Inorg. Chem. **2005**, *44*, 5483–5494

Methyl Transfer from $CH_3Co^{III}Pc$ to Thiophenoxides Revisited: Remote Substituent Effect on the Rates

Wlodzimierz Galezowski*

Department of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznan, Poland

Received March 4, 2005

A two-step mechanism of the reaction of $CH_3Co^{III}Pc$ (Pc = dianion of phthalocyanine) with thiophenoxides in DMA has been confirmed, and the visible spectrum of the inactive transient, $CH_3Co^{III}Pc(SAr)^-$, has been determined. Rapid rates for ligation of $CH_3Co^{III}Pc$, yielding $CH_3Co^{III}Pc(S–C_6H_4–X)^-$, are virtually independent of X; this step proceeds probably by an I_d mechanism. Kinetic data for the follow-up methyl-transfer step yield second-order rate constants and stability constants for $CH_3Co^{III}Pc(S–C_6H_4–X)^-$ consistent with those estimated from concentration dependence of the amplitude of the ligand-exchange step. Cyclic voltammetry provides first reduction potential for $CH_3Co^{III}Pc(DMA)$ of –1.42 V vs Fc^+/Fc, which makes an OSET mechanism unlikely. Homolytic decay of $CH_3Co^{III}Pc(SAr)^-$ has also been ruled out. All of the kinetic data, including Hammett's $\rho = -2.3 \pm 0.1$, N-donor inhibition, and alkyl group effect, Me > Et, indicate that the reaction is a normal S_N2 methyl transfer, only very fast. Methyl transfer to aliphatic thiolates is also rapid and follows the same S_N2 mechanism. Exceptional methyl-transfer reactivity of the phthalocyanine model sharply contrasting with the inertness of methylcobaloxime is explained.

Introduction

Thiolates are the most common methyl acceptors in enzymatic methyl transfers. Methionine synthase catalyzed methyl transfer from methylcobalamin (MeCbl)[1] to homocysteine has been the most studied enzymatic methyl-transfer reaction for decades.[2] This reaction has also been referred to as "difficult", since in the absence of the protein, it proceeds extremely slowly. As shown by Norris and Pratt, methylcobinamide ($MeCbi^+$) is a substantially more effective methyl donor than MeCbl.[3] However, most of the enzymatic enhancement occurs in the homocysteine-binding module of the enzyme, and mechanisms other than the initially proposed S_N2 have also been recently discussed.[2] Methyl transfer from the leading MeCbl model, methylcobaloxime, to thiolates has been controversial. While Schrauzer and Stadlauber reported some kinetic data,[4] especially for the BF_2-containing methylcobaloxime, Brown and Kallen[5] and later Marzilli et al.,[6] claimed virtually complete inertness of the Co−C bond toward nucleophilic attack. Isolation of thiolate adducts with methylcobaloxime was possible with virtually no loss of the cobalt-bonded methyl group.[6]

Recent studies on axial base inhibition of methyl transfer from methylcobalt(III) phthalocyanine ($CH_3Co^{III}Pc$) suggest that any trans axial ligation results in alkyl-transfer inactivity of the organocobalt(III) substrate.[7] (Examples of heterolytic Co−C bond cleavage in six-coordinate complexes such as $AdoCbl(CN)^-$ [8] cannot be classified as alkyl (formally cation) transfers.) Alkanethiolates do not coordinate to the cobalt center in methylcorrinoids.[3,9,10] This certainly makes the demethylation of $MeCbi^+$ easier. In contrast, methylcobaloximes and methylated Costa-type models show very strong demand for six-coordination.[11] These electron-

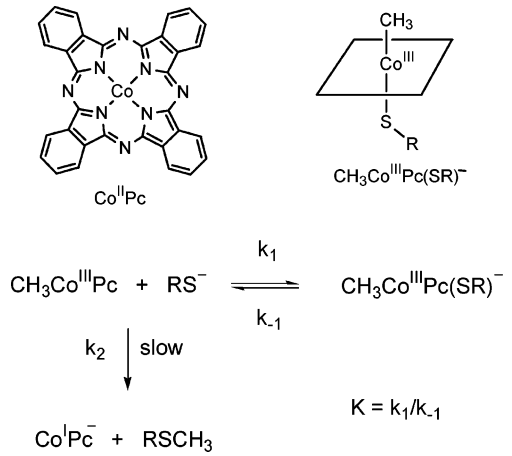
* E-mail: wlodgal@amu.edu.pl

(1) Abbreviations: Pc, dianion of phthalocyanine; MeCbl, methylcobalamin; $MeCbi^+$, methylcobinamide; Ado, adenosyl; DMA, dimethylacetamide; DMSO, dimethyl sulfoxide; DBU, 1,8-diazabicyclo[5.4.0]-undec-7-ene; TBAP, tetrabutylammonium perchlorate; TPP, dianion of 5,10,15,20-tetraphenylporphyrin.

