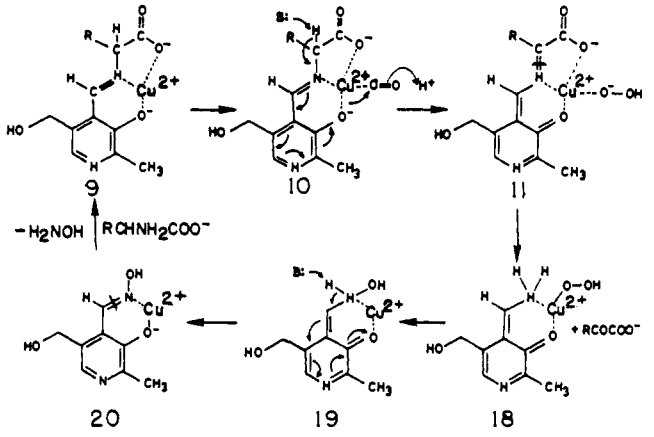
Scheme IV. Proposed Mechanism for Vitamin B_6 Catalyzed Oxidative Deamination[18]



The isolation of hydroxylamine from the methanol solution of the reaction mixture by Tatsumoto et al.[18] may be due to slower decomposition of hydroxylamine in methanol solution; thus in their systems, formation of ammonia was not observed as the only deamination product.

The formation of hydroxylamine seems to be characteristic of oxidative deamination only in model systems. In contrast, hydroxylamine has been found to inhibit oxidative deamination in enzyme systems.[35] Also, the formation of hydrogen peroxide, which is commonly observed in enzymic deaminase reactions, has not been observed in model studies. There is a parallel here, in that hydrogen peroxide and hydroxylamine are isoelectronic and represent half of the four-electron oxidative capability of dioxygen (the keto acid constitutes the other half). The lack of identification of hydrogen peroxide in model systems may very well be due to the catalase activity of the transition-metal complexes present, just as the loss of hydroxylamine in the present catalytic system may be due to similar catalase-like activity of Cu(II) complexes. The role of Cu(II) ion in oxidative deamination in biological systems is yet to be explored.

(35) Green, A. L. *Biochem. Pharmacol.* **1964**, *13*, 249. 3.
(36) Cohn, M.; Urey, H. C. *J. Am. Chem. Soc.* **1938**, *60*, 679.

Concluding Remarks

The oxidative deamination reaction occurs at optimum rates in alkaline solutions. The reaction rates are negligible below pH 9.0. Of the metal ions studied [Co(II), Mn(II), Ni(II), Cu(II), and Zn(II)], Cu(II) was found to be most effective in catalyzing the deamination of (sulfophenyl)glycine mediated by pyridoxal 5'-phosphate or 5'-deoxypyridoxal. The deamination reaction proceeded about 5 times faster in the presence of 5'-deoxypyridoxal than in the presence of pyridoxal 5'-phosphate. The principle Schiff base complex species involved in the rate-determining step of deamination of (sulfophenyl)glycine was found[21] to be the monohydroxo complex of the Cu-Schiff base chelate. The most novel and fundamental finding in this study is the rapid stoichiometric conversion of the Cu(II) complex of the Schiff base species to the oxime of the coenzyme. This oxime participates as an intermediate in the oxidative deamination cycle until the deamination of substrate amino acid reaches completion. In this process, the amino acid seems to displace a hydroxylamine molecule, which rapidly decomposes to ammonia. Reasonable mechanisms illustrated in Schemes III and IV (we prefer Scheme IV) are proposed that seem to account for formation of both keto acid and oxime of the coenzyme.

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Registry No. 1, 134653-57-9; **2**, 54-47-7; **3**, 1849-49-6; **3** (oxime), 826-71-1; **5**, 134653-58-0; **6**, 5363-54-2; MPG, 24593-48-4; D-PG, 875-74-1; NH_3, 7664-41-7; $Cu(NO_3)_2$, 3251-23-8; $Mn(NO_3)_2$, 10377-66-9; $Co(NO_3)_2$, 10141-05-6; $Ni(NO_3)_2$, 13138-45-9; $Zn(NO_3)_2$, 7779-88-6.

Stereochemical Studies on Reversible Metal-Nitrogen Transfer of Alkyl and Aryl Groups in Chiral Cobalt(III) Porphyrins. Relevance to the Mechanism of a Metabolic Heme Inactivation Process

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Abstract: Resolution of the antipodes of chiral σ-alkyl- and σ-aryl-cobalt(III) complexes of etioporphyrin I was first achieved, where the latter was shown to be much more stable than the former toward thermal racemization. Use of these antipodes for stereochemical studies on the mechanism of reversible cobalt-nitrogen transfer of alkyl and aryl groups in cobalt porphyrins revealed that the transfers from cobalt to nitrogen and from nitrogen to cobalt both take place in intramolecular fashions.

Introduction

During the xenobiotic metabolism of phenylhydrazine, the prosthetic group of the hemoprotein is denatured into an abnormal green pigment, which has been identified as *N*-phenylprotoporphyrin IX.[1] Ortiz de Montellano et al. have demonstrated that this reaction occurs via the transient formation of a protein-stabilized intermediate bearing a σ-phenyl-iron bond. Model studies have demonstrated that σ-aryl groups bonded to iron(III) porphyrins undergo an oxidative transfer reaction to the pyrrole nitrogen upon aerobic acid workup, giving the corresponding N-substituted porphyrins.[2] Furthermore, iron(II) N-substituted

(1) Lavallee, D. K. *The Chemistry and Biochemistry of N-Substituted Porphyrins*; VCH: New York, 1987; pp 261-298 and references cited therein.

