Cobaloxime π-Cation Steric and Stereoelectronic Effects: The Amazing Effect of a Single Methyl Group Adjacent to the Site of Reaction

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Abstract: Typically, β-hydroxylalkylcobaloximes are very sensitive to acid, readily forming transient cobaloxime π-cations which can either be trapped with nucleophiles or undergo irreversible alkene loss. Surprisingly, 2,3-dihydroxy-3,7-dimethyl-6-octenyl cobaloxime (**1**) was found to be stable to acid treatment, including that by the strong acid camphorsulfonic acid. A comparative study of the acid stability of 2,3-dihydroxypropyl cobaloxime (**8**), 2,3-dihydroxylbutyl cobaloxime (**9**), and 2,3-dihydroxy-3-methylbutyl cobaloxime (**10**) was done, showing that **8** and **9** exhibit normal acid sensitivity whereas **10** is stable to acid. The inclusion of an additional methyl group in going from **9** to **10** completely turns off an otherwise very facile reaction, presumably due to severe steric effects of the py(dmgH)$_2$Co moiety of the cobaloxime which forces the acyclic chain of **10** to adopt a conformation which is stereoelectronically nonproductive for cobaloxime π-cation formation.

Synthetic organic reactions using coenzyme B_{12} and B_{12}-model compounds have been developed over the past decade or so[1] (Figure 1). Until recently, the main focus was on radical reactions. In addition to novel and diverse radical reactions, B_{12} and B_{12}-model compounds display interesting and potentially useful ionic reactivity. Cobaloxime π-cations have been known as reactive intermediates since 1972.[2] We recently reported the first examples of C−C bond formation by nucleophilic substitution of cobaloxime π-cations with allylsilane and pyrrole C-nucleophiles.[3] We also demonstrated that the reaction with an alcohol oxygen nucleophile to form an ether proceeds with retention of configuration[4] and that the reaction with a pyrrole to form a C−C bond proceeds with retention of configuration.[5] Other C−C bond constructions using cobaloxime π-cations have subsequently been reported.[6]

In the course of our ongoing studies of C−C bond constructions using cobaloxime π-cations, we envisioned that β-hydroxyalkylcobaloxime **1** might undergo cyclization reactions as shown in Scheme 1. Cobaloxime **1** was prepared by the reaction of NaCo(dmgH)$_2$py with linalool epoxide following a literature procedure.[7]

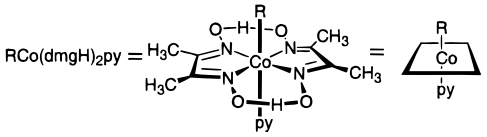
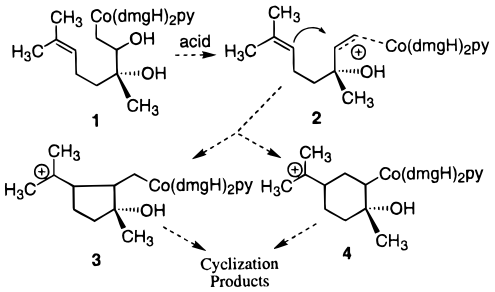


Figure 1. Different representations of alkyl cobaloxime structure.

Scheme 1



We were surprised to find that **1** was completely unreactive with the mild acid/base catalyst pyridinium paratoluenesulfonate (PPTS), which has proven so successful for cobaloxime π-cation formation in our previous work in this area. To our further surprise, **1** was completely resistant to treatment with 2.2 equiv of the strong acid camphorsulfonic acid (CSA) for 48 h in 2:1 $CHCl_3$:CH_3OH solvent at room temperature. This is an unusual result. Although no quantitative studies have been done on the cation-stabilizing effect of the cobaloxime in cobaloxime π-cations, qualitative evidence in comparison with literature data on the ease of formation of triphenylmethyl cations[8] suggests that the formation of a cobaloxime π-cation from a β-hydroxyalkylcobaloxime is probably more facile than formation of triphenylmethyl cation from triphenylmethanol or a triphenylmethyl ether. For example, silica gel (see ref 3) or the traces of acid in $CDCl_3$ are generally sufficient to catalyze cobaloxime π-cation formation.

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(2) Golding, B. T.; Sakrikar, S. J. *J. Chem. Soc., Chem. Commun.* **1972**, 1183−1184. For a discussion of the history of cobaloxime π-cation chemistry see ref 3 below.