(2) Matthews, R. G. *Acc. Chem. Res.* **2001**, *34*, 681.
(3) Norris, P. R.; Pratt, J. M. *BioFactors* **1996**, *5*, 240.
(4) Schrauzer, G. N.; Stadlauber, E. A. *Bioinorg. Chem.* **1974**, *3*, 353.
(5) Brown, K. L.; Kallen, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 1894.
(6) Polson, S. M.; Hansen, L.; Marzilli, L. G. *Inorg. Chem.* **1997**, *36*, 307.
(7) Galezowski, W. *Inorg. Chem.* **2005**, *44*, 1530.
(8) Brasch, N. E.; Haupt, R. J. *Inorg. Chem.* **2000**, *39*, 5469.
(9) Hogenkamp, H. P. C.; Bratt, G. T.; Kotchevar, A. T. *Biochemistry* **1987**, *26*, 4723.
(10) (a) Garr, C. D.; Sirovatka, J. M.; Finke, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 11142. (b) Garr, C. D.; Sirovatka, J. M.; Finke, R. G. *Inorg. Chem.* **1996**, *35*, 5912.
(11) Marzilli, L. G.; Summers, M. F.; Bresciani-Pahor, N.; Zangrando, E.; Charland, J.-P.; Randaccio, L. *J. Am. Chem. Soc.* **1985**, *107*, 6880 and references therein.

10.1021/ic0503378 CCC: $30.25
Published on Web 06/25/2005

Scheme 1. Methyl Transfer from $CH_3Co^{III}Pc$ to Thiolates (S_N2 Mechanism)[a]



[a] In this scheme, no distinction is made between $CH_3Co^{III}Pc$, possibly the actual reactive species, and inactive $CH_3Co^{III}Pc(DMA)$. The two forms exist in rapid equilibrium.

deficient complexes are not as good CH_3^+ donors as expected. An intermediate strength Lewis acid, CH_3Co^{III}-Pc,[7] showed, in turn, an outstanding methyl-transfer ability toward benzenethiolate,[12] despite postulated extensive ligation of the substrate (Scheme 1). The methyl transfer is so fast that the thiophenoxide adduct cannot be isolated and conventional ligand binding studies are not viable.

In accordance with other binding nucleophiles,[7] atypical (for S_N2) saturation-type concentration dependencies of the rate constants are observed in the thiophenoxide reaction. Similar saturation-type kinetics caused by strong affinity of thiolates for the cobalt center in phthalocyanine complexes has also been seen in the reactions of Co(II) tetrasulfophthalocyanine with thiolates in water[13] and DMF.[14] This is likely to be observed no matter if the adduct or ligand-free substrate is the reactive species.

In view of the inertness of $MeCbi^+$ and methylcobaloxime toward alkanethiolates, one may also suspect that fast methyl-transfer rates between $CH_3Co^{III}Pc$ and benzenethiolate result from some specific features of aromatic thiolates. Displacement reactions promoted by aromatic thianions are usually faster than those of aliphatic thiolates of similar basicity, which used to be explained either by favorable interaction of the aromatic ring with the substrate or by the fact that aromatic thiolates are "softer".[15] As thiolates are not only excellent nucleophiles but also good electron donors, mechanisms involving outer- or inner-sphere electron transfer should also be considered.[16]

Rapid rates for demethylation of the phthalocyanine model may seem to present a wild exception among extremely slow thiolate reactions of MeB_{12} and related complexes. Therefore, a more detailed study of this system seems warranted. The spectrum of the transient $CH_3Co^{III}Pc(SPh)^-$, which has not been reported yet, is of interest, as well as possible changes in this spectrum with varying electron-donation properties of the thiolate. Remote substituent effect on the reaction spectra and the rates should provide a deeper insight into the mechanism, and perhaps some of the mechanistic alternatives to S_N2 can be ruled out. It seems worthwhile to study whether the alkyl group effect, Me > Et, and N-donor inhibition observed for the dealkylations of $RCo^{III}Pc$ with variety of nucleophiles[7] will also hold for the thiolate reaction.

The methyl-transfer reactions from $CH_3Co^{III}Pc$ to thiolates bear no immediate relevance to biological systems, where the equatorial system is different, but they are probably the most rapid nonenzymatic methyl transfers from methylcobalt(III) known. It is of importance to gain more confidence that these fast reactions, in fact as fast as enzymatic methyl transfer from MeCbl to homocysteine,[17] really are S_N2 processes.