(2) (a) Ortiz de Montellano, P. R.; Kunze, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 6534. (b) Kunze, K. L.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1981**, *103*, 4225. (c) Augusto, O.; Kunze, K. L.; Ortiz de Montellano, P. R. *J. Biol. Chem.* **1982**, *257*, 6231. (d) Kunze, K. L.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1983**, *105*, 1380. (e) Ortiz de Montellano, P. R.; Kunze, K. L.; Beilan, H. S. *J. Biol. Chem.* **1983**, *258*, 45.

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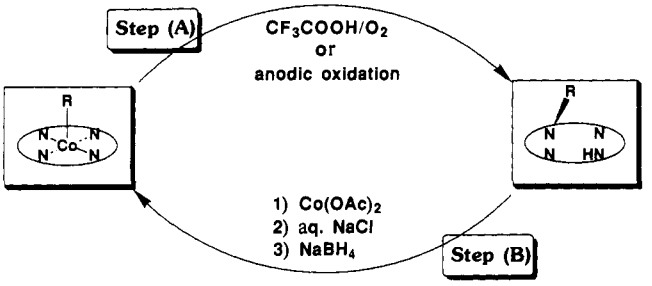
Scheme I



porphyrins, possible intermediate species for the formation of the iron-free N-substituted porphyrins, can revert to the parent organoiron(III) porphyrins by reductive transfer in the presence of sodium dithionite.[3] A similar reversible transfer occurs in the case of cobalt porphyrins[4-6] (Scheme I), which has been extensively studied by double-labeling methods coupled with mass spectrometry in order to clarify whether the transfer proceeds in an intramolecular or intermolecular fashion. Dolphin et al. observed no deuterium scrambling when a mixture of ethyl(tetraphenylporphinato)cobalt(III) and (ethyl-d_5)(tetraphenylporphinato-*2,3,7,8,12,13,17,18-*d_8)cobalt(III) was subjected to electrochemical oxidative transfer but considerable scrambling when a mixture of (*N*-ethyltetraphenylporphinato)cobalt(II) and (*N*-(ethyl-d_5)-tetraphenylporphinato-2,3,7,8,12,13,17,18-d_8)cobalt(II) was subjected to reductive transfer with $NaBH_4$ and concluded that the oxidative cobalt to nitrogen transfer (step A) occurs *intramolecularly*, while the reductive nitrogen to cobalt transfer (step B) occurs *intermolecularly*.[4] On the other hand, Callot et al. later reinvestigated the reductive transfer using the combination of (*N*-(phenyl-d_5)tetraphenylporphinato-d_{20})cobalt(II) and its nondeuterated analogue and claimed that step B should also occur *intramolecularly*. This is on the basis of the observations that the degree of deuterium scrambling after the transfer reaction depends on the mass spectrometry heating time and that (σ-phenyl-d_5)(tetraphenylporphinato-d_{20})cobalt(III) and its nondeuterated analogue scramble only when the mixture is subjected to mass spectroscopy.[5] Therefore, to date, the consensus has been given only for the *intramolecular* mechanism of the oxidative cobalt to nitrogen transfer (step A), while the mechanism of the reductive nitrogen to cobalt transfer (step B) has remained ambiguous due to the thermal lability of the cobalt–carbon bonds in organocobalt(III) porphyrins.

In the present paper, we wish to provide a conclusive answer to the transfer mechanism by a novel approach using cobalt(II) complexes of chiral N-substituted etioporphyrins I (**2**) and chiral organocobalt(III) etioporphyrins I (**3**). Etioporphyrin I is of C_{4h} symmetry due to the alternating arrangement of the methyl and ethyl groups along the periphery of the porphyrin ring and has enantiotopic faces (prochiral). Therefore, N-substituted etioporphyrins I and cobalt(III) etioporphyrins I should be chiral due to the presence of the N-substituents and/or the axial groups on either of the two enantiotopic faces. We have recently succeeded in the resolution of the optical antipodes of *N*-methyletioporphyrin I (**1a**) by HPLC.[7] This achievement prompted us to attempt the resolution of the optical antipodes of other N-substituted homologous and organocobalt(III) etioporphyrins I and to study the stereochemical course of the reversible cobalt–nitrogen transfer of alkyl and aryl groups in these chiral cobalt porphyrins.

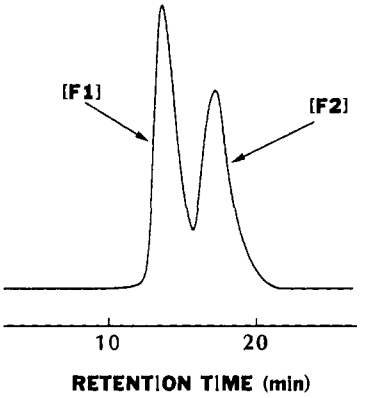


Figure 1. HPLC profile of phenyl(etioporphyrinato)cobalt(III) (**3c**) with the analytical column (see Experimental Section) at a flow rate of 0.5 mL·min^{-1} using hexane/2-propanol (97/3 v/v) as eluent at room temperature monitored at 390 nm. [F1] and [F2] denote the first and second eluted fractions, respectively.