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(4) Grubb, L. M.; Branchaud, B. P. *J. Org. Chem.* **1997**, *62*, 2, 242−243. See also Grubb, L. M.; Brown, K. A.; Branchaud, B. P. *Tetrahedron Lett. 1***998**, *39*, 3447−3448

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(6) (a) Gill, G. B.; Pattenden, G.; Roan, G. A. *Tetrahedron Lett.* **1996**, *37*, 9369−9372. (b) Gill, G. B., Pattenden, G., Roan, G. A. *Tetrahedron Lett.* **1997**, *38*, 703−706. (c) Kettschau, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 2027−2028. (d) Kettschau, G.; Pattenden, G. *Synlett* **1998**, 783−784.

(7) Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 243−246.

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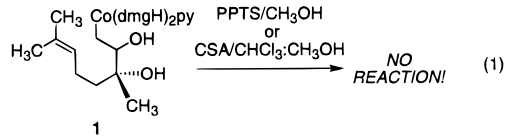
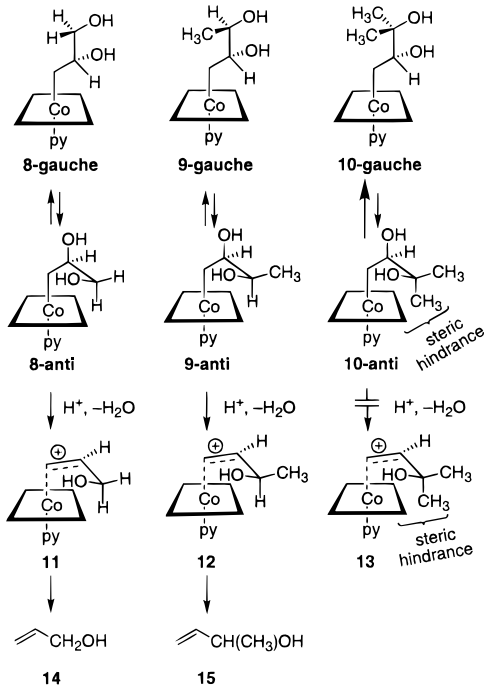


What could be the cause of the very unusual stability of **1**? Study of hand-held and computer molecular models led to the hypothesis shown in Scheme 2. Formation of a cobaloxime π-cation is believed to proceed from a conformation with the C−Co and β-leaving group bonds are oriented anti to each other, as in **8-anti**, **9-anti**, and **10-anti**. Such a conformation provides optimal orbital overlap for the C−Co bond to donate its electron density to push out the leaving group to form the cobaloxime π-cation. This model for the mechanism is consistent with the retention-of-configuration results obtained in the formation of C−O bonds[4] and C−C bonds.[5,6] For compounds such as **8** and **9** it is possible to attain the necessary conformation for reaction (**8-anti** or **9-anti**) since a small H can be placed next to the very large and bulky dimethylglyoxime equatorial ligands. For compounds such as **1** and **10**, the necessary conformation for reaction (such as **10-anti**) will have to have an alkyl or methyl group next to the dimethylglyoxime equatorial ligands. Molecular models suggest that conformations such as **10-anti** should have severe steric hindrance. Such steric hindrance should be even worse in cobaloxime π-cations such as **13**, raising the energy of such cobaloxime π-cations to very high and practically unattainable levels under standard reaction conditions. The conclusion of such an analysis is that β-hydroxyalkylcobaloximes such as **8** and **9** should display "normal" reactivity, since it is relatively easy for them to attain the productive anti conformation for reaction, whereas more substituted β-hydroxyalkylcobaloximes such as **1** and **10** should be essentially unreactive because they cannot attain the anti conformation (such as **10-anti**) and instead stay predominantly in sterically less demanding, but unreactive, conformations such as **10-gauche**.

To test this hypothesis β-hydroxyalkylcobaloximes **8**, **9,** and **10** were prepared by reaction of epoxyalcohols **5**, **6,** and **7** with

Scheme 2



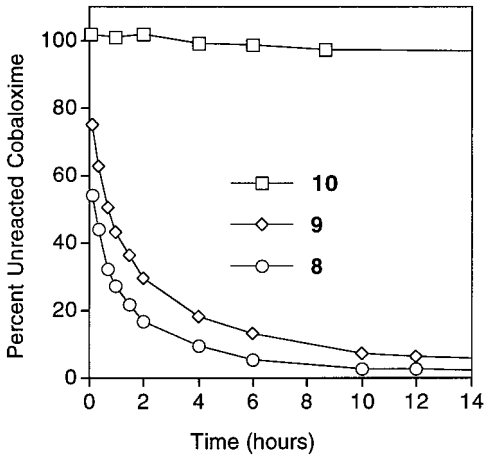
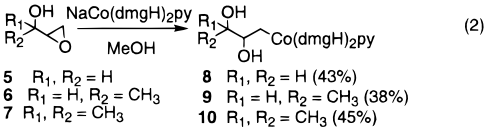