Experimental Section

Materials. $CH_3Co^{III}Pc$ and $CH_3CH_2Co^{III}Pc$ were prepared as described earlier,[7] and their solutions were handled in dim light. All of the chemicals were purchased from Aldrich. Dimethylacetamide (DMA) was purified and stored as described elsewhere.[12] Liquid thiols were freshly vacuum distilled and kept under argon. 4-Nitrobenzenethiol was sublimed under reduced pressure, which substantially improved its purity. In conformity with the earlier study,[12] sodium benzenethiolates were used. The salts were prepared as described earlier for sodium thiophenoxide.[12] *N*-Methylimidazole (*N*-MeIm) (double distilled) was used without further purification.

Rate Measurements. The rates were determined spectrophotometrically in excess thiolate. All of the stopped-flow runs were performed on an Applied Photophysics SX.17 MV instrument under anaerobic conditions. Before measurements, the circulating liquid, in which the drive syringes were immersed, was deoxygenated with argon, then a portion of sodium thiosulfate/Tris buffer was added. An aqueous solution of the same mixture was passed through the instrument before measurements to remove possible traces of oxidants and followed by rinsing with deoxygenated DMA. Extreme care was exercised to avoid air oxidation of dilute thiolate solutions, which were always freshly prepared under argon and anaerobically transferred to the drive syringes. Effectiveness of these measures was tested by using thiophenoxide dissolved in sodium borohydride (0.0005 M) solution, which should eliminate disulfides. The rates were similar to those obtained in the absence of borohydride. Co^IPc^- was formed regardless of the presence of borohydride. When a 0.0005 M sodium borohydride solution is combined with CH_3Co^{III}-Pc in a stopped flow, a relatively slow demethylation is observed which could, in part, result from photochemical cleavage of the Co−C bond. (Solutions of concentrated mixtures of $CH_3Co^{III}Pc$ and Co^IPc^- in DMSO-d_6 in the presence of sodium borohydride are stable in the dark for a prolonged period of time.)

All of the kinetic measurements were performed under pseudo-first-order conditions in excess nucleophile and/or ligand, if applicable. The concentration of the organocobalt complex was $\sim 1 \times 10^{-5}$ M. In regular kinetic measurements, the rates were measured mainly at two wavelengths, 660 nm (substrate decay) and 700 nm (the absorption band of the Co^IPc^- product). The rates for the slower second (alkyl transfer) step measured at 660 nm were larger than

(12) Galezowski, W.; Lewis, E. S. *J. Phys. Org. Chem.* **1994**, *7*, 90.
(13) Leung, P. S.; Hoffmann, M. R. *J. Phys. Chem.* **1989**, *93*, 434.
(14) Tyapochkin, E. M.; Kozliak, E. I. *J. Porphyrins Phthalocyanines* **2001**, *5*, 405.
(15) Freter, R.; Pohl, E. R.; Wilson, J. M.; Hupe, D. J. *J. Org. Chem.* **1979**, *44*, 1771.
(16) Lewis, E. S. *J. Am. Chem. Soc.* **1989**, *111*, 7576 and references therein.
(17) Bandarian, V.; Matthews, R. G. *Biochemistry* **2001**, *40*, 5056.

those determined at 700 nm, unless the illuminating light intensity had been appropriately reduced. Photolability of $CH_3Co^{III}Pc$ has been noted earlier. In dilute solutions of basic thiophenoxide, double exponential curves were observed. At [thiolate] > 0.002 M, the first rapid step was beyond the stopped-flow range. (See examples of kinetic curves and end-point plots in Supporting Information). The observed rate constants were found from nonlinear least-squares fits using the Applied Photophysics software. Double-exponential fits were not necessary, because the time scales for the two processes, rapid ligand binding and slower alkyl transfer, were so different.

The formation constant, *K*, was determined from the concentration dependence of the end-point, *A*, of the fast step (absorbance drop at 660 nm) as a ratio intercept/slope of the linear dependence of $1/(A_o - A)$ vs 1/[thiolate], where A_o is the absorbance of $CH_3Co^{III}Pc$ with no thiolate present (see Figure S6, Supporting Information). Point-by-point reaction spectra were obtained from kinetic runs. The wavelength was changed every 2 nm in the region of the absorption bands, especially around the sharp Q-band (about 660 nm). Reproducibility of kinetic runs acquired on the Applied Photophysics instrument was fairly good as witnessed by the transient spectra determined for a reaction time as short as 10 ms. Absorbance of thiolates obscured the spectral region below 360 nm. Red solutions of 4-nitrobenzenethiolate did not allow for the determination of the reaction spectra at wavelengths <600 nm. The 700 nm band of $Co^{I}Pc^{-}$ formed in the 4-nitrobenzenethiolate reaction disappeared in a slow process, which was, however, considerably faster in concentrated solutions of the nucleophile and would complicate determination of the rate for methyl transfer at concentrations >0.02 M. A similar slow process was also observed in concentrated solutions of 3,4-dichlorothiophenoxide, yielding a mixed spectrum of $Co^{I}Pc^{-}$ and probably $Co^{II}Pc(3,4\text{-}Cl_2C_6H_3S)$ (λ_{max} = 672 nm and a 530 nm charge-transfer band); the latter was identical with the spectrum of the product of $Co^{II}Pc$ with 3,4-$Cl_2C_6H_3SNa$ in air. These slow secondary reactions did not interfere with the determination of the methyl transfer rates and were not further studied.