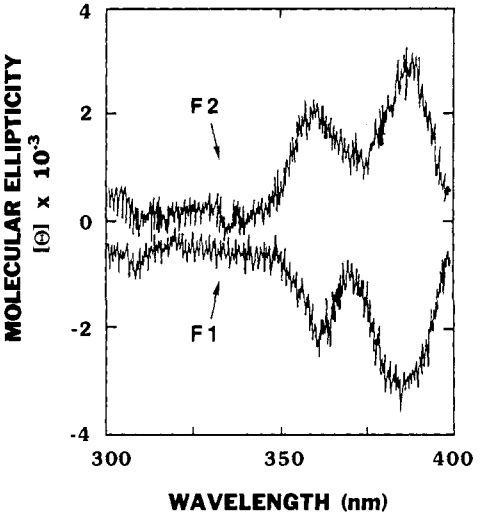


Figure 2. CD spectra of the antipodes of phenyl(etioporphyrinato)cobalt(III) (**3c**) in CH_2Cl_2 (5.9×10^{-6} M) in a quartz cell of 1-cm path length.

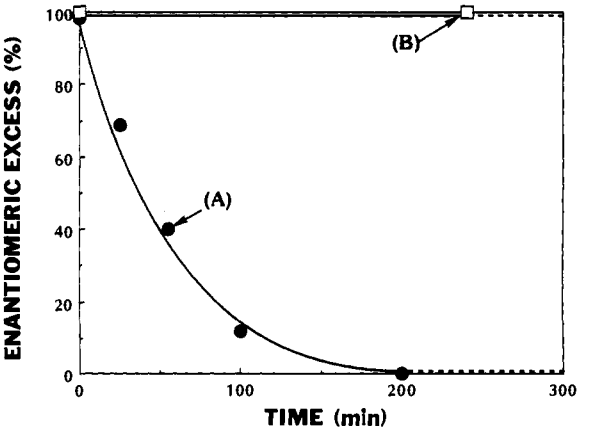


Figure 3. Racemizations of the antipodes ([F1]) of ethyl(etioporphyrinato)cobalt(III) (**3b**) at 47 °C (A) and phenyl(etioporphyrinato)cobalt(III) (**3c**) at 60 °C (B) in hexane/2-propanol (99/1 v/v). Enantiomeric excess (ee) was determined by HPLC.

Results and Discussion

Resolution and Thermal Stability of the Optical Antipodes of Chiral Organocobalt(III) Etioporphyrins I (3a–c). The antipodes of a series of chiral organocobalt(III) etioporphyrins I (**3a–c**) were

(3) (a) Mansuy, D.; Battioni, P.; Dupre, D.; Sartori, E. *J. Am. Chem. Soc.* **1982**, *104*, 6159. (b) Battioni, P.; Mahy, J. P.; Gillet, G.; Mansuy, D. *J. Am. Chem. Soc.* **1983**, *105*, 1388. (c) Battioni, P.; Mahy, J. P.; Delaforge, M.; Mansuy, D. *Eur. J. Biochem.* **1983**, *134*, 241. (d) Mansuy, D.; Battioni, P.; Mahy, J. P.; Gillet, G. *Biochem. Biophys. Res. Commun.* **1982**, *106*, 30.

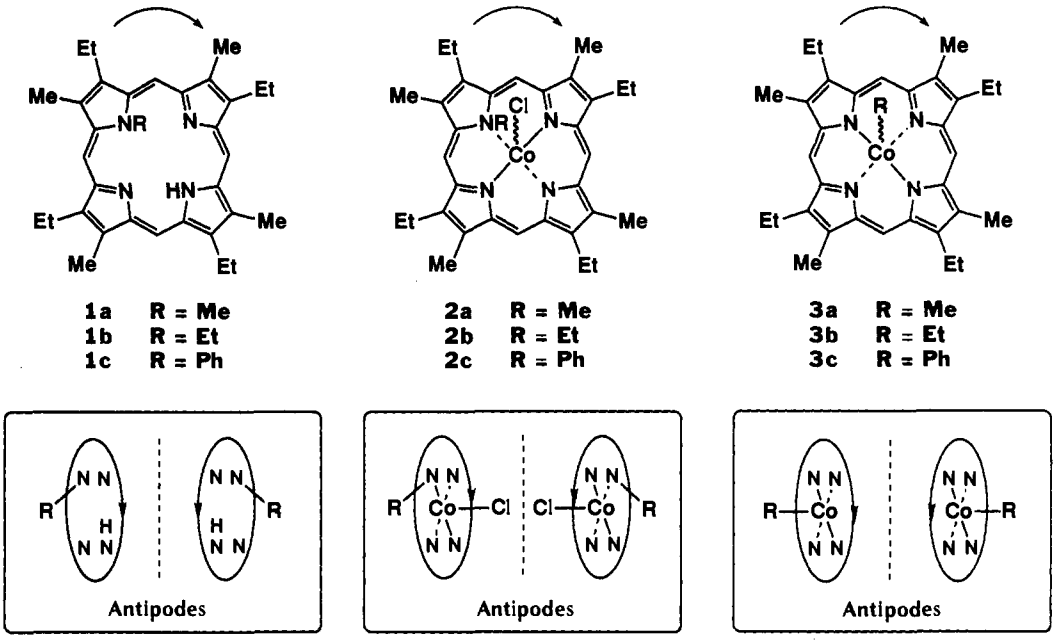
(4) Dolphin, D.; Halko, D. J.; Johnson, E. *Inorg. Chem.* **1981**, *20*, 4348.