Figure 2. Plot of reaction progress for treatment of **8**, **9**, and **10** with 2 equiv of PPTS in CD_3OD at 23 °C. At the indicated times the reactions were monitored by ^{1}H NMR for the disappearance of starting material (**8**, **9**, **10**) and the appearance of products (**14**, **15**).

Table 1. Relative Initial Rates of Reaction for **8**, **9**, and **10**

compd (concn, mM)	equiv PPTS (concn, mM)	relative initial rate
8 (45 mM)	1.01 (45 mM)	2.9
9, 4:3 mixture of diastereomers (44 mM)	1.03 (45 mM)	1.0
10 (41 mM)	1.11 (45 mM)	0
8 (47 mM)	1.98 (93 mM)	5.7
9, 4:3 mixture of diastereomers (46 mM)	2.04 (95 mM)	1.9
10 (44 mM)	2.04 (90 mM)	0

$NaCo(dmgH)_2py$ (eq 2). Treatment of **8**, **9,** and **10** with PPTS in CD_3OD led to the results shown in Figure 2 and summarized in Table 1. Consistent with the hypothesis described in the preceding paragraph, **8** and **9** exhibit "normal" facile formation of cobaloxime π-cations **11** and **12** (not observed by ^{1}H NMR) followed by irreversible alkene loss to form **14** and **15** (observed by ^{1}H NMR). In contrast, **10** is unreactive under the same conditions and was found to be unchanged after 50 h (data not shown).



The reactivity of **9** compared to that of **10** is a an extraordinary example of the possible magnitude of steric and stereoelectronic effects in the appropriate system. In acyclic systems such as those studied here, one might have expected that there should be sufficient conformational flexibility for any of the compounds to assume a reactive conformation. However, the shape and size of the $py(dmgH)_2Co$ moiety give it exceptional steric bulk,[9] so much so that *the introduction of a single methyl group*, into **10** compared to **9**, *in an open-chain, conformationally flexible molecule completely turns off an otherwise very facile reaction!*

Experimental Section

Materials and Methods. Gravity chromatography was performed with Mallinckrodt silica gel (60−230 mesh). Flash chromatography was performed with EM Science silica gel 60 (finer than 230 mesh).

(9) Welker and co-workers have observed that the $Co(dmgH)_2py$ group has a large steric effect in Diels−Alder reactions, shifting endo-selective reactions into exo-selective ones: (a) Richardson, B. M., Welker, M. E. *J. Org. Chem.* **1997**, *62*, 1299−1304. (b) Chapman, J. J.; Welker, M. E. *Organometallics* **1997**, 7477−755. (c) Adams, T. A.; Welker, M. E.; Day, C. S. *J. Org. Chem.* **1998**, *63*, 3683−3686.

Commercial reagent grade solvents and chemicals were used as received unless otherwise noted. THF was distilled under N_2 from K/benzophenone just prior to use. Pyridine was distilled over CaH_2 at atmospheric pressure and stored over molecular sieves. Pyridinium *p*-toluenesulfonate (PPTS) was purified by recrystallization from acetone. *m*-Chloroperbenzoic acid was purified by washing a chloroform solution with $KH_2PO_4-Na_2HPO_4$ buffer (pH 7.5), drying the organic layer over $MgSO_4$, and then suction filtering, concentrating, and then drying in vacuo. Triphenylmethane was purified by recrystallization from anhydrous ethanol. All reactions involving cobaloximes, which are slightly air-sensitive, were performed in solutions that had been deoxygenated by bubbling N_2 or Ar through a syringe needle through the solutions for 1 min/mL of solvent. For the same reason, solutions of cobaloximes obtained in chromatography were concentrated in vacuo as soon as possible after collection, with the temperature of the water bath during evaporation not exceeding 35 °C. Melting (decomposition) points for metal−1,2-dioxime complexes vary with conditions and therefore are not diagnostic tools.[10] ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ unless otherwise noted. Residual $CHCl_3$ was defined as 7.26 ppm for ^{1}H NMR and the central solvent peak as 77.00 ppm for ^{13}C NMR. Residual acetone was defined as 2.05 and 29.92 ppm, and residual methanol was defined as 3.31 and 49.15 ppm for ^{1}H and ^{13}C spectra, respectively. Alkylcobaloximes have a broad ^{13}C NMR resonance for the carbon attached to the cobalt due to quadrapolar relaxation of the carbon by the cobalt.[11]