In pseudo-first-order conditions, there is always a possibility that some other nucleophiles exist in solution, either impurities or possible solvolysis products, but none of them could compete with thiolates, especially in view of the high yields of thioethers. Pseudo-first-order conditions are favorable here, with potential impurities less reactive than thiolates. An important point is that in neutral solution, $RCo^{III}Pc$ complexes are stable in the presence of disulfides or thiols at least for an hour. Disulfides, even in trace quantities, according to Hogenkamp,[18] can react with cob(I)alamin to give the Co(II) complex and thiolate ion. In the phthalocyanine system, in excess of strongly basic thiolates, this could not be observed since $Co^{II}Pc$ is readily reduced by them. With less basic 4-NO_2-thiophenoxide, a slow follow-up oxidation is possible (see above). The major concern was the possible loss of thiolate. The control runs with borohydride showed that oxidation was not a substantial problem. Occasionally, DBU was added to thiophenoxide solutions to revert possible protolysis of the thiolate by traces of water, but this had little effect on the rates.

Kinetics of cyanide binding by $CH_3Co^{III}Pc$ was measured by monitoring the rise in absorbance at 508 nm. Teterabutylammonium cyanide was used.

Cyclic voltammetry was carried out as described elsewhere.[7] The potentials were internally referenced to Fc^{+}/Fc couple (+0.47 V vs SCE in DMA).[19]

(18) Hogenkamp, H. P. C.; Bratt, G. T.; Sun, S. *Biochemistry* **1985**, *24*, 6428.

Table 1. Yields of Light Hydrocarbon Products of the Reactions of $RCo^{III}Pc$ with Thiophenoxides and Bromide in DMA

		yield (%)		
R	nucleophile	CH_4	$CH_2{=}CH_2$	CH_3CH_3
CH_3	PhSNa	0.07	0.28	0.04
CH_3CH_2	PhSNa	traces	1.8	0.2
CH_3	2,6-$Cl_2C_6H_3SNa$	0.003	0.6	0.2
CH_3CH_2	2,6-$Cl_2C_6H_3SNa$	traces	0.5	0.08
CH_3	Bu_4NBr[a]	0.04	0.34	0.03

[a] 0.03 M, 24 h, at room temperature.

Conductances of sodium salts of thiophenoxides were measured as described elsewhere,[7] with the exclusion of air.

Product Studies. The reactions of $CH_3Co^{III}Pc$ or $CH_3CH_2Co^{III}Pc$ with thiophenoxides always gave $Co^{I}Pc^{-}$ and thioethers, in good yield, within seconds. The thioether products were identified either by GC as described earlier for thioanisole[12] or by ^1H NMR spectra in a DMSO-d_6 solution. For selected thiolates, the gas phase over solution was GC analyzed for light hydrocarbons as described elsewhere.[7] An example of such an assay is given below, and the results are collected in Table 1.

$CH_3CH_2Co^{III}Pc$ with PhSNa in DMA. A solution of $CH_3CH_2Co^{III}Pc$ (12 mg, 0.02 mmol) and PhSNa (60 mg, 0.45 mmol) in 10 mL of DMA was sealed in a vial under argon in the dark. The solution turned yellow-green. GC analysis of the gas phase[7] gave ethylene (1.8%) and ethane (0.2%).

Results and Discussion

Cyclic Voltammograms. Cyclic voltammograms of $CH_3Co^{III}Pc$ in DMA are similar to those measured in DMF.[7] The only difference of interest is the behavior of the first reduction peak at −1.42 V, $(E_{pc} - E_{pa})/2$, vs Fc^{+}/Fc couple (Figure 1), which at a scan rate of 0.1 V/s is irreversible but at about 10 V/s (20 ± 1 °C) reaches quasi-reversibility ($E_{pc} - E_{pa}$ > 60 mV). A new oxidation peak, the potential of which agrees with that for the oxidation of $Co^{I}Pc^{-}$, is observed on reverse sweep only when $CH_3Co^{III}Pc$ has been reduced. This peak is most pronounced at intermediate scan rates. Analysis of voltammograms measured at varied scan rates[20] gives a rate constant of 2.8 ± 0.6 s^{-1} at 20 ± 1 °C for unimolecular Co−C bond cleavage in $[CH_3CoPc]^{-}$, yielding $Co^{I}Pc^{-}$ and presumably a methyl radical.[21] At ambient temperatures and scan rates up to 50 V/s, the first reduction of $CH_3CH_2Co^{III}Pc$ still remains irreversible. No convincing explanation for the larger stability of $[CH_3CoPc]^{-}$ in DMA than in DMF[7] is offered.

