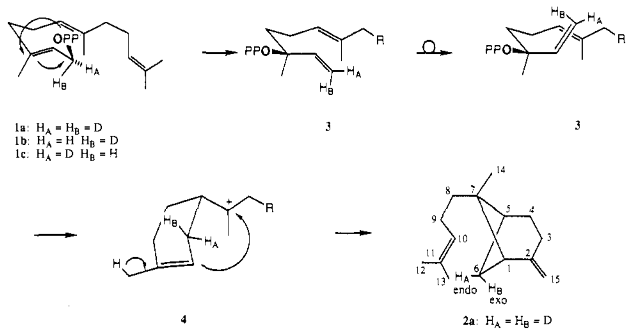
Scheme II



10 Hz) and δ 1.43 (d, J = 10 Hz) were assigned to H-6_{endo} and H-6_{exo}, respectively, based on the reported magnetic anisotropy of the puckered cyclobutane ring of the pinene skeleton.[9] In support of these assignments was the absence of vicinal coupling between H-6_{exo} and either H-1 or H-5, consistent with the 100° dihedral angle between the neighboring protons.[10] The assignments were confirmed unambiguously by the observed NOE enhancement of the δ 2.31 signal (H-6_{endo}) upon irradiation of the H-8 protons of the proximal side chain.

Incubation of $[1,1\text{-}^2H_2]$FPP (**1a**)[11] with crude bergamotene synthetase at 4 °C for 48 h yielded 110 nmol of β-bergamotene (**2a**, Scheme II) which, after dilution with 5 mg of (±)-β-bergamotene as carrier and purification by column chromatography, was analyzed by 61.4 MHz ^{2}H NMR revealing the expected signals at δ 1.41 and 2.30 (Figure 1A). Incubation of (1*S*)-$[1\text{-}^2H_1]$FPP (**1b**)[11] at 30 °C for 4 h with bergamotene synthetase yielded 92 nmol of β-bergamotene (**2b**). ^{2}H NMR analysis showed deuterium enrichment only in the H-6_{exo} position at δ 1.41 (Figure 1B). Finally, two incubations of (1*R*)-$[1\text{-}^2H_1]$FPP (**1c**)[11] yielded 146 nmol of β-bergamotene (**2c**) which showed deuterium enrichment only in the complimentary H-6_{endo} position at δ 2.30 (Figure 1C).

The above results clearly demonstrate that FPP can be converted into β-bergamotene by a cell-free preparation from *Pseudeurotium ovalis*, mediated by a new sesquiterpene cyclase, bergamotene synthetase. Further, the results show that this cyclization occurs with net retention of configuration of C-1 of FPP.[12] Similar results have also been obtained for the cyclization of FPP to the sequiterpene hydrocarbon trichodiene.[16] Since cyclization of FPP to form 6-membered rings requires initial isomerization to nerolidyl pyrophosphate (NPP, **3**) to avoid formation of a ring with a trans double bond,[1] present work is directed toward investigating the intermediacy of NPP in the cyclization of FPP to β-*trans*-bergamotene.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM22172 and GM30301). We would like to thank Dr. John S. Oliver for the preparation of (1*S*)-$[1\text{-}^2H]$farnesyl pyrophosphate.

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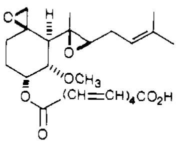
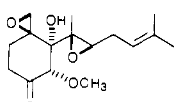
(10) The MacroModel structure of **2** was solved for the lowest energy conformation with a MM2 force field to give the dihedral angles H1,C1,C6,H-6_{exo} = 99.2°, and H5,C5,C6,H-6_{exo} = 100.7°.

(11) Harrison, P. H. M.; Oliver, J. S.; Cane, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 5922.

(12) This conclusion is based upon the reasonable assumption that β-*trans*-bergamotene has the absolute configuration as illustrated, consistent with the known absolute configurations of fumigillin[13] (i) and ovalicin[14] (ii), the



i



ii

demonstrated conversion of β-*trans*-bergamotene to ovalicin,[2b] and the expectation that the introduction of oxygen at C-1 of ovalicin proceeds with retention of configuration.[15] The absolute configuration of β-*trans*-bergamotene is currently under investigation.