2,3-Dihydroxy-3,7-dimethyl-6-octenyl Cobaloxime (1). This compound was previously reported by Pattenden and co-workers, without experimental details.[12] In our procedure $CoCl_2 \cdot 6H_2O$ (1.54 g, 6.46 mmol) was added to deoxygenated MeOH (20 mL) and then dimethylglyoxime (1.50 g, 12.9 mmol), 50% NaOH (1.04 g, 12.9 mmol), and pyridine (0.56 g, 7.04 mmol) were added. The mixture was bubbled with N_2 for 10 min, and the atmosphere above the mixture was then replaced with H_2 (via balloon) and the mixture bubbled with H_2 for 5 more min. A deoxygenated solution of 1,2-epoxylinalool (1.0 g, 5.9 mmol),[13] in MeOH (10 mL) was added dropwise over the course of 1 h. During this addition period, the reaction mixture was stirred at room temperature under H_2, and the pH of the mixture was monitored frequently; 50% NaOH was added dropwise as necessary to maintain a pH > 9. The mixture was also periodically bubbled with H_2 over the course of the addition. The mixture was stirred for 3 h at room temperature and then concentrated in vacuo leaving a brown viscous residue. Three per cent pyridine/H_2O (15 mL) was added to the residue and swirled. The mixture was cooled and the resulting precipitate was collected by suction filtration and rinsed with 3% pyridine/H_2O and 50% Et_2O/ hexane. Removal of solvents in vacuo provided 2.13 g of a yellow powder (67% yield, mp 154−159 °C). The compound which was purified by gravity column chromatography had a mp of 165 °C (dec), the same value as the published data. ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 1.8 H), 1.02 (s, 0.8 H) 1.3 (dt, J = 12, 13.5, 1 H), 1.5−2.4 (m, 3 H), 1.59 (s, 0.6 H), 1.61 (s, 0.4 H), 1.66 (s, 3 H), 2.16 (s, 3 H), 2.64 (d, J = 9.6 Hz, 0.6 H), 2.70 (d, J = 9.6 Hz, 0.4 H), 5.08 (m, 1 H), 7.33 (t, J = 6.9, 2 H), 7.74 (t, J = 7.5, 1 H), 8.55 (d, J = 2 H).

Preparation of 1,2-Epoxy-3-hydroxybutane (6). This compound was previously made by Sharpless.[14,15] The yield of the product was low. To a solution of 3-buten-2-ol (3.6 g, 50 mmol) and of $VO(acac)_2$ (186 mg, 0.14 mmol) in refluxing CH_2Cl_2 (20 mL) was added, dropwise over a period of 1 h, ∼5.26 g (58.4 mmol) of anhydrous *tert*-butyl hydroperoxide. The reaction mixture was refluxed for one more hour and then cooled with ice. To the mixture was added ice-cooled water (20 mL) and then 10% sodium sulfite (1.3 g). The mixture was checked for remaining *tert*-butyl hydroperoxide with a KI-starch paper. The organic layer was washed with water and then dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give the crude epoxide. Gravity column chromatography (CH_2Cl_2) gave 0.44 g of an oil (10% yield). The material was a mixture of diastereomers. ^{1}H NMR ($CDCl_3$) δ 1.24 (dd, J = 0.9, 6.3, 1.95 H), 1.29 (d, J = 6.6, 1.05 H), 2.2 (br s, 1 H), 2.71 (m, 1 H), 2.79 (m, 1 H), 2.95 (m, 0.35 H), 2.99 (m, 0.65 H), 3.58 (quint, 0.35 H), 3.98 (dq, J = 3.3, 6.6, 0.65 H).