The increased stability of $[CH_3CoPc]^{-}$ compared with one-electron reduced methylcorrinoids, which give reversible voltammograms only at low temperatures and high sweep

(19) Lever, A. B. P.; Milaeva, E. R.; Speier, G. In *Phthalocyanines, Properties and Applications*; Leznoff, C. C., Lever A. B. P., Eds.; Wiley-VCH: New York, 1993; Vol 3, p 8.

(20) Heinze, J. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 831.

(21) Interestingly, a rate constant of 3 ± 1 s^{-1} was measured for a unimolecular decomposition of transient species formed in the reaction of Co(II) tetrasulfophthalocyanine, $Co^{II}(TSPc)^{4-}$, with methyl radicals by Sorek, Y.; Cohen, H.; Meyerstein, D. *J. Chem. Soc., Faraday Trans. I* **1989**, *85*, 1169. This rate constant was tentatively ascribed to the homolytic decay of $[CH_3Co^{III}(TSPc)]^{4-}$, which in view of infinite stability of $CH_3Co^{III}Pc$ is extremely unlikely. However, if one-electron-reduced $[CH_3Co^{III}(TSPc)]^{4-}$ was the transient, the rate would be consistent with the findings of the present work.

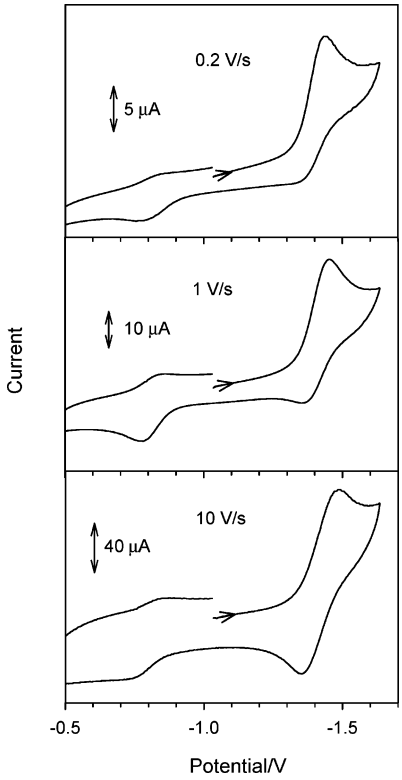


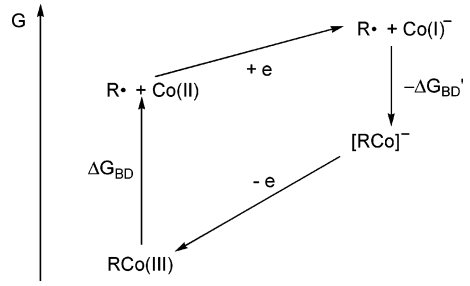
Figure 1. Cyclic voltammograms for $CH_3Co^{III}Pc$ in DMA. Potentials vs Fc^+/Fc couple measured at a platinum electrode, $[CH_3Co^{III}Pc] = 2 \times 10^{-4}$ M and [TBAP] = 0.2 M.

rates,[22] seems to be consistent with electron deficiency of the phthalocyanine model. The first reduction potentials for MeCbl are 0.65,[22] 0.55, or 0.29 V (base-off MeCbl)[23] more negative than that for CH_3CoPc. However, no simple correlation with the reduction potentials exists, even among porphyrinic models. For instance, the anion radical of $CH_3Co(TPP)$ is quite stable in CH_2Cl_2 at room temperature, scan rate 0.1 V/s,[24] but not in DMSO; [25] it is more stable than $[CH_3CoPc]^-$, characterized by a ~0.4 V less negative redox potential. Even though it is intuitively appealing that Co−C bonds in easier reduced complexes will be more stable, the reduction potential for RCo^{III}(chel) itself cannot be directly related to Co−C bond cleavage. As follows from a thermodynamic cycle depicted in Scheme 2, the lowering of the free energy of Co−C bond dissociation in the anion radical, $\Delta G_{BD}'$, relative to ΔG_{BD} for the parent complex, is proportional to the gap in the reduction potentials (eq 1, where F is the Faraday constant).

