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Dioxygen Uptake by Cobalt(II) Complexes of Macrocyclic Polyamines. Effects of Chelate Ring Size and Substituents

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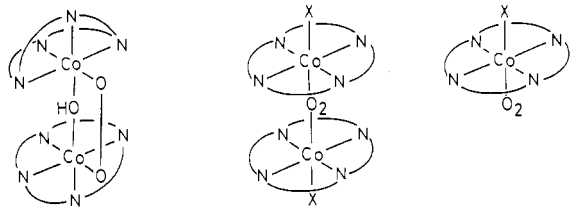
The effects of macrocyclic chelate ring sizes on the structure, reversibility, and binding constants of O_2 adducts in aqueous solutions have been studied with cobalt(II) complexes of cyclic derivatives of trien (**1·0**), 2,3,2-tet (**2·0**), and tetren (**3·0**). The sequence of the chelate rings is systematically altered by elongating the methylene chain (n) bridge across the two terminal amines of the acyclic polyamines for each system. The trien cyclized derivatives with n = 2–4 all yield μ-peroxo–μ-hydroxo adducts, whereas a trien homologue with n = 5 gives a μ-peroxo adduct. The Co(II) complexes of 2,3,2-tet- and tetren-derived macrocycles all produce μ-peroxo adducts, of which the latter products are in general more stable than the former products. Complexes of a tetraamine (**1·5**) and a pentaamine ligand (**3·5**), each of which constitutes a large 8-membered chelate ring moiety, demonstrate a reversible O_2-binding ability in carbonate solutions. Modification of macrocyclic tetraamines by two amides makes more electron-donating ligands having more rigid N_4 coplanarities (due to the two imide anions' coordination), which renders the same μ-peroxo formation more facile. A 14-membered monooxo tetraamine complex (**7**) forms a similarly stable μ-peroxo adduct. The most significant substituent effect occurs with a bulky naphthylmethyl group that makes a 1:1 O_2 adduct of the 14-membered dioxo tetraamine complex kinetically inert.

Introduction

The interaction of molecular oxygen with cobalt(II) chelates has been extensively studied because of their similarity to biological O_2 carriers[1-4] as well as their potential as catalysts for the insertion of oxygen into organic substrates.[5] The polyamine ligands such as porphyrins,[6,7] salicylidenamines,[8] aliphatic polyamines,[9] amino acids or peptides,[10] and unsaturated macrocyclic tetraamines[11] are well recognized to promote the O_2 affinity of Co(II). However, until recently little attention had been paid to saturated macrocyclic polyamine systems despite their useful properties for the O_2 uptake investigation. The advantages of these polyamines are (1) the metal complexes are thermodynamically and kinetically extremely stable,[12] (2) the N donor atom numbers and ring sizes can be successively altered, so that the basic skeletons can be easily optimized, and (3) functional group(s) can be systematically introduced into macrocycles without much difficulty for evaluation of their steric and/or electronic effects on the O_2 uptake.

Our previous publications presented thermodynamic and kinetic data on oxygen affinities of Co(II) complexed with 12- (**1·2**), 13- (**1·3**), and 14-membered tetraamines N_4 (**2·3**),[13] a 16-membered pentaamine N_5 (**3·3**),[14] a pyridyl-containing 16-membered N_5,[15] and a 14-membered dioxo tetraamine (**5·0**).[16] The ring size was found to be a critical factor in the determination of the stability and structure of the O_2 adducts in the N_4 system, the μ-peroxo–μ-hydroxo structure I with the



μ-peroxo–μ-hydroxo adduct I | μ-peroxo adduct II | superoxo adduct III

smaller sized **1·2** and **1·3** and the μ-peroxo structure II with the larger **2·3**.[13] Insertion of the fifth N donor atom into the macrocyclic rings, as shown by **3·3**, increases the O_2 affinity both kinetically and thermodynamically while maintaining the same O_2 adduct structure II.[14] With the dioxo tetraamine **5·0** we observed the μ-peroxo adduct at room temperature, but the superoxo complex III was identified in the presence of imidazole or pyridine as an axial base at low temperature.[16] These results encouraged us to further investigate the saturated macrocyclic polyamine systems modified with more variety of ring sizes and substituents. It was hoped that such an exploration might eventually lead to discovery of novel and useful O_2 uptake systems. For the present approach, we have completed the synthesis of tetraamines **1·4–1·6**, **2·4**, and **2·5**, pentaamines **3·4–3·6**, substituted 14-membered tetraamines **4·1–4·6**, and substituted 14-membered dioxo tetraamines **5·1–5·6**. The intermediate oxo ligand, monooxo tetraamine **7**, was also synthesized (see Figure 1 for the structures).

Experimental Section

Materials. Macrocyclic tetraamines **1·4–1·6**, **2·4**, and **2·5** and pentaamines **3·4–3·6** were prepared according to the method of Richman and Atkins.[17] They were purified by recrystallization as hydrochloride or hydrobromide salts. Macrocyclic dioxo tetraamines **5·1–5·6** were prepared according to the method of Tabushi et al.,[18] wherein 2,3,2-tetraamine (3,7-diazanonane-1,9-diamine) was refluxed with an appropriate alkylated dimethyl malonate in dry CH_3OH for 3 days. The products were recrystallized from benzene–ethanol. Substituted 14-membered macrocyclic tetraamines **4·1–4·6** were obtained by reduction of the corresponding dioxo tetraamines **5·1–5·6**

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Table I. Mixed Protonation Constants[a] and Melting Points of the Ligands