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A Dissociative Pathway for Equilibration of a Hydrido CoL(H)$^{2+}$ Complex with CO$_2$ and CO: Ligand-Binding Constants in the Macrocyclic [14]Dienecobalt(I) System

Carol Creutz,* Harold A. Schwarz,* James F. Wishart,
Etsuko Fujita, and Norman Sutin

Chemistry Department, Brookhaven National
Laboratory, Upton, New York 11973

Received September 27, 1988

Metal hydride complexes are central to many catalytic processes, and their reactivity is of interest in its own right.[1] Metal carbon dioxide complexes and metallocarboxylates are often intermediates in CO$_2$ reduction and water-gas shift systems.[2] Despite the importance of these complexes, few thermodynamic and kinetic data for their formation exist. Here we report the results of pulse-radiolysis experiments yielding equilibrium and kinetic data for the binding of H$^+$,[3] CO$_2$,[4,5] and CO to the low-spin d^8 macrocyclic[6] cobalt(I) complex[7] CoL$^+$ in aqueous solutions. In the CoL$^+$ system (which has found application in both the photoreduction of water[8] to H$_2$ and electroreduction[9] of CO$_2$ to

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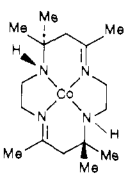
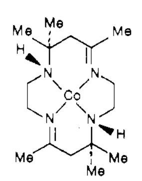
(6) (a) L = 5,7,7,12,14,14-(CH$_3$)$_6$-1,4,8,11-tetraazacyclotetradeca-4,11-diene. *N*-*d,l*-CoL(H$_2$O)(ClO$_4$)$_2$$^{6b-e}$ was prepared via published methods.



N-meso



N-*d,l*

(b) Goedken, V. L.; Kildahl, N. K.; Busch, D. H. *J. Coord. Chem.* **1977**, *7*, 89. (c) A number of isomers are possible for ML complexes;[6d,e] in this work those arising from "primary" and "secondary" substitution of the "*d,l*" configuration are important. Primary denotes the face on which the 1,8-N-H protons are located; secondary, that on which the 7,14-axial CH$_3$ groups are found. (d) Warner, L. G.; Rose, N. J.; Busch, D. H. *J. Am. Chem. Soc.* **1968**, *90*, 6938; **1967**, *89*, 703. (e) Schwarz, C. L. Ph.D. Thesis, Wayne State University, 1988.

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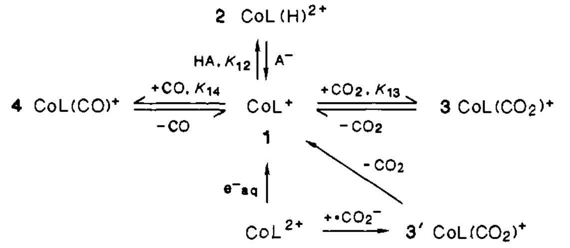
Scheme I



CO), all three adducts $CoL(H)^{2+}$, $CoL(CO_2)^+$, and $CoL(CO)^+$ may be present at equilibrium (on the time scale of seconds), and equilibration is achieved exclusively via dissociation to CoL^+.

In pulse-radiolysis experiments, reduction of aqueous *N-d,l*-CoL^{2+} with e_{aq}^- yields CoL^+.[10] In aqueous *tert*-butyl alcohol containing only added proton donor HA, CoL^+ undergoes protonation by a general acid pathway[3] to give $CoL(H)^{2+}$ (species **2**, Scheme I). Depending on the nature and concentrations of HA species present, the lifetime of CoL^+ at pH < 12 ranges from ~0.5 ms (HA = H_2O, 10^{-3} M borate buffer, pH 9) to <1 μs (e.g., 0.02 M pH 6 phosphate buffer); the $CoL(H)^{2+}$ product persists for several minutes. The formation constant K_{12} (Scheme I) for $CoL(H)^{2+}$ was found to be 5×10^{11} M^{-1} (25 °C, 0.3 M ionic strength) by monitoring the equilibrium CoL^+ absorption ($\epsilon_{630} = 1.10 \times 10^4$ M^{-1} cm^{-1}) in phosphate solutions as a function of pH in the range of 9.4–11.3.