$$\Delta G_{BD}' = \Delta G_{BD} + F(E^{o}_{RCo(III)/[RCo]^-} - E^{o}_{Co(II)/Co(I)}) \quad (1)$$

If we replaced $\Delta G_{BD}'$ and ΔG_{BD} with $\Delta G_{BD}^{\ddagger\prime}$ and $\Delta G_{BD}^{\ddagger}$,[26] respectively, which for the two analogous endoergic processes may not be an unreasonable approximation, eq 1 would not predict any conspicuous lability of the MeCbl anion radical. The shift in reduction potentials between MeCbl and cob(II)alamin, 0.75 V (Savéant's data), is larger than that of ~0.6 V for the phthalocyanine or TPP model, a difference that corresponds to a noticeable 3.5 kcal/mol lowering of the free energy barrier, which would be, however, canceled by the larger $\Delta G_{BD}^{\ddagger}$ value for homolysis of MeCbl[27] than $CH_3Co(TPP)$[28] or CH_3CoPc. Perhaps the above analysis fails to explain the lability of the MeCbl anion radical because of crude assumptions, uncertainty in redox potentials measured in different solvents, or differences in trapping conditions[27] and trans ligation.

Scheme 2. Thermodynamic Cycle Showing the Relationship between Co−C Bond Dissociation Free Energies in an Alkylcobalt(III) Complex and Corresponding Anion Radical



One important stabilizing factor may be the delocalization of the extra charge in the one-electron-reduced species. We could speculate that large, conjugated equatorial ligands such as phthalocyanine should diminish excess electron density in the axial system more efficiently than corrin. However, recently, Brunold's DFT calculations[29] cast doubt on the belief[27,30] that the lowest unoccupied molecular orbital (LUMO) in alkylcorrinoids has a substantial Co−C antibonding character. The fact that the LUMO has negligible contribution from Co atomic orbitals as well as those of the axial alkyl group agrees with the tendency of $CH_3Co(TPP)$ to form a ligand-centered anion radical rather than the Co(II) complex.[24] Nevertheless, possible correlation with the size of the equatorial conjugated arrangement is still worth consideration, because activation energy of the Co−C bond cleavage in the anion radical may be correlated to an intramolecular charge transfer from the ligand-centered π orbital, occupied by the odd electron, to a higher energy Co−C antibonding orbital. Since, in systems with enlarged, planar, conjugated systems energy of the former orbital will be lowered, relative to that of the latter, faster decay of one-electron reduced alkylcorrinoids than their phthalocyanine or TPP congeners could be accounted for.

Reaction Spectra. The reaction spectra shown in Figure 2 are representative of all of the strongly basic thiophenoxides (4-CH_3O, 4-CH_3, H, and 4-Cl derivatives). Within milliseconds, an equilibrium between the substrate and the transient is established (Scheme 1). The amplitude of the

(22) Lexa, D.; Savéant, J.-M. *J. Am. Chem. Soc.* **1978**, *100*, 3220.
(23) Kim, M.-H.; Birke, R. L. *J. Electroanal. Chem.* **1983**, *144*, 331.
(24) Kadish, K. M.; Han, B. C.; Endo, A. *Inorg. Chem.* **1991**, *30*, 4502.
(25) Fauvet, M. P.; Gaudemer, A.; Bouckly, P.; Devynck, J. *J. Organomet. Chem.* **1976**, *120*, 439.
(26) In fact, we assume here only that $\Delta G_{BD}^{\ddagger} - \Delta G_{BD} = \Delta G_{BD}^{\ddagger\prime} - \Delta G_{BD}'$, that is, equal free energy barriers for reverse reactions.
(27) Martin, B. D.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 585.
(28) Fukuzumi, S.; Miyamoto, K.; Suenobu, T.; Van Caemelbecke, E.; Kadish, K. M. *J. Am. Chem. Soc.* **1998**, *120*, 2880.
(29) Stich, T. A.; Brooks, A. J.; Buan, N. R.; Brunold, T. C. *J. Am. Chem. Soc.* **2003**, *125*, 5897.
(30) (a) Rubinson, K. A.; Itabashi, E.; Mark, H. B. *Inorg. Chem.* **1982**, *21*, 3571. (b) Rubinson, K. A.; Parekh, H. V.; Itabashi, E.; Mark, H. B. *Inorg. Chem.* **1983**, *22*, 458.