ligand	log K	log K_2	log K_3	log K_4	log K_5	mp, °C
1·0 (trien)[b]	9.7_3	9.1_2	6.6_5	3.6_8		
1·2 (cyclen)[b]	10.5_1	9.4_9	≃1.6	≃0.8		265 dec[c]
1·3	10.9_1	9.9_1	≃1.6	≃0.9		233 dec[c]
1·4	10.5_7	9.5_6	4.1_3	≃2		267 dec[c]
	(10.98)	(9.75)	(4.86)	(2.00)[d]		
1·5	10.3_7	9.3_5	5.2_9	≃2		272 dec[c]
1·6	10.5_8	9.4_6	5.6_3	≃2		288 dec[e]
2·0 (2,3,2-tet)	10.7_7	9.5_8	7.1_7	5.6_7		
	(10.34)	(9.42)	(8.20)	(5.58)[f]		
2·3 (cyclam)[b]	11.2_3	10.3_0	≃1.5	≃0.8		199[g] (lit.[h] 185)
2·4	10.7_6	9.9_4	3.6 ± 0.5	1.5 ± 0.5		258 dec[e]
2·5	9.9_3	9.4_0	5.5_4	3.0 ± 0.5		253 dec[c]
3·0	10.3_6	9.6_5	8.5_0	4.7_0	2.4	
3·3[i]	10.4_2	9.2_7	7.0_6	<2	<2	254 dec[e]
3·4	10.5_0	9.7_3	7.9_7	<2	<2	254 dec[e]
3·5	10.1_5	9.5_2	8.5_5	<2	<2	260 dec[e]
3·6	10.1_1	9.5_2	8.5_1	2.5 ± 0.5	<2	261 dec[e]
4·1	11.2_0	10.2_4	2.1 ± 0.5	≃1		173[g]
4·2	11.0_2	10.1_4	2.7 ± 0.5	≃1		139[g]
4·3	10.6_4	10.0_4	3.3 ± 0.5	≃1		158[g]
4·4	10.6_4	10.0_0	2.9 ± 0.5	≃1		143 (lit.[g] 145)
4·5	10.6_3	9.8_6	2.5 ± 0.5	≃1		150 (lit.[g] 155)
4·6	10.6_5	9.7_6	2.6 ± 0.5	≃1		253 dec[c]
5·0	9.3_4	5.4_2				175 (lit.[g] 177)
5·1	9.3_5	5.1_6				202[g]
5·2[j]	9.3_2	5.1_8				220[g]
5·3[j]	9.3_5	5.1_7				223 dec[g]
5·4[j]	9.3_7	5.2_1				224 dec (lit.[g] 217)
5·5[j]	9.2_1	5.2_1				218 (lit.[g] 225)
5·6[j]	9.3_4	5.1_1				240[g]
6	9.0_5	3.8_2				189[g]
7	10.2_4	6.9_0	2.9 ± 0.5			151[g]
8	8.0_7					161[g]

[a] All the values were determined at 35 °C and I 0.2 unless otherwise noted. [b] Reference 13. [c] Hydrochloride salt. [d] Reference 25. [e] Hydrobromide salt. [f] Barbucci, R.; Fabbrizzi, L.; Paoletti, P.; Vacca, A. *J. Chem. Soc., Dalton Trans.* 1973, 1763. [g] Free base. [h] Reference 18b. [i] Reference 14. [j] Determined at 35 °C and I 0.01 M.

with BH_3–THF. They were recrystallized from benzene–ethanol as free bases.

Macrocyclic monooxo tetraamine **7** was synthesized as follows: A 3-g (35-mmol) sample of methyl acrylate dissolved in 30 mL of dry CH_3OH was dropped slowly into 50 mL of a dry CH_3OH solution of 6.4 g (40 mmol) of 2,3,2-tet while the mixture was stirred at room temperature. The stirring was continued for 12 h at room temperature. After dilution with 220 mL of dry CH_3OH, the reaction mixture was refluxed for 24 h. The solvent was evaporated to ca. 50 mL, and the residue was allowed to stand overnight. The resulting white precipitates were separated by filtration and recrystallized from methanol to yield 4.2 g (50%) of pure **7**.

The purities of the macrocyclic products were all checked by thin-layer and gas chromatographic methods, which we have explored recently.[19] The structures of all the macrocycles were proven by ^1H NMR. Macrocyclic dioxo tetraamines **5** and monooxo tetraamine **7** show distinct M^+ peaks in their mass spectra. Saturated macrocyclic polyamines and their hydrochloride or hydrobromide salts **1–4** sometimes failed to show clear M^+ peaks. The melting points of all the macrocycles are listed in Table I, where the protonation constants K_i potentiometrically determined for the present study are also summarized. The stock solutions of cobalt(II) were prepared from analytical grade $CoCl_2$ and were standardized by titration with ethylenediaminetetraacetic acid (EDTA) by the method of Flaschka.[20]

Potentiometric Measurements. Potentiometric titrations were performed with a Kyoto Electronics automatic titrator, and the data were treated with the graphic method, aided by computer. The ligand hydrochloride or hydrobromide salts (**1**, **2**, and **3**; 1.0×10^{-3} M) were titrated with a standard NaOH solution (0.1 N) in the presence of equimolar cobalt(II), and the $-\log [H^+]$ (=pH) values were recorded every 5 min after the addition of each increment of base. Normally 2–3 min was required to reach the acid–base equilibria. In the case of **4** systems, it took ca. 30 min to attain the equilibrium at 35 °C. To the ligands **4**, **5**, and **7** in free form were added, respectively, 4,

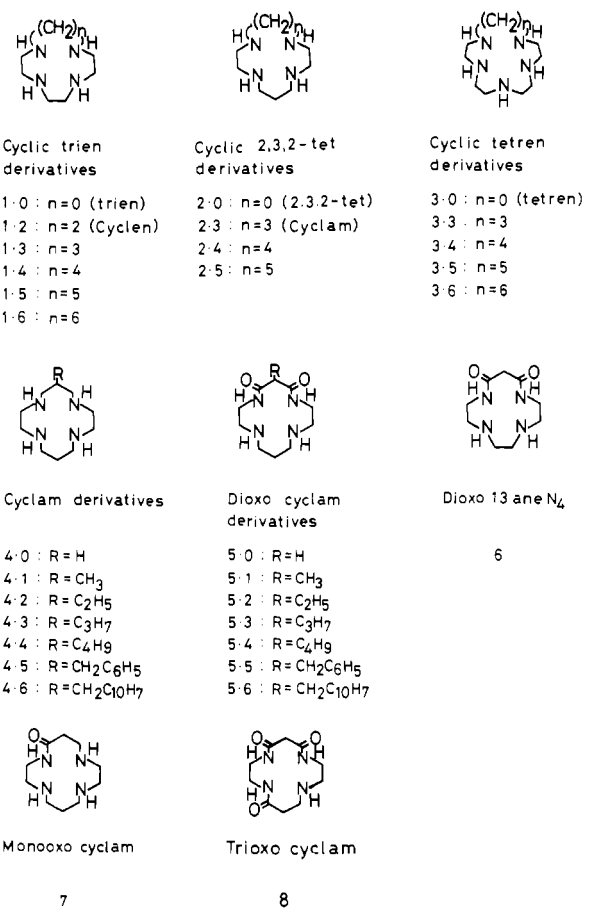

Figure 1. Macrocyclic polyamines of the present O_2 uptake study.