(5) (a) Callot, H. J.; Schaeffer, E. *Tetrahedron Lett.* **1980**, *21*, 1335. (b) Callot, H. J.; Metz, F. *J. Chem. Soc., Chem. Commun.* **1982**, 947. (c) Callot, H. J.; Metz, F.; Cromer, R. *Nouv. J. Chim.* **1984**, *8*, 759.

(6) Ogoshi, H.; Watanabe, E.; Koketsu, N.; Yoshida, Z. *J. Chem. Soc., Chem. Commun.* **1974**, 943.

(7) (a) Kubo, H.; Aida, T.; Inoue, S.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1015. (b) Konishi, K.; Miyazaki, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1990**, *112*, 5639.

Chart 1



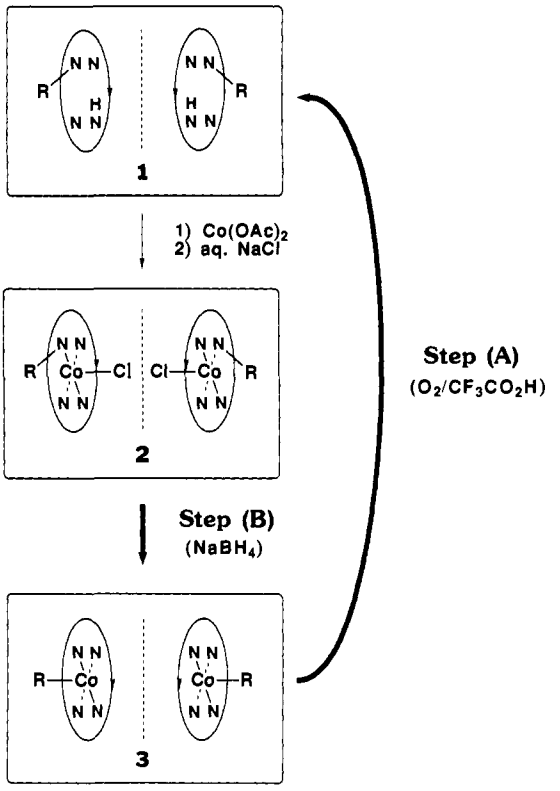
successfully resolved by HPLC on silica gel coated with cellulose tris(3,5-dimethylphenyl carbamate) and hexane/2-propanol (97/3 v/v) as eluent.[7] For example, phenyl(etioporphyrinato)cobalt(III) (**3c**) showed two elution peaks ([F1] and [F2], the first and second fractions, respectively) with comparable peak areas (Figure 1), whose circular dichroism spectra were perfect mirror images of each other (Figure 2).

The antipodes of **3c** are very reluctant to undergo thermal racemization. When a hexane/2-propanol (99/1 v/v) solution of the antipode [F1] was kept at 60 °C for 4 h and then analyzed by HPLC, no peak corresponding to the antipode [F2] appeared (Figure 3A). Quite surprisingly, no racemization was observed even upon refluxing in toluene for 24 h. In contrast, for obtaining the antipodes of the ethyl homologue (**3b**) in optically pure forms, it is necessary to collect the eluates in test tubes kept in the dark at a low temperature such as −78 °C. The antipode **3b**-[F1] hardly underwent racemization below 30 °C in hexane/2-propanol (99/1 v/v) but gradually racemized at a higher temperature such as 47 °C, where the enantiomeric excess (ee) decreased to 69 and 9% in 25 and 100 min, respectively (Figure 3B). Compared with the ethyl and phenyl homologues (**3b**,**c**), the methyl homologue (**3a**) appears to racemize much more easily. Although the HPLC pattern for the methyl homologue (**3a**) was almost the same as those for **3b** and **3c**, reanalysis of the eluate corresponding to the antipode [F1] (**3a**-[F1]) provided an HPLC pattern virtually identical with that of the racemic **3a** even when the eluate was collected and stored at −78 °C before analysis.

Racemization of the alkyl complexes of cobalt(III) etioporphyrin I (**3a**,**b**) possibly occurs via thermal homolysis of the σ-alkyl–cobalt bond followed by recombination of the resulting alkyl radical and cobalt(II) porphyrin.[8] Therefore, the σ-aryl–cobalt bond in the cobalt(III) porphyrin is much more stable than the corresponding σ-alkyl–cobalt bond toward thermal homolysis.

Stereochemical Profiles of the Transfer Reactions between Nitrogen and Cobalt. To investigate the stereochemical course of the transfer reactions (Scheme II), the antipode of chiral chloro(*N*-ethyletioporphyrinato)cobalt(II) (**2b**-[F1] (X = Cl)), derived from optically pure *N*-ethyletioporphyrin I (**1b**-[F1]; I in Figure 4),[7] was treated with $NaBH_4$ in THF/EtOH at −10 °C for 5 min (step B), where ethyl(etioporphyrinato)cobalt(III) (**3b**)

Scheme II



was formed with only a slight decrease in enantiomeric excess (80% ee, as determined by HPLC; II in Figure 4; peak area ratio of [F1] and [F2] being 9/1). It is likely that the racemization observed here is not associated with the transfer reaction but is due to the lability of the cobalt–carbon bond of the product **3b**, since optically pure **3b** was observed to racemize to the same degree after being stirred for 5 min in THF/EtOH at −10 °C in the presence of $NaBH_4$. When the 9/1 mixture of the antipodes of **3b** thus obtained after the transfer reaction was treated with CF_3CO_2H in CH_2Cl_2 at room temperature (~20 °C) under aerobic conditions (step A), *N*-ethyletioporphyrin I (**1b**) was produced without any decrease in enantiomeric excess (80% ee), where the antipode predominantly formed had the same configuration as that of the starting **2b** (III in Figure 4).