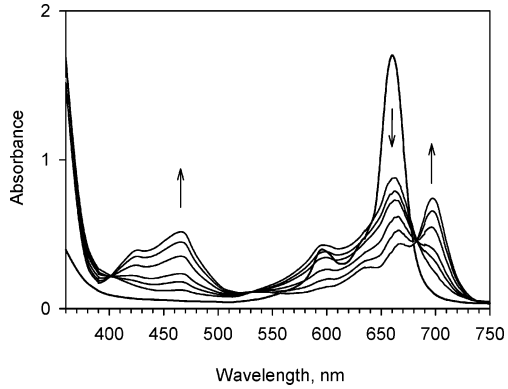


Figure 2. Reaction spectra of $CH_3Co^{III}Pc$ with 4-$CH_3C_6H_4SNa$ in DMA 25 °C for 0, 0.0125, 0.1, 0.2, 0.5, 1, and 5 s, [4-$CH_3C_6H_4SNa$] = 0.005 M and [$CH_3Co^{III}Pc$] = 1×10^{-5} M.

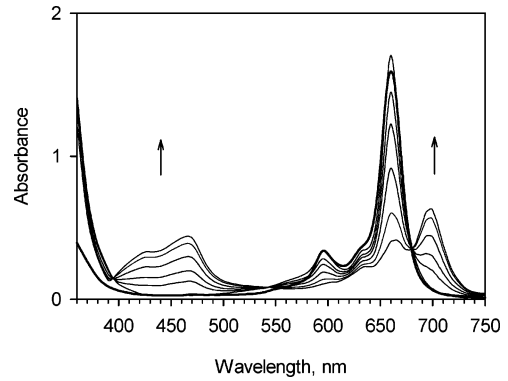


Figure 3. Reaction spectra of $CH_3Co^{III}Pc$ with 2,6-$Cl_2C_6H_3SNa$ in DMA 25 °C for 0 (thick line), 0.0125, 0.25, 0.5, 1, 2, and 5 s, [2,6-$Cl_2C_6H_3SNa$] = 0.005 M and [$CH_3Co^{III}Pc$] = 1×10^{-5} M.

spectral change accompanying the initial fast reaction is thianion concentration dependent, and the rates are first order in the thianion (see Tables S1−S5 in Supporting Information). Visible spectra of the transient species do not vary significantly as the remote substituent is changed from the electron-donating 4-CH_3O to the moderately electron-withdrawing 4-Cl. Both the Q-band at 660 nm and the ~600 nm overtone are very broad (Figure 2). There is no marked metal to (equatorial) ligand charge-transfer band, associated with the Co^{I} oxidation state, in the spectra of the transient species. These spectra are, however, unlike those of the other $RCo^{III}Pc(L)$ complexes.[7] As a matter of fact, they resemble the spectrum of $Co^{II}Pc(DMA)$, only the Q-band appears less intense at its maximum and broader. The spectra of the follow-up process exhibit three clean isosbestic points, thus indicating there are no further mechanistic complications. Regardless of the basicity of the thiolate, the final spectrum is always that of $Co^{I}Pc^{-}$.

In accordance with our earlier observations,[12] the 684 nm isosbestic point is different from that for $CH_3Co^{III}Pc$ and $Co^{I}Pc^{-}$ at 678 nm (Figure 2). Also, two other isosbestic points do not include the spectrum of the substrate. By contrast, with the less basic and more sterically hindered 2,6-dichlorothiophenoxide, the initial change in 660 nm absorbance is small (Figure 3). The Q-band intensity initially even slightly rises with a cosmetic red shift. The spectrum is not exactly that of the **2,6-Cl_2**[31] complex, since at 0.005 M thiolate $CH_3Co^{III}Pc(DMA)$ prevails,[32] but it is clear that the

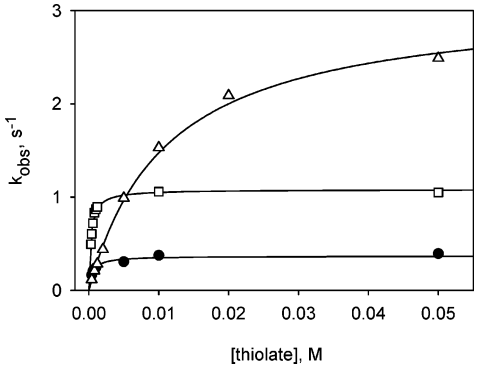
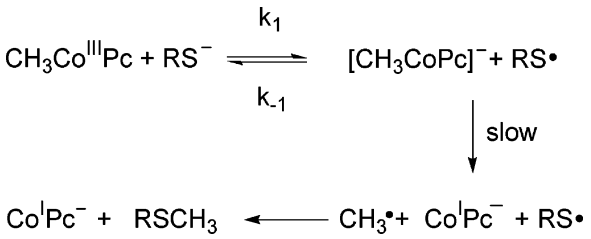


Figure 4. Representative concentration dependencies of k_{obs} for the methyl-transfer step of the reactions of $CH_3Co^{III}Pc$ with thiophenoxides in DMA (25 °C): 2,6-dichloro- (triangles), 4-chloro- (squares), and 3,4-dichloro-thiophenoxide (dots).