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Table II. Molar Ratios of Absorbed O_2 to Co(II) Complexes

ligand	$[O_2]/[Co(II)$ complex]	ligand	$[O_2]/[Co(II)$ complex]
1·0 (trien)[a]	0.49	4·1[c]	0.49
1·2 (cyclen)[a]	0.48	4·2[c]	0.50
1·3[a]	0.49	4·3[c]	0.50
1·4[a]	0.50	4·4[c]	0.49
1·5[a]	0.49	4·5[c]	0.50
1·6[b]	no absorption	4·6[c]	0.49
		5·0 (dioxocyclam)[d]	0.50
2·0 (2,3,2-tet)[c]	0.49	5·1[d]	0.50
2·3 (cyclam)[c]	0.51	5·2[d]	0.50
2·4[c]	no absorption	5·3[d]	0.51
2·5[c]		5·4[d]	0.52
3·0 (tetren)[a]	0.50	5·5[d]	0.50
3·3[a]	0.50	5·6	0.61,[d] 0.66,[e] 0.88[f]
3·4[a]	0.50		
3·5[b]	0.46	6[c]	
3·6[b]		7 (monooxocyclam)[c]	0.50

[a] Measured at 25 °C in phosphate-borate buffer, pH 8.3. [b] Measured at 35 °C in phosphate-borate buffer, pH 8.3. [c] Measured at 35 °C in lutidine buffer, pH 8.2. [d] Measured at 35 °C in nonbuffer, pH ≃10. [e] Measured at 25 °C in nonbuffer, pH ≃10. [f] Measured at 5 °C in nonbuffer, pH ≃10.

2, and 3 equiv of $HClO_4$, and the mixtures were titrated. The titrations were conducted under an argon atmosphere (wet through 1 N NaOH) for determination of Co^{2+}–L formation constants and in air for oxygenation constants. All the solutions were adjusted to 0.2 M (0.01 M for **5**) ionic strength, I, by addition of $NaClO_4$ (KNO_3 for **5**) and maintained at 35.0 ± 0.1 °C.

Measurement of O_2 Uptake. The measurements of O_2 uptake were performed by using an oxygen monitor with an oxygen electrode (Yellow Springs Instrument Co., Inc.). The zero point was calibrated with 5% $NaHSO_3$ aqueous solution and the 100% point with freshly distilled (in air) water. Air-saturated water is 0.222, 0.258, and 0.397 mM at 35, 25, and 5 °C, respectively.[21] The O_2 uptake was complete at alkaline pH, for which the following buffer systems were used: (a) phosphate–borate buffer, pH 8.3, for **1**, **2**, and **3** systems; (b) lutidine–HCl buffer, pH 8.2, for **4** and **7** systems; (c) nonbuffer solution, pH ≃10, for **5** systems.

The oxygen electrode was attached to a vessel containing 8.0 mL of each buffer solution saturated with air at a fixed temperature. After the systems were sealed, 1 μmol of a Co(II) complex in 0.1 mL of buffer solution (prepared under Ar) was injected by a microsyringe into the vessel. After the solution was stirred for 5–120 min (depending on the ligands), the diminution of $[O_2]$ was recorded. For example, the $[CoL^{1\cdot3}]$ complex (1 μmol) absorbed 24% of the oxygen at 25 °C after an equilibration time of 5 min, and hence the quantity of O_2 bound to the complex was calculated as 8.0 × 0.258 × 0.24 = 0.495 μmol. Thus, the composite of the O_2 adduct is established as 2:1 $CoL^{1\cdot3}:O_2$. The results for other Co(II) complexes are summarized in Table II.

Reversible O_2 Uptake in the Presence of Carbonate. A 10-mL sample of 0.2 M $NaHCO_3$ solution was adjusted to pH 7.4 by bubbling CO_2 gas through it. Then, 0.01 mmol of a ligand and an equimolar $CoCl_2$ solution were added under an O_2 atmosphere. After O_2 adducts were formed (as judged by the UV spectra), CO_2 gas was bubbled through the solution. The brown color of the O_2 adducts turned to pale pink only with the complexes of **1·5** and **3·5**, when the pH values were read as 7.1. The O_2 adducts were formed again by air bubbling. The reversible O_2 uptake was observed by the UV absorption at 310 nm (see Figure 2).

Under the same conditions, the O_2 adducts containing ligands **1·0**–**1·4** were rapidly oxidized to Co(III) species, as detected by an appearance of the typical pink color; $\lambda_{max} \simeq 510$ nm for Co(III). For other Co(II) macrocyclic systems, CO_2 gas had little interaction with the O_2 adducts.

Electrophoresis Study. Electrophoresis was performed by using a Gelman semimicro electrophoresis chamber and an Atto VC stabilizer, SJ-1051. Gelman Sepraphore 111 (6 × 11 cm) was used as the supporting medium for each run. After equilibration for 10 min, aqueous solutions of O_2 adducts were applied to the Sepraphore strips to undergo elution at 300 V for 10 min. The spots were visible as brown. Electrolyte solutions used were (a) Tris–HCl buffer, pH 7.4; (b) Tris–HCl–$NaHCO_3$ buffer, pH 7.4; (c) $NaHCO_3$–Na_2CO_3 buffer, pH 9.2. The electrophoretic mobilities for appropriate O_2 adducts were calculated with reference to those for the **2·3** (cyclam) system. The results are tabulated in Table III.

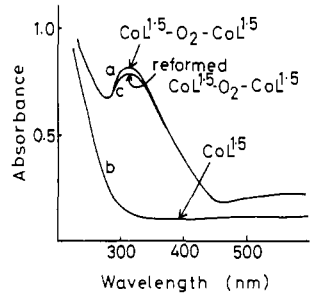

Figure 2. Change of UV spectra for the O_2 adduct of **1·5**: (a) spectrum for the O_2 adduct of **1·5** (λ_{max} 310 nm (ϵ 4000)); (b) spectrum a after CO_2 gas bubbling; (c) spectrum b after air bubbling.

Table III. Electrophoretic Mobilities for the O_2 Adducts with Macrocyclic Polyamines

ligand	electrophoretic mobility[a] Tris–HCl buffer, pH 7.4	Tris–HCl–$NaHCO_3$ buffer, pH 7.4	$NaHCO_3$–Na_2CO_3 buffer, pH 9.2
2·3 (cyclam)	1.00	1.00	1.00
1·2	0.92	1.00	1.10
1·3	1.00	1.00	1.20
1·4	1.00	0.89	1.20
1·5	1.00	0.44	0.52
3·4	1.00		0.62[b]
3·5	1.00		0.50[b]

[a] The values are calculated with reference to those of **2·3** (cyclam). [b] The value is not so accurate because of the tailing of the spot.

Calculations of the Potentiometric Results. We have already described a general calculation procedure for 1:1 metal–ligand complex formation constants,[22] and the results showed good agreement with our polarographic results and potentiometric results by Yang and Zompa.[23] For some cobaltous complexes, we have reported the calculation results in ref 13 (**1·0**–**1·3** and **2·3**) and ref 14 (**3·3**). Moreover, a similar calculation procedure was applicable to the determination of the oxygenation constants of the cobaltous complexes.[13-15] In the present study, the same calculation procedures were used for **1·4**–**1·6**, **2·0**, **2·4**, **2·5**, **3·4**, **3·5**, and **4**.