In pH 6 solutions containing 10^{-3} M CoL^{2+} and saturated either with 1% CO_2 in N_2 or pure CO, >95% of e_{aq}^- reduces CoL^{2+} to CoL^+ in <1.0 μs, and >90% of the product CoL^+ subsequently reacts with CO_2 or CO to form **3** or **4**, respectively ($k_{13} = 1.7 \times 10^8$ M^{-1} s^{-1} and $k_{14} = 5.0 \times 10^8$ M^{-1} s^{-1} at 25 °C). Since equilibration of **3** and **4** with $CoL(H)^{2+}$ occurs on a much longer time scale, reasonably pure preparations of the CO_2 and CO adducts could be studied before the equilibration: The spectrum of **4** $CoL(CO)^+$ determined by pulse radiolysis ($\epsilon_{860} = 125$ M^{-1} cm^{-1}; sh 400 nm, $\epsilon = 700$ M^{-1} cm^{-1}) is virtually identical with that measured on dissolving *N-d,l*-$[CoL(CO)]ClO_4$ in CH_3CN.[11] The spectrum determined for the CO_2 adduct **3** in water at 60 °C is similar ($\lambda_{max} = 530$ nm, $\epsilon_{eff} = 500$ M^{-1} cm^{-1}) to that found in CH_3CN[5] at 25 °C. However, as is also found[5] for CH_3CN solvent, aqueous solutions of **3** are thermochromic: at ~0 °C in water, the 530-nm band has little intensity, and a 440-nm ($\epsilon = 400$ M^{-1} cm^{-1}) band dominates the visible spectrum. This thermochromism, which is independent of $[CO_2]$ and pH, may be due to reversible binding of a solvent molecule as proposed[12,13] for $CoL(CH_3)^{2+}$ and/or to an η^2-/η^1-CO_2 isomerism. A third CO_2-containing species **3′** (λ_{max} 460 nm, $\epsilon = 210$ M^{-1} cm^{-1}) is formed from the reaction of CoL^{2+} with formate radical[10b] $^{\bullet}CO_2^-$ ($k = 8.5 \times 10^8$ M^{-1} s^{-1} in CO_2-saturated 0.1 M $NaHCO_2$). We believe **3** and **3′** to be *d,l*-isomers that differ in the face,[6c] primary (**3**) or secondary (**3′**), to which CO_2 is bound. Isomer **3′** is unstable with respect to **3** ($K_{3'3} \geq 5$).

"Ligand-binding" equilibrations amongst $CoL(H)^{2+}$ and $CoL(CO_2)^+$ or $CoL(CO)^+$ are observed on the 0.1–10 s timescale. The positions of the equilibria between $CoL(CO_2)^+$ and $CoL(H)^{2+}$ (**3** → **2**) and between $CoL(CO)^+$ and $CoL(H)^{2+}$ (**4** → **2**) were studied between pH 4 and 8 for CO_2 (3×10^{-4}–3×10^{-2} M) and CO (10^{-4}–10^{-3} M) solutions, and the CO_2 results are presented in Figure 1. Binding constants for CO_2 and CO, $K_{13} = 4.5 \times 10^8$ M^{-1} and $K_{14} = 1.6 \times 10^8$ M^{-1}, are obtained by combining K_{12} and K_{32} or K_{42}. By contrast, in CH_3CN solvent,[5,11] binding of CO is strongly favored over that of CO_2. Protonation of **3** to yield a hydroxycarbonyl complex (metallocarboxylic acid) is not found at pH > 3.5; however, **3′** exhibits a pK_a of 3.1, a value similar to that[15,16] of $(en)_2Co(OH_2)(CO_2H)^{2+}$.