(8) (a) Abeles, R. H.; Dolphin, D. *Acc. Chem. Res.* **1976**, *9*, 114. (b) Halpern, J. *Acc. Chem. Res.* **1982**, *15*, 238. (c) Halpern, J. *Science* **1985**, *227*, 869. (d) Guilard, R.; Kadish, K. M. *Chem. Rev.* **1988**, *88*, 1121. (e) Tsou, T-T.; Loots, M.; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 623. (f) Geno, M. K.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1238.

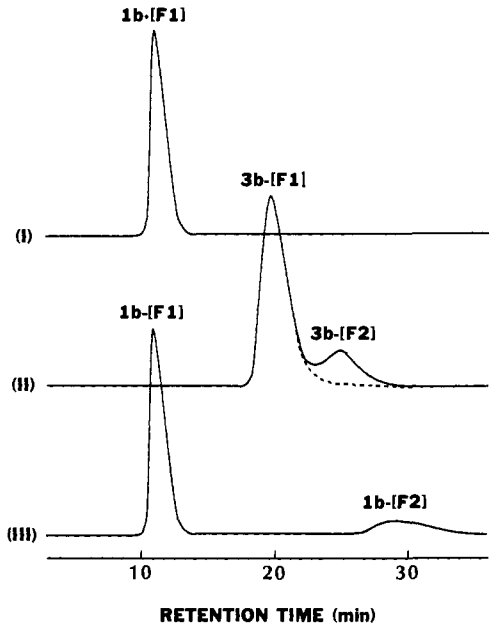


Figure 4. HPLC profiles of the starting *N*-ethyletioporphyrin I (**1b**-[F1]) (I), ethyl(etioporphyrinato)cobalt(III) (**3b**) formed by the reductive transfer (step B) (II), and **1b** reproduced by the subsequent oxidative transfer (step A) (III). Eluents: hexane/2-propanol/diethylamine (95/5/0.1 v/v/v) (flow rate 1.0 mL·min^{-1}) for curves I and III, hexane/2-propanol (97/3 v/v) (flow rate 0.5 mL·min^{-1}) for curve II.

When the antipode of phenylcobalt(III) etioporphyrin I (**3c**-[F1]), which is much more stable compared with **3b** toward thermal racemization, was similarly subjected to the cobalt to nitrogen transfer (step A) followed by nitrogen to cobalt transfer (step B), **3c** was reproduced with perfect retention of the original configuration.

Retention of configuration, thus observed, after the sequence of two transfer reactions (steps A and B in Scheme II) is obviously a result of either double retention or double inversion of configuration. The acid-catalyzed oxidative transfer step (step A) should proceed with retention of configuration, taking into account the well-established *intramolecular* mechanism. Therefore, it can be concluded clearly that the reductive transfer step (step B) also occurs in an *intramolecular* fashion with retention of configuration.

Conclusion

The chemistry of chiral compounds is of general interest and significance, particularly from a biological standpoint. The present paper describes the first successful resolution of the optical antipodes of chiral organocobalt(III) complexes of etioporphyrin I, where the chirality arises from the axial bonding of an alkyl or aryl group from either side of the two enantiotopic faces of the metalloporphyrin plane. To our knowledge, these are the first C_{4h}-symmetric chiral organometallic compounds to be resolved, whose chirality is provided by labile metal–carbon bonding. From racemization profiles of the antipodes, the cobalt–carbon bond in (σ-aryl)cobalt(III) porphyrin is much more stable than that in the (σ-alkyl)cobalt homologue toward thermal homolysis. The above achievements enabled us to make a novel stereochemical approach to the mechanism of a biologically important model reaction, the reversible transfer of an alkyl (aryl) group between metal and nitrogen in cobalt porphyrins, and to conclude clearly that the transfers from metal to nitrogen and from nitrogen to metal both occur intramolecularly.

Experimental Section

Materials. Tetrahydrofuran (THF) and benzene (C_6H_6) were distilled over sodium benzophenone ketyl just before use. Ethanol (EtOH) was distilled over Mg treated with iodine and stored over 4A molecular sieves. Phenyllithium (2.0 M in cyclohexane/ether (70/30 v/v, Aldrich)) was used as received. Etioporphyrin I (EtioPH$_2$) was synthesized from *tert*-butyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate and recrystallized from chloroform ($CHCl_3$)/methanol (MeOH).[9] (Pyridine)bromocobalt(III) etioporphyrin I was prepared according to the procedure reported by Dolphin and Johnson.[10]

***N*-Methyletioporphyrin I (1a).** In a 500-mL round-bottom flask equipped with a reflux condenser were placed etioporphyrin I (1.20 g, 2.5 mmol), $CHCl_3$ (200 mL), methyl iodide (10 mL), and acetic acid (25 mL), and the mixture was stirred at 55 °C. After 40 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The separated organic layer was washed successively with aqueous ammonia (28%) and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue dissolved in a minimum volume of dichloromethane (CH_2Cl_2)/hexane (50/50 v/v) was loaded onto an alumina column (Merck, Art. 1097, activity II ~ III) prepared from a hexane slurry. Unreacted etioporphyrin I was first eluted with CH_2Cl_2/hexane (50/50 v/v) as a red band. The second violet band eluted with CH_2Cl_2 was concentrated to a small volume (ca. 50 mL), and then heptane (100 mL) was added. The mixture was slowly evaporated to leave a dark purple powder, which was identified as **1a** (0.75 g, 61% yield) by absorption and ^{1}H NMR spectra.[11]