For the oxo-containing ligands **5·0**–**5·6** and **7**, the calculations are described in sections 1 and 2 of the supplementary material. The titration curves in argon atmosphere for $Co^{II}L^5$ (as $2H^+$ salt) and $Co^{II}L^7$ (as $3H^+$ salt) indicated dissociation of four protons, suggesting the formation of doubly and singly deprotonated ligand complexes $[CoH_{-2}L^5]^0$ and $[CoH_{-1}L^7]^+$, respectively. We have already reported the similarly doubly deprotonated **5·0** complex with Cu(II) $CuH_{-2}L^{0}$.[24]

The titration curves in air for $Co^{II}L^5$ and $Co^{II}L^7$ systems were different from the anaerobic ones, implying interaction between $Co^{II}L$ and O_2 (see supplementary material). The separate O_2 uptake experiments and the characteristic absorption bands at 360–380 nm undoubtedly proved the O_2 adduct formation. The oxygenation constants of these cobaltous complexes were also determined potentiometrically. The details of the calculation procedures are noted in the supplementary material. All the calculated values are summarized in Table IV.

The definitions of the cobaltous complex formation constants and the oxygenation constants are shown in Scheme I.

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Scheme I

Formation Constants:

$$Co^{2+} + L \rightleftharpoons CoL^{2+}$$

$$K_{CoL} = [CoL^{2+}]/[Co^{2+}][L] \quad \text{for 1–4 except 3·6} \quad (1)^{13,14}$$

$$Co^{2+} + HL^{+} \rightleftharpoons CoHL^{3+}$$

$$K_{CoHL} = [CoHL^{3+}]/[Co^{2+}][HL^{+}] \quad \text{for 3·6} \quad (2)^{22}$$

$$Co^{2+} + L \rightleftharpoons CoH_{-2}L^{0} + 2H^{+}$$

$$K_{CoH_{-2}L} = [CoH_{-2}L^{0}][H^{+}]^2/[Co^{2+}][L] \quad \text{for 5} \quad (3)^{24}$$

$$Co^{2+} + L \rightleftharpoons CoH_{-1}L^{+} + H^{+}$$

$$K_{CoH_{-1}L} = [CoH_{-1}L^{+}][H^{+}]/[Co^{2+}][L] \quad \text{for 7} \quad (4)^{24}$$

Oxygenation Constants:

$$2Co^{2+} + 2L + O_2 + H_2O \rightleftharpoons (CoL)\text{–}(O_2)(OH)\text{–}(CoL)^{3+} + H^{+}$$

$$K_{O_2OH} = \frac{[(CoL)\text{–}(O_2)(OH)\text{–}(CoL)^{3+}][H^{+}]}{[Co^{2+}]^2[L]^2[O_2]} \quad \text{for 1·0–1·4} \quad (5)^{13}$$

$$2Co^{2+} + 2L + O_2 \rightleftharpoons (CoL)\text{–}O_2\text{–}(CoL)^{4+}$$

$$K_{O_2} = \frac{[(CoL)\text{–}O_2\text{–}(CoL)^{4+}]}{[Co^{2+}]^2[L]^2[O_2]} \quad (6)^{13,14}$$

for **1·5**, **2·0**, **2·3**, **3·3–3·5**, and **4**

$$2Co^{2+} + 2L + O_2 \rightleftharpoons (CoH_{-2}L)\text{–}O_2\text{–}(CoH_{-2}L) + 4H^{+}$$

$$K_{O_2}(\text{dioxo}) = \frac{[(CoH_{-2}L)\text{–}O_2\text{–}(CoH_{-2}L)][H^{+}]^4}{[Co^{2+}]^2[L]^2[O_2]}$$

for **5·0–5·5** and **5·6** ($7.1 < pH < 7.5$) (7)

$$Co^{2+} + L + O_2 \rightleftharpoons (CoH_{-2}L)\text{–}O_2$$

$$K_{O_2}(1{:}1) = \frac{[(CoH_{-2}L)\text{–}O_2][H^{+}]^2}{[Co^{2+}][L][O_2]} \quad (8)$$

for **5·6** ($6.5 < pH < 7.1$)

$$2Co^{2+} + 2L + O_2 \rightleftharpoons (CoH_{-1}L)\text{–}O_2\text{–}(CoH_{-1}L)^{2+} + 2H^{+}$$

$$K_{O_2}(\text{mono}) = \frac{[(CoH_{-1}L)\text{–}O_2\text{–}(CoH_{-1}L)^{2+}][H^{+}]^2}{[Co^{2+}]^2[L]^2[O_2]}$$

for **7** (9)

Conversion of K_{O_2} into $\mathcal{H}_{O_2}$. The formats (10) and (11) are more

$$2CoL + O_2 \rightleftharpoons (CoL)\text{–}O_2\text{–}(CoL)$$

$$\mathcal{H}_{O_2} = [(CoL)\text{–}O_2\text{–}(CoL)]/[CoL]^2[O_2] \quad (M^{-2})$$

for μ-peroxo adduct II (10)

$$CoL + O_2 \rightleftharpoons (CoL)\text{–}O_2$$

$$\mathcal{H}_{O_2} = [(CoL)\text{–}O_2]/[CoL][O_2] \quad (M^{-1})$$

for superoxo adduct III (11)

convenient for comparison of the O_2 affinities among various polyamine systems. These can be determined from eq 12–15. The calculated $\mathcal{H}_{O_2}$ values are summarized in Table IV. Similarly, the equilibrium constant $\mathcal{H}_{O_2OH}$ is defined (eq 16) for the μ-peroxo–μ-hydroxo adduct I. The calculated $\mathcal{H}_{O_2OH}$ values are included in Table IV.

$$\mathcal{H}_{O_2} = K_{O_2}/(K_{CoL})^2 \quad \text{for 1·5, 2·0, 2·3, 3·4, 3·5, and 4} \quad (12)$$

$$\mathcal{H}_{O_2} = K_{O_2}(\text{mono})/(K_{CoH_{-1}L})^2 \quad \text{for 7} \quad (13)$$

$$\mathcal{H}_{O_2} = K_{O_2}(\text{dioxo})/(K_{CoH_{-2}L})^2$$

for **5·0–5·5** and **5·6** ($7.1 < pH < 7.5$) (14)

$$\mathcal{H}_{O_2} = K_{O_2}(1{:}1)/K_{CoH_{-2}L} \quad \text{for 5·6 } (6.5 < pH < 7.1) \quad (15)$$