Preparation of 1,2-Epoxy-3-hydroxy-3-methylbutane (7). This compound was prepared in the same manner as that for 1,2-epoxylinalool. 2-Methyl-3-buten-2-ol (4.3 g, 50 mmol) and $VO(acac)_2$ (186 mg, 0.7 mmol) were added to methylene chloride (40 mL) and then refluxed. Seventy per cent *tert*-butyl hydroperoxide (9.66 g, 75 mmol) was added dropwise to the mixture over the course of 1.5 h. The mixture was refluxed for 3 h. The resulting solution was washed sequentially with 10% sodium bisulfite solution and water, dried over $MgSO_4$, and concentrated to give the crude epoxide. The crude epoxide was purified by gravity column chromatography (CH_2Cl_2) to give a total of 2.46 g of material (48% yield). ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3H), 1.29 (s, 3 H), 2.10 (br s, 1 H), 2.69 (dd, J = 3.5,5.1, 1 H), 2.77 (dd, J = 2.7, 5.1, 1 H), 2.91 (dd, J = 2.7, 3.5, 1 H).

2,3-Dihydroxypropyl cobaloxime (8). This compound was prepared in the same manner as that for 2,3-dihydroxy-3,7-dimethyl-6-octenyl cobaloxime (**1**). Reaction of glycidol (0.37 g, 5 mmol) with $NaCo(dmgH)_2py$ gave 0.39 g of material (18% yield). Water was added to the concentrated reaction mixture to precipitate the material in this case. Crude material (0.57 g, 26% yield) was recovered from mother liquid by extraction. This compound reacts with even a slight amount of acid. ^{1}H NMR (acid free $CDCl_3$; by filtration through basic alumina) δ 0.95 (t, J = 9.6, 1 H), 1.94 (d, J = 9.6, 1 H), 2.15 (s, 12 H), 3.04 (m, 1 H), 3.35 (m, 2 H), 7.34 (dt, J = 1.2, 6.6, 2 H), 7.75 (dt, J = 1.5, 7.5, 1 H), 8.54 (dd, J = 1.5, 6.6, 2 H). ^{13}C NMR (acid free $CDCl_3$; by filtration through basic alumina) δ 7.73, 25.51, 61.22, 69.94, 120.91, 133.36, 145.233, 146.04. MS (EI and FAB) 443 (M^+), 364 $(M - py)^+$, 289. HRMS calculated for $C_{16}H_{26}N_5O_6Co$ (M^+) 443.12147, found 443.12130.

2,3-Dihydroxybutyl Cobaloxime (Mixture of Diastereomers) (9). This compound was prepared in the same manner as that for 6,7-dihydroxy-2,6-dimethyl-2-octenyl cobaloxime. Reaction of 1,2-epoxy-3-hydroxybutane (0.42 g, 4.77 mmol) with $NaCo(dmgH)_2py$ gave 0.84 g of crude material (38% yield). Water was added to the concentrated reaction mixture to precipitate the material in this case. An analytical sample was obtained by gravity column chromatography (0−7% MeOH/$CHCl_3$). Each diastereomer also was separated by gravity column chromatography. This compound reacts with even a slight amount of acid. ^{1}H NMR (acid free $CDCl_3$; by filtration through basic alumina) δ 1.04 (d, J = 6.3, 3 H + overlapping t, 1 H), 2.08 (d, J = 9.3, 0.65 H), 2.16 (s, 12 H + overlapping d, 0.35 H), 2.57 (dd, J = 7.8, 9.6, 0.35 H), 2.84 (dd, J = 3.3, 9.9, 0.65 H) 3.47 (quint, J = 6.6, 0.35 H), 3.58 (dt, J = 6, 9.3, 0.65 H). ^{13}C NMR (acid free $CDCl_3$; by filtration through basic alumina) δ 7.71. 12.72, 14.65, 24.95 (br), 26.37 (br), 65.21, 65.59, 72.47, 74.71, 120.85, 133.26, 133.29, 145.26, 145.83, 145.87, 145.92. MS (EI and FAB) 458 (M + 1), HRMS calculated for $C_{17}H_{28}N_5O_6Co$ (M^+) 457.13712, found 457.13720. IR (KBr) 3431, 2969, 2902, 2868, 1560, 1444, 1234, 1085, 766, 698, 517.

2,3-Dihydroxybutyl cobaloxime (one diastereomer, small R_f value on TLC) (9): ^{1}H NMR (acid free $CDCl_3$; by filtration through basic alumina) δ 1.00 (t, J = 9.9, 1 H), 1.04 (d, 6.3, 3 H), 2.07 (d, J = 9.9, 1 H), 2.15 (s, 12 H), 2.83 (dd, J = 3, 9.9, 1 H), 3.58 (dt, J = 3, 6.6, 1 H), 7.33 (dt, J = 1.5, 6.6, 2 H), 7.74 (dt, J = 1.5, 7.5, 1 H), 8.54 (dd, J = 1.5, 6.6, 2 H). MS (EI and FAB) 458 (M + 1), 378, 289. HRMS calculated for $C_{17}H_{28}N_5O_6Co$ (M^+) 457.13712, found 457.13720.

