected at room temperature on a Philips PW 1100 diffractometer in the range $6 < 2\theta < 52°$ and corrected for absorption, the R value is 0.069 (R_w = 0.074) [R = 0.071 and R_w = 0.076 for the "inverted" structure due to the polarity of the space group]. The hydrogen atoms, both located from a ΔF map or put in calculated positions, were introduced as fixed contributors prior to the last stage of refinement (U_{iso} = 0.08 Å^2). The final coordinates reported correspond to the correct enantiomorph. There are two crystallographically independent molecules A and B in the asymmetric unit. The reported values refer to molecule A.

bonding rearrangement in two adjacent pyrroles. Thus, the two-electron oxidation leads from the tetraprotic porphyrinogen **1** to the diprotic ligand **6**. Four-electron oxidation should in principle lead to a nonprotic tetraaza macrocycle containing two such cyclopropane units.

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Supplementary Material Available: Schakal drawings and complete listings of crystallographic data, fractional atomic coordinates, anisotropic thermal parameters, and bond distances and angles for complexes **4** and **5** (16 pages); listing of observed and calculated structure factors (61 pages). Ordering information is given on any current masthead page.

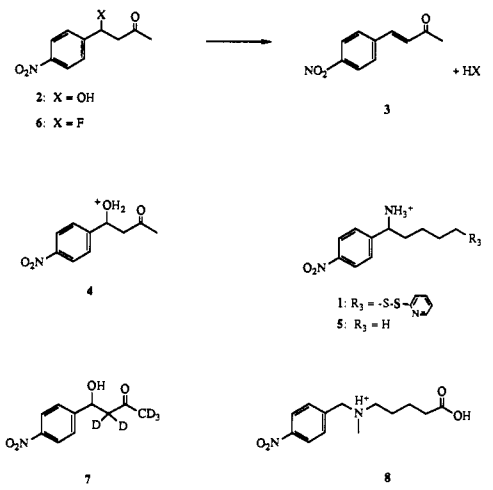

Figure 1. Haptens and substrates for the antibody-catalyzed dehydration reaction.

An Antibody-Catalyzed Dehydration Reaction

Tetsuo Uno† and Peter G. Schultz*

Department of Chemistry, University of California Berkeley, California 94720

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Enzymatic eliminations and additions of water, such as those involving dehydration of citrate, malate, and phosphoglycerate, represent an important class of biochemical reactions. One approach for generating antibodies that catalyze these reactions involves generating a combining site with a general base positioned for proton abstraction.[1] Alternatively, antibodies could be generated that stabilize the protonated form of the OH group, converting it to the much better leaving group, H_2O. In order to test this hypothesis, we asked whether antibodies generated against positively charged hapten **1** would catalyze the dehydration of β-hydroxy ketone **2** to enone **3** (Figure 1). Hapten **1** mimics the oxonium ion **4** formed by protonation of substrate by an active site amino acid residue or buffer.

Hapten **1** was synthesized by reduction of 4-benzoylbutyric acid to the corresponding keto alcohol with borane followed by reductive amination, nitration (cupric nitrate and trifluoroacetic anhydride),[2] and selective hydrolysis to afford 5-(nitrophenyl)-4-(trifluoroacetamido)pentanol. Formation of the tosylate followed by treatment with potassium thioacetate, deprotection with $NaBH_4$, and subsequent reaction with 2,2′-dithiobispyridine afforded hapten **1**.[3] The hapten was conjugated to the thiolated carrier proteins, keyhole limpet hemocyanin (KLH) and bovine serum albumin, via a disulfide exchange reaction.[4] Immunization with the KLH conjugate and generation of monoclonal antibodies were carried out as described previously.[5] Antibodies were purified to homogeneity (as determined by SDS polyacrylamide gel electrophoresis and constant specific activity) by protein A affinity chromatography followed by cation exchange chromatography.[6]

The antibody-catalyzed dehydration of **2** to **3** was performed in 10 mM MES, MOPS, or CHES buffer of 100 mM ionic strength adjusted with NaCl at 37 °C. The initial velocity was determined spectrophotometrically by monitoring the absorbance increase at 330 nm (products were confirmed by high-performance liquid chromatography).[7] Antibody 20A2F6 showed the highest reaction rate acceleration compared to the uncatalyzed reaction. The reaction catalyzed by 20A2F6 demonstrates saturation kinetics: the kinetic constants K_m and k_{cat} were determined to be 1.1 mM and 2.1×10^{-2} h^{-1} (pH 7.0), respectively, by constructing a Hanes-Woolf plot.[8] The pseudo-first-order rate constant of the background reaction in water (k'_{H_2O}) is 4.0×10^{-5} h^{-1}, affording a value of $k_{cat}/k'_{H_2O} = 1200$.[9] For comparison, the second-order rate constants of the acetic acid and acetate-catalyzed reactions (37 °C, 100 mM ionic strength) are 3×10^{-4} M^{-1} h^{-1} and 0.7×10^{-4} M^{-1} h^{-1}, respectively.[10] The catalytic activity of antibody 20A2F6 was competitively inhibited by the addition of the inhibitor **5** (K_i = 16 μM), demonstrating that catalysis takes place in the antibody combining site (Figure 2). In addition, antibody 20A2F6 does not catalyze the dehydration reaction of the isomeric *o*-nitrophenyl substrate to any detectable extent.[11]

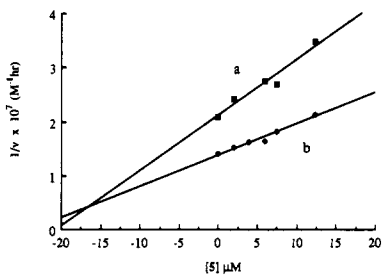

Figure 2. Competitive inhibition of antibody 20A2F6 by **5**. The concentration of 20A2F6 was 10 μM in 10 mM MOPS, 95 mM NaCl, pH 7.0. Two concentrations of **2** were used: (a) 386 μM; (b) 663 μM.

* Author to whom correspondence should be addressed.

† On leave from Kao Corp., Japan.

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(3) Hapten **1** was purified by silica gel chromatography (EtOAc/EtOH) and characterized by NMR, mass spectrometry, infrared, and ultraviolet spectroscopy.

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(7) The reaction was initiated by adding 20 μL of a stock solution of the substrate in CH_3CN to 980 μL of 10 μM 20A2F6 in assay solution: $\Delta\epsilon_{280}$ = 16800 was used to calculate the reaction rate. The concentration of 20A2F6 was determined by absorbance at 280 nm (ϵ(1 cm; 0.1%) = 1.37) and 150000 for the molecular weight of IgG.

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(9) The pseudo-first-order rate constant of the background reaction in water (k_{H_2O}) was determined by measuring velocities in the pH range between 5.5 and 6.5 (10 mM MES, 100 mM ionic strength adjusted with NaCl, 2% CH_3CN) at 37 °C. The background reaction rate was pH independent in this range, and the value of k_{H_2O} was calculated from the relation $v = k_{H_2O}[H_2O][2] = k'_{H_2O}[2]$.

(10) These values were determined by the method of Bell and Baugham: Bell, R. P.; Baugham, E. C. *J. Am. Chem. Soc.* **1937**, *32*, 4059.

(11) The β-hydroxy ketone substrates were synthesized by cross aldol condensation of acetone and 4′-nitrobenzaldehyde or 2′-nitrobenzaldehyde in the presence of a catalytic amount of sodium hydroxide and purified by silica gel chromatography (EtOAc/hexanes).

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