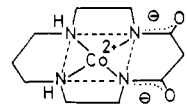
$$\mathcal{H}_{O_2OH} = K_{O_2OH}/(K_{CoL})^2 \quad \text{for 1·0–1·4} \quad (16)$$

Discussion

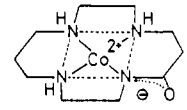
Metal–Ligand Equilibria under Argon Atmosphere. The calculation of K_{CoL} values established the formation of 1:1 Co:L complexes for all the saturated tetra- (**1**, **2**, **4**) and pentaamines (**3**). Of the tetraamine systems, **1·3** forming (5,5,5,6) chelate rings gives the most stable complex, while of the pentaamines, it is **3·3** with (5,5,5,5,6) chelate rings. A more interesting fact is that large 7- (**1·4**, **2·4**, and **3·4**), 8- (**1·5**, **2·5**, and **3·5**), and 9-membered chelate rings (**1·6**) can be formed with Co(II), whose coordinate bondings are known to be labile in nature. Obviously this is due to the effect of "multiple juxtapositional fixedness"[12b] (MJF) of the macrocyclic complexes that places high-energy barriers for configuration changes and, as a result, thwarts the ligand dissociation. Very recently, the 7-membered chelate ring formation was reported with Ni(II) in the **1·4** complex.[26] With **3·6**, Co(II) forms only a monoprotonated complex, $CoHL^{3+}$, in the buffer pH region of 6.5–7.5. Such a protonated metal complex is not unusual with macrocyclic ligands[22,26] whose stability should also come from the MJF effect.

The titration curves for dioxo systems **5·0–5·6** (see section 2, supplementary material) show the formation of the doubly deprotonated 1:1 complexes $CoH_{-2}L^{0}$ at a slightly alkaline pH ($\simeq$8). Other complex species CoL^{2+} and $CoH_{-1}L^{+}$ could not account for the data. Earlier, similar deprotonation and simultaneous metal inclusion were observed with Cu(II) and Ni(II) interactions with **5** and **6**, which represent the dual properties of dioxo-free macrocycles and peptides.[24,27,28]

In the case of the monooxo tetraamine system (**7**), the titration data (see section 1, supplementary material) undoubtedly showed the formation of the monodeprotonated complex $CoH_{-1}L^{+}$. The equilibrium occurred in this system at a lower pH range (6.5–7.0) than in the dioxo system, since the monooxo system involves only one amide hydrogen to be dissociated. The inclination of 14-membered (5,6,5,6-chelates) tetraamines N_4 to occupy the corners of a square-planar structure would be enhanced with more imide anions. However, the 14-membered trioxo derivative (**8**) failed to form a Co(II) complex. The coordinated bond strength of Co(II) possibly is not sufficient enough to drive off all of the three amide hydrogens. Copper(II), on the other hand, was found to form a stable $CuH_{-3}L^{-}$ complex with **8**.[29]



square-planar structure of doubly deprotonated complex 5·0



square-planar structure of monodeprotonated complex 7

The substituents incorporated into **2·3** (cyclam) and **5·0** (dioxocyclam) in general serve to reduce the complex stabilities, most likely for steric reasons.

Oxygenation Equilibria. (1) Saturated Polyamine Systems 1–4. The slightly pink Co(II) complexes of dioxo-free macrocyclic polyamines **1–4** react with O_2 to form brown oxygenated species, except for complexes of **1·6** and **2·5**, which are inert to O_2. The O_2 adducts showed UV absorption maxima at 310–380 nm ($\epsilon \simeq 10^3$), which are indicative of μ-peroxo binuclear complexes.[3] The O_2 uptake study supported this notion; i.e., 1 mol of O_2 was absorbed by 2 mol of the

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Table IV. Formation and Oxygenation Constants of Co(II) Complexes[a]