***N*-Ethyletioporphyrin I (1b).** EtioPH$_2$ (200 mg, 0.42 mmol), $CHCl_3$ (20 mL), ethyl iodide (20 mL), and acetic acid (1 mL) were added at room temperature to a 100-mL glass tube, which was then sealed and placed in an oil bath thermostated at 90 °C. After 7 days, the tube was opened and the reaction mixture was poured into saturated aqueous $NaHCO_3$. The separated organic layer was treated similarly to the case for **1a**, affording **1b** (98 mg, 47% yield) as a dark purple powder. HRMS for $C_{34}H_{43}N_4$ (MH^+): calcd m/z 507.3488; obsd m/z 507.3475. UV–vis λ_{max}, nm (log ϵ): 406 (4.95), 505 (3.90), 538 (3.71), 584 (3.63), 641 (3.27). ^{1}H NMR: δ 10.11 (s, 2 H, meso), 9.96 (s, 2 H, meso), 3.83–3.98 (m, 8 H, pyr-CH_2CH$_3$), 3.66–3.27 (s × 4, 12 H, pyr-CH$_3$), 1.88–1.42 (m, 8 H, pyr-CH$_2$CH_3), −2.32 (t, 3 H, *N*-CH$_2$CH_3), −3.22 (br, 1 H, NH), −5.22 (q, 2 H, *N*-CH_2CH$_3$).

Chloro(*N*-methyletioporphyrinato)cobalt(II) (2a). To a 50-mL round-bottom flask containing a CH_2Cl_2 solution (5 mL) of **1a** (200 mg, 0.41 mmol) were added an acetonitrile (CH_3CN) suspension (30 mL) of $CoCl_2 \cdot 6H_2O$ (380 mg, 1.6 mmol) and 2 drops of 2,6-di-*tert*-butylpyridine. After the mixture was stirred at room temperature for 2 h, the solvent was removed under reduced pressure. The residue dissolved in CH_2Cl_2 (12 mL) was washed successively with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered out. The filtrate was evaporated to dryness under reduced pressure, and the residue dissolved in a minimum volume of $CHCl_3$ was loaded onto an alumina column (Merck, Art. 1097, activity II ~ III) prepared from a $CHCl_3$ slurry. A green fraction eluted with $CHCl_3$/MeOH (90/10 v/v) was collected and washed with saturated aqueous NaCl. The separated organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness, and the residue was recrystallized from $CHCl_3$/ether to give **2a** (178 mg, 78% yield) as purple crystals. Anal. Calcd for $C_{33}H_{39}N_4CoCl \cdot H_2O$: C, 67.63; H, 6.71; N, 9.56. Found: C, 67.35; H, 6.92; N, 9.28. UV–vis λ_{max}, nm (log ϵ): 309 (4.14), 389 (4.64), 424 (4.78), 540 (3.80), 585 (3.91). ^{1}H NMR:[12] δ 43.59, 31.91, 21.81, 18.61 (s × 4, 12 H, pyr-CH$_3$), 38.23, 29.05, 28.35, 22.93, 21.32, 20.93, 18.61, 17.03 (s × 8, 8 H, pyr-CH_2CH$_3$), 12.87, 10.86, −4.41, −4.98 (s × 4, 4 H, meso), 11.64, 9.23, 8.17, 4.81 (s × 4, 12 H, pyr-CH$_2$CH_3), −56.87 (s 3 H, *N*-CH$_3$).

Chloro(*N*-ethyletioporphyrinato)cobalt(II) (2b). **2b** was prepared in 85% yield from **1b** in a manner similar to that described for the preparation of **2a**. Anal. Calcd for $C_{34}H_{41}N_4CoCl \cdot H_2O$: C, 66.07; H, 7.01; N, 9.06. Found: C, 66.30; H, 6.86; N, 8.80. UV–vis λ_{max}, nm (log ϵ): 310 (4.18), 383 (4.67), 427 (4.85), 542 (3.84), 585 (3.96). ^{1}H NMR:[12] δ 40.88, 29.67, 20.24, 16.66 (s × 4, 12 H, pyr-CH$_3$), 35.66, 26.41, 26.08, 19.84, 18.99, 18.42, 16.22, 15.49 (s × 8, 8 H, pyr-CH_2CH$_3$), 10.02, 7.66, −5.68, −6.37 (s × 4, 4 H, meso), 9.65, 6.39, 5.70, 2.62 (s × 4, 12 H, pyr-CH$_2$CH_3), −44.80 (s, 3 H, *N*-CH$_2$CH_3), −121.33 (br, 2 H, *N*-CH_2CH$_3$).