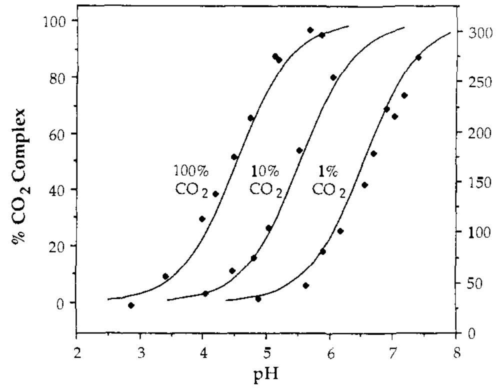


Figure 1. The **3** ⇌ **2** equilibrium, $CoL(CO_2)^+ + H^+ \rightleftharpoons CoL(H)^{2+} + CO_2$, as a function of pH and CO_2 concentration in 0.1 M formate solution, 25 °C. The right axis is the equilibrium 530-nm molar absorptivity; the left axis is the fraction of $CoL(CO_2)^+$ [3]/([3] + [2]) at equilibrium. The CO_2 concentrations are, left to right, 3.2×10^{-2}, 3.2×10^{-3}, and 3.2×10^{-4} M; the curves are calculated for $K_{32} = 1.1 \times 10^3$. The $CoL(CO_2)^+$ species **3′**, formed by the $^{\bullet}CO_2^-$ reaction in these solutions converts to **3** in times comparable to that required for the **3** → **2** reaction.

The key feature of the equilibration mechanism is dissociation to CoL^+. The kinetics of the slow equilibration (studied in 0.5 M *tert*-butyl alcohol solutions in the absence of formate to eliminate complications from **3′** → **1**) are consistent within 50% with the rate constants calculated from the mechanism and the values of the independently determined proton-transfer rate constants.[17,18] Thus for the transformation **2** → **3** no direct insertion of CO_2 into the Co–H bond is found ($k < 3$ M^{-1} s^{-1}). In contrast to a number of "CO_2 complexes" characterized by pulse-radiolytic methods,[19] homolysis of **3** (to CoL^{2+} + $^{\bullet}CO_2^-$) is negligible (the calculated homolysis rate constant is ca. 10^{-8} s^{-1}). Of great practical importance in these experiments is the general base catalysis of $CoL(H)^{2+}$ deprotonation; by addition of A^- (and HA) to the solutions the equilibrations can be conveniently accelerated.

The present dissociative mechanism is reminiscent of behavior found for $Co^I(dmgH)_2$ substitution reactions.[20] The general base catalysis of the $CoL(H)^{2+}$ equilibrations with CO_2 and CO, while at present apparently unique to this system, is to be expected when metal protonation occurs by a general acid path.[21]

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(10) (a) Pulse radiolysis was performed by using 40–200-ns pulses of electrons from a 2 MeV Van de Graaff accelerator; between 5×10^{-8} and 5×10^{-6} M radicals were produced per pulse; the optical pathlength was 6 or 2 cm and $[CoL^{2+}]$ was 0.1–1 mM. (b) $^{\bullet}CO_2^-$ is formed both by the reaction of $^{\bullet}OH$ with HCO_2^- and by the reaction of e_{aq}^- with CO_2.

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(14) (a) Addition of $CH_3^{\bullet}$ to primary *d,l*-$CoL(H_2O)^{2+}$ yields secondary *d,l*-$CoL(CH_3)(H_2O)^{2+}$.[14b] Evidently the water molecule in the primary position blocks radical addition at this site. (b) Schwarz, C. L.; Chou, M. H.; Szalda, D. J. To be published.

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(17) k_{HA} for **1** → **2** at 0.1 M ionic strength, 25 °C: (HA, k(M^{-1} s^{-1})) HCO_2H, 1.7×10^8; CH_3CO_2H, 1.1×10^8; $H_2PO_4^-$, 0.8×10^8; HCO_3^-, 2.5×10^6; H_3BO_3, 0.7×10^5. Values of k_{A^-} were calculated from the equilibrium constants and k_{HA}.

(18) The rate expression for equilibration of CO_2^- and H^+ complexes is $k_{obsd} = k_{31}f_{12} + k_{21}(1 - f_{12})$ where $f_{12} = (\sum k_{HA}[HA])/(\sum k_{HA}[HA] + k_{13}[CO_2])$ and $k_{21} = \sum k_{A^-}[A^-]$. The expression for CO and H^+ complexes is analogous.

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