ligand	formation const (complex type)	oxygenation const (O_2 adduct type)	$\mathcal{H}_{O_2}$[b] ($\mathcal{H}_{O_2\cdot OH}$[c])
1·0 (trien)[d]	$(4.3 \pm 0.6) \times 10^{10}$ (K_{CoL}[e])	$(1.3 \pm 0.2) \times 10^{28}$ ($K_{O_2\cdot OH}$[f])	(7.0×10^{6})
1·2 (cyclen)[d]	$(6.2 \pm 1.0) \times 10^{13}$ (K_{CoL})	$(2.8 \pm 0.4) \times 10^{28}$ ($K_{O_2\cdot OH}$)	(6.3)
1·3	$(1.9 \pm 0.3) \times 10^{14}$ (K_{CoL})	$(6.7 \pm 1.0) \times 10^{29}$ ($K_{O_2\cdot OH}$)	(1.6×10^{1})
1·4	$(4.7 \pm 0.7) \times 10^{11}$ (K_{CoL})	$(4.3 \pm 0.6) \times 10^{27}$ ($K_{O_2\cdot OH}$)	(1.9×10^{4})
1·5	$(7.0 \pm 1.0) \times 10^{9}$ (K_{CoL})	$(2.2 \pm 0.3) \times 10^{26}$ (K_{O_2}[g])	4.5×10^{6}
1·6	$(1.1 \pm 0.1) \times 10^{9}$ (K_{CoL})	no reaction	
2·0 (2,3,2-tet)	$(3.2 \pm 0.5) \times 10^{13}$ (K_{CoL})	$(1.1 \pm 0.1) \times 10^{31}$ (K_{O_2})	1.0×10^{9}
2·3 (cyclam)[d]	$(5.1 \pm 0.8) \times 10^{12}$ (K_{CoL})	$(1.2 \pm 0.2) \times 10^{27}$ (K_{O_2})	5.0×10^{1}
2·4	$(2.6 \pm 0.4) \times 10^{12}$ (K_{CoL})	immediately autoxidized	
2·5	$(5.0 \pm 0.7) \times 10^{11}$ (K_{CoL})	no reaction	
3·0 (tetren)[h]	$(4.6 \pm 0.7) \times 10^{13}$ (K_{CoL})	$(1.4 \pm 0.2) \times 10^{43}$ (K_{O_2})	6.8×10^{15}
3·3	$(8.9 \pm 1.3) \times 10^{15}$ (K_{CoL})	$(5.9 \pm 0.9) \times 10^{39}$ (K_{O_2})	7.4×10^{7}
3·4	$(2.4 \pm 0.3) \times 10^{15}$ (K_{CoL})	$(7.4 \pm 1.1) \times 10^{39}$ (K_{O_2})	1.3×10^{9}
3·5	$(3.5 \pm 0.5) \times 10^{11}$ (K_{CoL})	$(2.7 \pm 0.4) \times 10^{30}$ (K_{O_2})	2.3×10^{7}
3·6	$(2.3 \pm 0.3) \times 10^{7}$ (K_{CoHL}[i])		
4·1	$(1.1 \pm 0.1) \times 10^{12}$ (K_{CoL})	$(1.8 \pm 0.3) \times 10^{29}$ (K_{O_2})	1.4×10^{5}
4·2	$(1.0 \pm 0.1) \times 10^{11}$ (K_{CoL})	$(3.9 \pm 0.6) \times 10^{28}$ (K_{O_2})	3.7×10^{6}
4·3	$(4.4 \pm 0.6) \times 10^{10}$ (K_{CoL})	$(3.5 \pm 0.5) \times 10^{28}$ (K_{O_2})	1.8×10^{7}
4·4	$(1.4 \pm 0.2) \times 10^{10}$ (K_{CoL})	$(7.2 \pm 1.1) \times 10^{27}$ (K_{O_2})	3.7×10^{7}
4·5	$(1.9 \pm 0.3) \times 10^{9}$ (K_{CoL})	$(2.4 \pm 0.3) \times 10^{27}$ (K_{O_2})	6.6×10^{6}
4·6	$(3.2 \pm 0.5) \times 10^{9}$ (K_{CoL})	$(2.5 \pm 0.3) \times 10^{27}$ (K_{O_2})	2.4×10^{8}
5·0	$(7.7 \pm 1.1) \times 10^{-12}$ ($K_{CoH_{-2}L}$[j])	$(2.4 \pm 0.3) \times 10^{-9}$ (K_{O_2}(dioxo)[k])	4.0×10^{13}
5·1	$(1.3 \pm 0.2) \times 10^{-12}$ ($K_{CoH_{-2}L}$)	$(1.9 \pm 0.3) \times 10^{-9}$ (K_{O_2}(dioxo))	1.2×10^{15}
5·2	$(6.5 \pm 0.9) \times 10^{-13}$ ($K_{CoH_{-2}L}$)	$(7.9 \pm 1.2) \times 10^{-10}$ (K_{O_2}(dioxo))	1.9×10^{15}
5·3	$(6.0 \pm 0.9) \times 10^{-13}$ ($K_{CoH_{-2}L}$)	$(1.4 \pm 0.2) \times 10^{-9}$ (K_{O_2}(dioxo))	3.8×10^{15}
5·4	$(4.8 \pm 0.7) \times 10^{-13}$ ($K_{CoH_{-2}L}$)	$(9.3 \pm 1.4) \times 10^{-10}$ (K_{O_2}(dioxo))	5.6×10^{15}
5·5	$(3.7 \pm 0.5) \times 10^{-12}$ ($K_{CoH_{-2}L}$)	$(9.4 \pm 1.4) \times 10^{-10}$ (K_{O_2}(dioxo))	6.8×10^{13}
5·6	$(9.3 \pm 1.4) \times 10^{-13}$ ($K_{CoH_{-2}L}$)	$(2.7 \pm 0.4) \times 10^{-9}$ (K_{O_2}(2:1)[k])	3.1×10^{15}
		$(4.7 \pm 0.7) \times 10^{-5}$ (K_{O_2}(1:1)[l])	5.0×10^{7}[m]
6	$(2.3 \pm 0.3) \times 10^{-10}$ ($K_{CoH_{-2}L}$)	immediately autoxidized	
7	$(3.1 \pm 0.4) \times 10^{1}$ ($K_{CoH_{-1}L}$)[n]	$(3.3 \pm 0.5) \times 10^{16}$ (K_{O_2}(mono)[o])	3.4×10^{13}[p]

[a] All the constants (with the confidence limits) were determined at 35 °C and I 0.2 M unless otherwise noted. [b] Defined by eq 10; units M^{-2}. [c] Defined by eq 16; units M^{-1}. [d] Reference 13. [e] Defined by eq 1; units M^{-1}. [f] Defined by eq 5; units M^{-3}. [g] Defined by eq 6; units M^{-4}. [h] Reference 14. [i] Defined by eq 2; units M^{-1}. [j] Defined by eq 3. [k] Units M. [l] Defined by eq 7; dimensionless. The value was determined at 35 °C and I 0.01 M. [m] Defined by eq 8; dimensionless. The value was determined at 35 °C and I 0.01 M. [n] Defined by eq 15; units M^{-1}. [o] Defined by eq 4; dimensionless. [p] Defined by eq 9; units M^{-2}.

Co(II) complexes (see Table II). Further, the potentiometric study identified the μ-peroxo–μ-hydroxo form I for **1·4** and the μ-peroxo form II for **1·5**, **2·0**, **3·4–3·6**, and **4·1–4·6**.

The binding mode of O_2 with macrocyclic tetraamine complexes is determined by the size and sequence of chelate rings. The (5,6,5) chelate ring sequence (derived from 2,3,2-tet) (**2·0**) could well place the N_4 donors on a plane (trans configuration) that leaves only axial sites for the formation of the monobridging μ-peroxo adduct II, while the tighter (5,5,5) sequence of trien (**1·0**) allows only cis arrangements for the N_4 atoms, resulting in the dibridging μ-peroxo-μ-hydroxo adducts I. The μ-peroxo structure (II) is common to Co(II) porphyrin systems.[6,30] Among **1·3**, **2·3**, and **2·4** systems that share the basic (5,6,5) chelate ring sequence, formation of (5,6,5,6) chelates by **2·3** would be most appropriate for the μ-peroxo adduct II, as this is the only one forming a stable II structure.

It is particularly interesting that, while the dibridging O_2 adduct is prevalent for the trien derivatives (**1**), the monobridging species II was found exceptionally with **1·5**, which contains a large 8-membered chelate ring. From this result, the **1·5** cobaltous complex might be suspected to have a square-planar configuration ready for the formation of the μ-peroxo adduct II. Very recently, a square-planar configuration of **1·5** was disclosed in the Ni(II) complex.[31]

In the case of **1·6**, the 9-membered (cyclononane) chelate ring would cause great distortion to the basal N_4 plane and shield an apical position from O_2 attack.

Comparing the pentaamine systems with the tetraamine systems, one generally finds larger $\mathcal{H}_{O_2}$ values for the former. This is due to the stabilizing effect of axial ligation of the fifth nitrogen atom.[14] The **3·4** complex, consisting of a (5,5,5,5,7) chelate sequence, shows the greatest O_2 affinity of all the saturated macrocyclic polyamine systems.

(2) Dioxo (5) and Monooxo (7) Systems. The solutions of the doubly deprotonated complexes $CoH_{-2}L^0$ of **5·0–5·5** are all yellow under Ar atmosphere and, upon exposure to air, become slightly blue. They have characteristic absorption bands of the μ-peroxo adduct II at 360–380 nm ($\epsilon \simeq 500$).[3] The quantitative measurements of O_2 uptake showed a 2:1 $[CoH_{-2}L^0]:[O_2]$ ratio for the systems (see Table II). The potentiometric data were accounted for by μ-peroxo adduct formation. Similar results were obtained for the monooxo complex $CoH_{-1}L^+$ with **7**.