Chloro(*N*-phenyletioporphyrinato)cobalt(II) (2c). To a 50-mL round-bottom flask containing an aerated CH_2Cl_2 solution (14 mL) of phenyl(etioporphyrinato)cobalt(III) (**3c**; preparation given below) (70 mg, 110 μmol) was added CF_3CO_2H (7 mL) at room temperature. The color of the solution turned rapidly from red to green. The reaction mixture, after being stirred for 30 min at room temperature, was neutralized with aqueous ammonia (28%). The separated organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and

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(10) (a) Clarke, D. A.; Dolphin, D.; Grigg, R.; Johnson, A. W.; Pinnock, H. A. *J. Chem. Soc. C* **1968**, 881. (b) Reference 5c.
(11) McEwen, W. K. *J. Am. Chem. Soc.* **1946**, *68*, 711.
(12) Assignments were made by reference to those for (acetato)(*N*-methyl- or *N*-ethyloctaethylporphinato)cobalt(II) (Aoyagi, K.; Toi, H.; Aoyama, Y.; Ogoshi, H. *Chem. Lett.* **1987**, 467).

evaporated to dryness under reduced pressure. To the residue dissolved in CH_2Cl_2 (2 mL) was added an CH_3CN suspension (10 mL) of $Co(O_2CCH_3)_2 \cdot 4H_2O$ (150 mg, 602 μmol), and the mixture was stirred for 30 min at room temperature. After the solvent was removed, the residue was dissolved in CH_2Cl_2. The solution was then washed successively with water and saturated aqueous NaCl and dried over anhydrous Na_2SO_4, followed by filtration. The filtrate was evaporated to dryness, and the residue was chromatographed on alumina (Merck, Art. 1097, activity II ~ III). Unreacted **3c** was eluted as a red band with $CHCl_3$. When the eluent was changed to $CHCl_3$/MeOH (90/10 v/v), a green band was eluted, which after evaporation to dryness gave **2c** (35 mg, 49% yield) as purple crystals. UV-vis λ_{max}, nm (log ε): 308 (4.21), 384 (4.74), 425 (4.89), 538 (3.90), 586 (4.03). ^1H NMR:[12] δ 41.23, 29.58, 20.85, 16.40 (s × 4, 12 H, pyr-CH_3), 35.90, 26.82, 26.08, 19.60, 19.31, 18.91, 16.40, 15.22 (s × 8, 8 H, pyr-CH_2CH_3), 10.92, 8.83, -6.42, -7.08 (s × 4, 4 H, meso), 9.56, 6.16, 5.61, 2.81 (s × 4, 12 H, pyr-CH_2CH_3), 1.50 (s, 3 H, C_6H_5, *m*-H and *p*-H), -57.60 (s, 2 H, C_6H_5, *o*-H).

Methyl(etioporphyrinato)cobalt(III) (3a). To a 300-mL round-bottom flask equipped with a three-way stopcock containing chloro(*N*-methyletioporphyrinato)cobalt(II) (**2a**) (35 mg, 60 μmol) and $NaBH_4$ (60 mg) was added THF (100 mL) under dry nitrogen at room temperature, and the mixture was stirred in the dark for 1 h. Then, the solvent was removed under reduced pressure at room temperature and the residue dissolved in a minimum volume of CH_2Cl_2 was loaded onto a dry silica gel column (silica gel 60; Merck, Art. 7734). A red fraction eluted with CH_2Cl_2 was collected in a flask kept in the dark and evaporated to dryness under reduced pressure at room temperature. Recrystallization of the residue from CH_2Cl_2/hexane gave a reddish brown powder, which was identified as **1a** (28 mg, 94% yield) by ^1H NMR and absorption spectra.[10]

Ethyl(etioporphyrinato)cobalt(III) (3b). **3b** was similarly prepared from chloro(*N*-ethyletioporphyrinato)cobalt(II) (**2b**) in 95% yield and identified by ^1H NMR and absorption spectra.[10]

Phenyl(etioporphyrinato)cobalt(III) (3c). To a 50-mL round-bottom flask fitted with a three-way stopcock containing a C_6H_6 suspension (5 mL) of (pyridine)bromocobalt(III) etioporphyrin I (50 mg, 65 μmol) was added dropwise an ether/cyclohexane (70/30 v/v) solution (0.2 mL) of phenyllithium (400 μmol) under dry nitrogen, and the mixture was stirred at room temperature. After 6 min, MeOH (10 mL) was added, and the resulting solution was slowly concentrated to a small volume to give a reddish brown powder, which was identified as **1c** (23 mg, 56% yield) by ^1H NMR and absorption spectra.[10]

Procedures. Optical Resolution by HPLC. Resolutions of the optical antipodes of **1a,b** and **3a-c** were carried out by using a 0.46 × 250 mm (the analytical column) or 20 × 500 mm (the preparative column) HPLC column packed with silica gel coated with cellulose tris(3,5-dimethylphenyl carbamate) as a chiral stationary phase. HPLC experiments with the analytical column were performed on a JASCO Type TWINCLE equipped with a JASCO Type 875-UV variable-wavelength detector at a flow rate of 0.5 or 1.0 mL·min^{-1} at room temperature and monitored at 390 nm. HPLC experiments with the preparative column were performed on a JASCO Type 887-PU pump equipped with a JASCO Type 875-UV variable-wavelength detector, a JASCO Type 802-SC system controller, and a JASCO Type 892-01 column selector at a flow rate of 10.0 mL·min^{-1} at room temperature and monitored at 350 nm. The HPLC column pack was prepared by the method reported by Okamoto et al.[13]

Resolution of the Antipodes of 1b. **1b** (4 mg) was dissolved in CCl_4 (20 mL), and an aliquot (20 μL) of the solution was subjected to HPLC with the analytical column using hexane/2-propanol/diethylamine (95/5/0.1 v/v/v) as eluent at a flow rate of 1.0 mL·min^{-1}. Two peaks were observed with retention times of 10.9 (**1b**-[F1]) and 28.6 min (**1b**-[F2]), respectively. For miligram-scale resolution, 3-mL portions of a solution (100 mg of **1b** in 50 mL of CCl_4) were loaded onto the preparative column with hexane/2-propanol/diethylamine (85/15/0.1 v/v) as eluent.