2,3-Dihydroxybutyl Cobaloxime (The Other Diastereomer, Large R_f Value on TLC) (9). This compound reacts with even a slight amount of acid. ^{1}H NMR (acid free $CDCl_3$; by filtration through basic alumina) δ 0.93 (t, J = 9.9, 1 H), 1.00 (d, J = 6, 3 H), 2.10 (d, J = 6.6, 1 H), 2.14 (s, 12 H), 2.55 (dd, J = 7.5, 9.3, 1 H), 3.44 (quint, J = 6.6, 1 H), 7.33 (dt, J = 1.2, 7.2, 2 H), 7.74 (dt, J = 1.5, 7.8, 1 H), 8.53 (d, J = 5.1, 2 H). ^{13}C NMR (acid free $CDCl_3$; by filtration through basic alumina) δ 7.70, 12.71, 14.65, 26.36, 65.60, 74.72, 120.87, 133.28, 145.30, 145.88, 145.94. MS (EI) 457 (M^+), 378 $(M - py)^+$, 289. MS

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(FAB) 458 (M + 1), 378 (M − py)$^+$, 289. HRMS calculated for $C_{17}H_{28}N_5O_6Co$ (M^+) 457.13712, found 457.13720. IR (KBr) 3480, 2963, 2910, 2858, 1605, 1561, 1496, 1449, 1374, 1232, 1121, 1089, 1038, 764, 735, 699, 517.

2,3-Dihydroxy-3-methylbutyl cobaloxime (10). This compound was prepared in the same manner as that for 6,7-dihydroxy-2,6-dimethyl-2-octenyl cobaloxime. Reaction of 1,2-epoxy-3-hydroxy-3-methylbutane (0.77 g, 7.61 mmol) with $NaCo(dmgH)_2py$ gave 1.46 g of material (41% yield). Water was added to the concentrated reaction mixture to precipitate the material in this case. An analytical sample was obtained by preparative TLC. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3 H + overlapping 1 H), 0.98 (s, 3 H), 2.05 (overlapping d, J = 9.6, 1H), 2.10 (s, 12 H), 2.55 (d, J = 9.6, 1 H), 7.29 (t, J = 6.9, 2 H), 7.71 (t, J = 6.9, 2 H), 8.48 (d, J = 4.5, 1 H). ^{13}C NMR ($CDCl_3$) d 7.66, 7.70, 18.53, 21.60, 25.50 (br), 67.40, 76.18, 120.85, 133.29, 145.26, 145.72, 145.79. MS (EI and FAB) 472 (M + 1), 392 (M − py), 289. HRMS calculated for $C_{18}H_{31}N_5O_6Co$ (M + 1) 472.16059, found 472.16060. IR (KBr) 3482, 2971, 2911, 1606, 1560, 1449, 1375, 1232, 1087, 972, 950, 764,701, 515.

Representative General Procedure of Kinetic Study on Quantitative Analysis of *β*-Hydroxy Cobaloxime. 2,3-Dihydroxypropyl cobaloxime **8** (10.0 mg, 0.0226 mmol), pyridinium *p*-toluenesulfonate (5.7 mg, 0.0227 mmol), and triphenylmethane (5.4 mg, 0.0221 mmol) were placed in an NMR tube. The tube was fitted with a rubber septum and purged with Ar. CD_3OD (2 mL) was deoxygenated by bubbling with Ar for >1 min/mL, and then 0.5 mL of this was added to the NMR tube containing the reactants. For reactions using $CDCl_3$, the solvent (2 mL) was passed through neutral alumina and deoxygenated by bubbling with Ar for >1 min/mL, and then 0.5 mL of this was added to the NMR tube containing the reactants. The tube was then purged with Ar and vortexed, and then the septum was covered with Parafilm. The tube could then be sealed or left unsealed, but protected with Parafilm and protected from ambient light. The spectra of the sample solution were taken at appropriate intervals after solvent addition: during the initial 2 h at about 15 or 20 min intervals, and then at approximately 1 h intervals. The relative amount of cobaloxime remaining at a given time was measured by analyzing the cobaloxime peak at δ 2.13 (12 H) compared to the Ph_3CH peak at δ 5.56 (1 H) used as an internal integration standard. As a control, the stability of a mixture solution of cobaloxime and Ph_3CH was measured in a same procedure without adding PPTS.

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