In an earlier ESR study,[16] we reported 1:1 $CoH_{-2}L^0$ dioxocyclam–O_2 complex formation at low temperature. In the present quantitative study at room temperature, the O_2 adducts exist mostly as 2:1 species, a fact correlating well with por-

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Table V. Formation Constants of Superoxo Adducts III

complex	log $\mathcal{K}_{O_2}(1:1)^a$	solvent
$CoH_{-2}L^{5,5}$	7.7[b]	water
Co(salen)[h]	4.2[c]	pyridine
Co(sal(+)bn)[h]	3.4[d]	pyridine
Co(sal(+)dpen)[h]	1.0[e]	pyridine
CoP[h]	0.3[f]	dimethylformamide
Co(myoglobin)	4.3[g]	water
Fe(myoglobin)	6.1[g]	water

[a] $\mathcal{K}_{O_2}(1:1)$ = [superoxo adduct III]/[O_2][metal complex] (M^{-1}). [b] This study. [c] Puxeddu, A.; Tauzher, G.; Costa, G. *Gazz. Chim. Ital.* **1980**, *110*, 69. [d] Reference 8. [e] Cesarotti, E.; Gullotti, M.; Pasini, A.; Ugo, R. *J. Chem. Soc., Dalton Trans.* **1977**, 757. [f] Reference 30. [g] Reference 32. [h] Abbreviations: salen = *N,N'*-ethylenebis(salicylideneaminate); sal(+)bn = *N,N'*-butane-2,3-diylbis(salicylideneaminate); sal(+)dpen = (1,2-diphenylethylene)-bis(salicylideneaminate); P = protoporphyrin IX dimethyl ester.

phyrin systems that also form 2:1 adducts at room temperature.[6,30]

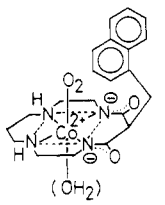
An effect of the dioxo group is manifested in a much greater $\mathcal{K}_{O_2}$ value for **5·0** than for the dioxo-free **2·3** (cyclam) (see Table IV), which is caused mainly by the stronger electron-donor ability of the imide anions. More electron density at the central Co^{2+} ion means more back-donation to O_2, resulting in a stronger Co–O_2 bond. However, the introduction of two oxo groups into saturated macrocyclic polyamines does not always work for the O_2 uptake. For example, the complex of the 13-membered dioxo macrocycle **6** (unlike the dioxo-free **1·3**) did not form a stable O_2 adduct, probably due to the tighter cavity with more rigid conformation (unable to fold). Thus, the 14-membered ring framework is essential for the O_2 uptake of the Co(II)–dioxo macrocycle systems.

The replacement with one imide anion, as seen for the monooxocyclam complex **7**, would be enough to promote the O_2 uptake, which explains the $\mathcal{K}_{O_2}$ value for system **7** being in the same order as that for system **5·0**.

(3) Effects of Substituents on the O_2 Affinities. Hemoglobin and myoglobin consist of hemes and globin proteins around them. The hydrophobic environments in the globin proteins serve to increase the O_2 affinity.[32] Another essential role of the globin proteins in oxyhemoglobin is to block the access of the heme group to keep the superoxo state III. We anticipated similar steric effects to be mimicked by our macrocyclic complexes by the attachment of bulky (lipophilic) substituents. Of the macrocyclic polyamines studied so far, the 14-membered tetraamines cyclam (**4**) and dioxocyclam (**5**) have been judged to have the best ring size for a heme model, and hence, we have put various substituents on them: **4·1–4·6** and **5·1–5·6**.

We have found that most of those substituents are not bulky enough to alter the μ-peroxo structure II (except for the naphthylmethyl group in **5·6**) seen for the unsubstituted cyclam **4·0** and dioxocyclam **5·0**. However, the $\mathcal{K}_{O_2}$ values become greater with bulkier substituents. Previously, we reported that the $\mathcal{K}_{O_2}$ value increases with higher basicity ($\sum \log K_i$) of the macrocyclic ligands.[15] In the present case, however, the $\sum \log K_i$ values do not significantly differ from **4·0** to **4·1**, ..., and **4·6**. The increasing hydrophobicity may account for the greater O_2 affinity of the substituted macrocyclic complexes, as reported for the Fe(II)–porphyrin system.[33]

The yellow **5·6** complex of naphthylmethyl-substituted dioxocyclam reacted with O_2 to form a greenish blue oxygenated species. The potentiometric data at the titration range $1.2 < a < 2.3$ ($6.5 <$ pH < 7.1), where the concentration of the cobaltous complex available is very low ($<10^{-4}$ M), fit to eq 8, indicating the formation of a 1:1 O_2 adduct (possibly superoxo complex III, as concluded for **5·0** at low temperature).[16] Where the complex concentration is higher ($>10^{-4}$ M) at $2.3 < a < 3.5$ ($7.1 <$ pH < 7.5), the titration data come to disobey eq 8 but fit eq 7, suggesting the formation of the μ-peroxo adduct II in this titration region. The oxygenation constants for the superoxo adduct III ($K_{O_2}(1:1)$) and for the μ-peroxo adduct II ($K_{O_2}(2:1)$) were both calculated (see Table IV). The quantitative study of O_2 uptake supports this conclusion. The ratio of the O_2 absorbed at 35 °C was measured three times to give constant 1.6:1 [$CoH_{-2}L^0$]:[O_2] at [$CoH_{-2}L^0$] = 1.25×10^{-4} M (see Table II). It is reasonable to conclude that the superoxo adduct (III) and the μ-peroxo adduct (II) coexist in equilibrium at this concentration. Furthermore, since the superoxo adduct III is known more stable at lower temperatures,[16,34] we performed the O_2 uptake measurement at 5 °C, where the [$CoH_{-2}L^0$]:[O_2] ratio, as expected, lowered to 1.1:1 (see Table II). The oxygen uptake by metal complexes (including hemes) generally occurs in the following two steps.[35]



proposed superoxo adduct for **5·6**

$$CoL + O_2 \rightleftharpoons (CoL)(O_2) \qquad \text{superoxo adduct III}$$

$$(CoL)(O_2) + CoL \rightleftharpoons (CoL)(O_2)(CoL)$$

$$\mu\text{-peroxo adduct II}$$

The bulky naphthylmethyl group would pose steric hindrance to the second reaction so as to kinetically stabilize the superoxo species. Such a steric effect of the naphthylmethyl group may be analogous to those of a picket fence[36] or cap[37] in Fe(II) porphyrins, a methoxy group in Co^{II}salen,[38] and a dry cave in Co(II)–16-membered macrocyclic unsaturated polyamine systems.[11] However, *a novel finding in the present system is that the 1:1 O_2 adduct can be obtained inert in aqueous solutions at room temperature.*[39] Further structural modifications of **5** might hit on more stable 1:1 O_2 adducts. It is of interest to note that the dioxo-free analogue **4·6** cannot hold O_2 at the 1:1 stage. This is probably because the steric effect of the naphthylmethyl group diminishes in the more flexible environments of cyclam.