Resolution of the Antipodes of 3a. A 10-μL portion of a CCl_4 solution of **3b** (2 mg/20 mL) was subjected to HPLC resolution with the analytical column using hexane/2-propanol (97/3 v/v) as eluent at a flow rate of 1.0 mL·min^{-1}. Two peaks were observed with retention times of 6.3 (**3a**-[F1]) and 7.4 min (**3a**-[F2]), respectively. However, the isolation of the antipodes in optically pure forms was unsuccessful due to rapid racemization (see text).

Resolution of the Antipodes of 3b. Under similar conditions as for **3a** at a flow rate of 0.5 mL·min^{-1}, two peaks were observed with retention times of 19.7 (**3b**-[F1]) and 24.8 min (**3b**-[F2]), respectively. An eluate containing **3b**-[F1] was collected in a test tube kept in the dark at -78 °C, and the volatile fraction was stripped off by bubbling nitrogen gas at 0 °C. Reanalysis of the residue dissolved in toluene or hexane/2-propanol (97/3 v/v) gave a single peak with a retention time of 19.7 min, demonstrating the 100% enantiomeric excess (ee) of the antipode.

Resolution of the Antipodes of 3c. Under the same conditions as for **3b**, two peaks with retention times of 13.3 and 16.9 min were observed (Figure 1). A milligram-scale resolution of the antipodes of **3c** was carried out similarly to that for **1b** by using the preparative column with hexane/2-propanol (95/5 v/v) as eluent, where 2-mL portions of a CCl_4 solution of **3c** (30 mg/50 mL) were injected repeatedly.

Transfer of the Ethyl Group between Nitrogen and Cobalt. $NaBH_4$ (5 mg, 132 μmol) was added at -10 °C under dry nitrogen to a 20-mL Schlenk tube containing a deoxygenated THF/EtOH (40/60 v/v) solution (2 mL) of the antipode ([F1]) of chloro(*N*-ethyletioporphyrinato)cobalt(II) (**2b**) (10 mg, 17 μmol) derived from optically pure *N*-ethyletioporphyrin I (**1b**-[F1]). After the complete consumption of **2b**, as determined by thin-layer chromatography, the mixture was taken to dryness at -10 °C under reduced pressure. A small aliquot of the resulting **3b** was dissolved in cold CCl_4 (ca. 0 °C), and the solution was subjected to HPLC analysis to determine the enantiomeric excess. To the remaining **3b** dissolved in CH_2Cl_2 at -78 °C was added CF_3CO_2H (0.3 mL), and the mixture was then exposed to air and allowed to warm to 20 °C. After being stirred for 5 min, the reaction mixture was treated with aqueous ammonia (28%) and the separated organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure at room temperature. The residue dissolved in a minimum volume of CH_2Cl_2 was chromatographed on alumina (Merck, Art. 1097, activity II ~ III) with CH_2Cl_2 as eluent. A violet band was collected and evaporated to dryness to give **1b** (3.4 mg, 41% based on starting **1b**), which was subjected to HPLC analysis to determine the enantiomeric excess.

Transfer of the Phenyl Group between Nitrogen and Cobalt. To a 50-mL round-bottom flask containing a CH_2Cl_2 solution (7 mL) of the antipode ([F2]) of phenyl(etioporphyrinato)cobalt(III) (**3c**) (26 mg, 42 μmol) was added CF_3CO_2H (1 mL) at room temperature, and the mixture was stirred for 30 min at room temperature under aerobic conditions. The reaction mixture was neutralized with aqueous ammonia, and the separated organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure at room temperature. To the residue dissolved in CH_2Cl_2 (3 mL) was added an CH_3CN suspension (15 mL) of $Co(O_2CCH_3)_2 \cdot 4H_2O$ (78 mg, 313 μmol), and the mixture was stirred at room temperature for 30 min. After the volatile fraction was removed from the reaction mixture, the residue was treated by a procedure similar to that described for the preparation of racemic **2c** to give **2c** (10 mg, 35% yield), which was identified by thin-layer chromatography and absorption spectroscopy. To a 100-mL round-bottom flask containing a THF solution (30 mL) of **2c** thus obtained (15 μmol) was added $NaBH_4$ (18 mg, 476 μmol) at room temperature under dry nitrogen, and the mixture was stirred for 1 h. The reaction mixture was treated similarly to the case for **3a** to give **3c** (9 mg, 98% yield), which was analyzed by HPLC to determine the enantiomeric excess.

Measurements. ^1H NMR spectra were measured in $CDCl_3$ on a JEOL Type GSX-270 spectrometer operating at 270 MHz, where the chemical shifts were determined with respect to internal $CHCl_3$ (δ 7.28). Absorption and circular dichroism spectra were measured in CH_2Cl_2 on a JASCO Type U-best 50 spectrometer and a JASCO Type J-500 spectropolarimeter, respectively, by using a quartz cell of 1-cm path length.

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