The $K_{O_2}(1:1)$ value for **5·6** is larger than those reported for porphyrin and salen systems (Table V). The unprecedentedly strong O_2 binding apparently results from an extremely strong

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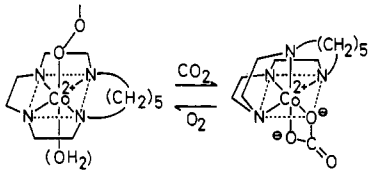

Figure 3. Proposed mechanism for the reversible O_2 uptake of the **1·5** system in carbonate buffers.

σ-donor effect of the imide anions. The O_2 adduct of **5·6** is so stable that it can remain intact in solution under Ar atmosphere at room temperature for 1 week, as judged by measurement of the absorption at λ_{max} 380 nm (ϵ 2000).

(4) Reversible O_2 Uptake in the Presence of Carbonate. Higher CO_2 pressure facilitates liberation of O_2 from oxyhemoglobin, due to the binding of CO_2 to the amino group of the NH_2-terminal residue. This O_2 liberation is an essential function of CO_2, facililating gas exchange in our body. We have discovered that CO_2 promotes the dissociation of O_2 from our oxygenated Co(II)–macrocyclic polyamine complexes **1·5** and **3·5**, although the mechanism may be biologically irrelevant.

A solution of 0.2 M $NaHCO_3$ was adjusted to pH 7.4 by bubbling CO_2 gas, wherein the cobaltous complexes of **1·5** and **3·5** were oxygenated. Then, CO_2 gas was bubbled through the solutions, causing the brown O_2 adducts to turn pale pink, at which time the pH value was read as 7.1. In phosphate buffers of the same pH, the mere N_2 bubbling did not trigger dissociation of O_2 from the oxygenated **1·5** and **3·5** systems. This indicates that the contact with CO_2 (or carbonate) causes the O_2 dissociation.

The electrophoresis study suggested the interaction of carbonate ion with cobaltous **1·5** and **3·5** complexes. The electrophoretic movements of the **1·5** and **3·5** systems were abnormally retarded with respect to other macrocyclic systems in carbonate buffer solutions. The unusual behavior of the **1·5** and **3·5** complexes became normal in another buffer, and they moved at similar rates in others (see Table III). In the case of the free (uncomplexed) form or the Zn(II) complexes of **1·5** and **3·5**, such abnormal behavior was not observed.[29] An identical electrophoresis method has been employed to check the interaction of macrocyclic penta- and hexaamine cations (by protonations) with carbonate anions, which was supported by the quantitative polarographic measurements of 1:1 complex formations.[40]

The macrocycles **1·5** and **3·5** both contain 8-membered chelate rings. The fluctuating 8-membered chelate ring configuration and the bidentate chelate of the carbonate ion may be coupled for the reversible O_2 uptake. In the μ-peroxo complex of **1·5** some steric constraint from the trans arrangement of the trien part may be built into the basal 8-membered chelate rings. Thus, attack of a bidentate ligand carbonate ion would trigger an immediate rearrangement in the N_4 coordination to cis geometry, thereby leading to dissociation of the coordinated O_2. The resulting species may be a Co(II)–carbonato complex (Figure 3). It is to be noted that bidentate ligands sometimes work to make the otherwise unstable cis cyclam configuration stable.[41] In the case of the **3·5** system, the fifth N atom (possibly at an axial position) may be easily detached from Co^{2+} by an attack of carbonate ion. An immediate rearrangement to cis N_4 coordination would lead to the formation of a carbonato complex. This argument is compatible with the observations that the μ-peroxo adducts (e.g. **5·0**) containing rigid chelate conformations are not influenced by the CO_2 bubbling (see the Experimental Section). The interaction of the carbonate ion with the cobaltous **1·5** and **3·5** complexes, however, would not be sufficiently strong, and the O_2 adducts would be formed again by the mild air bubbling. These results imply that the cobaltous complexes **1·5** and **3·5** pick up O_2 at a relatively high pressure of O_2 and release it at low pressure in the presence of carbonate ions. This interesting property may find practical applications.

In summary, we have found that Co(II)–saturated macrocyclic polyamine complexes have several special advantages as O_2 carrier models: (1) they are water soluble, (2) the acid–base equilibrium titrations can easily determine the oxygenation constants, (3) the cobaltous complexes are very stable (dissociation can be ignored), and (4) the ligands can be equipped with various useful functions, e.g. (i) the ring size or chelate ring sequence, which regulates the structures of O_2 adducts, (ii) dioxocyclams, which increase the O_2 affinity while maintaining the μ-peroxo structure, (iii) bulky substituents on the dioxocyclam, which can stabilize the superoxo adduct in aqueous solutions at room temperature, and (iv) with **1·5** and **3·5**, the reversible O_2 binding, which is possible in the presence of CO_2 or carbonate ions. On the basis of the present results, we are designing more interesting and useful O_2 carriers.

Registry No. **1·3**, 295-14-7; **1·4**, 70072-63-8; **1·5**, 83616-30-2; **1·6**, 76025-63-3; **2·0**, 4741-99-5; **2·4**, 85118-60-1; **2·5**, 85828-16-6; **3·4**, 79569-23-6; **3·5**, 85828-17-7; **3·6**, 34391-14-5; **4·1**, 85828-18-8; **4·2**, 85828-19-9; **4·3**, 85828-20-2; **4·4**, 63972-27-0; **4·5**, 63972-25-8; **4·6**, 85828-21-3; **5·0**, 63972-19-0; **5·1**, 85828-22-4; **5·2**, 85828-23-5; **5·3**, 85828-24-6; **5·4**, 63972-22-5; **5·5**, 63972-20-3; **5·6**, 85828-25-7; **6**, 71248-02-7; **7**, 85828-26-8; **8**, 85828-27-9; CO_2, 124-38-9.

Supplementary Material Available: Titration curves and calculation procedures for oxygenation constants for monooxocyclam, dioxocyclam, and naphthylmethyl-substituted dioxocyclam (9 pages). Ordering information is given on any current masthead page.

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