Scheme 3. Outer-Sphere Electron-Transfer Mechanism for Demethylation of $CH_3Co^{III}Pc$ by Thiolates



Q-band in the spectrum of $CH_3Co^{III}Pc$(**2,6-Cl_2**) must be similar to that of $CH_3Co^{III}Pc(DMA)$, a situation previously observed in DMA with N-donor axial bases.[7] It seems plausible that with strongly electron-withdrawing substituents on the phenyl ring, the spectra of the adducts are "normal", that is, similar to those of the other $CH_3Co^{III}Pc(L)$ complexes. However, as the substituent becomes increasingly electron donating the Q-band loses its maximum intensity and broadens, possibly because of a charge transfer within the complex. Finally, the transient spectra characterized by broad Q-bands might be those of $[CH_3CoPc]^{-}$ anion radical produced via OSET (Scheme 3). This, however, in view of large differences in redox potentials (>0.9 V) between thiophenoxides[33] and $RCo^{III}Pc$ appears unlikely.

Concentration dependencies of the rates for alkyl-transfer reactions exhibit saturation (Figure 4). A trivial explanation for this would be an ion association of sodium thiophenoxides, provided the ion pairs were inactive or at least far less reactive than free ions. Ion association of sodium thiophenoxide in four solvents, including polar aprotic DMF, has been studied by Westaway et al.[34] Different reactivity of free thiophenoxide ions and solvent-separated ion pairs toward *n*-butyl chloride was found with free ions only 10−20% more reactive than solvent-separated ion pairs. Such a moderate difference would not account for the strong curvatures seen in Figure 4. Furthermore, in DMF, which is

(31) The substituted thiophenoxides will be hereafter labeled by bold designations of the substituents.
(32) The [$CH_3Co^{III}Pc$(**2,6-Cl_2**)$^{-}$]/[$CH_3Co^{III}Pc$] ratio, calculated for [**2,6-Cl_2**] = 0.005 M using the *K* value of Table 2, is 0.41.
(33) (a) Andrieux, C. P.; Hapiot, P.; Pinson, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1993**, *115*, 7783. (b) Larsen, A. G.; Holm, A. H.; Roberson, M.; Daasbjerg, K. *J. Am. Chem. Soc.* **2001**, *123*, 1723.
(34) Westaway, K. C.; Lai, Z. G. *Can. J. Chem.* **1988**, *66*, 1263.

Table 2. Kinetic Data for the Reaction of $CH_3Co^{III}Pc$ with Thiophenoxides in DMA (25 °C)

	methyl transfer			ligand binding		
substituent	k_2, $M^{-1}s^{-1}$ [a]	K, M^{-1} [a]	k_2/K, s^{-1} [b]	$10^{-6}k_1$, $M^{-1}s^{-1}$ [f]	K, M^{-1} [g]	k_{-1}, s^{-1} [h]
4-NO_2	81 ± 2	70 ± 10[e]	1.1 ± 0.1[e]			
2,6-Cl_2	255 ± 4	77 ± 7	3.7 ± 0.4			
3,4-Cl_2	750 ± 40	2100 ± 200	0.36 ± 0.01	1.2 ± 0.2	1700 ± 300	700 ± 100
4-Cl	3100 ± 200	2600 ± 100	1.19 ± 0.03	0.79 ± 0.04	2400 ± 100	330 ± 20
H	20000 ± 1000	10100 ± 700	1.97 ± 0.03	0.84 ± 0.08	13000 ± 2000	65 ± 6
	17900[c]	9400[c]	1.91 ± 0.02[c]			
4-Me	43000 ± 5000	23000 ± 3000	1.89 ± 0.02	0.79 ± 0.03	27000 ± 3000	29 ± 1
4-MeO	*d*	*d*	1.06 ± 0.03	0.9 ± 0.1	53000 ± 9000	17 ± 2

[a] Determined by eq 2. [b] Saturated k_{obs}. [c] Results from ref 12. [d] Not determined, because kinetic saturation was achieved at too low a concentration of the nucleophile. [e] These values from a nonlinear least-squares fit. [f] The rate constant for presumed thiolate binding to Co. [g] Stability constant for $CH_3Co^{III}Pc(SR)^-$, estimated from concentration dependence of a pre-methyl-transfer drop in 660 nm absorbance. [h] Rate constant for thiolate liberation from $CH_3Co^{III}Pc(SR)^-$, calculated from k_1 and K.

in many respects similar to DMA, ion association was visible for concentrations above 7×10^{-3} M. An interaction that weak could not disturb this kinetic study even if free ions were considerably more reactive than ion pairs. Nevertheless, conductivity of sodium thiophenoxide and sodium 4-chlorothiophenoxide in DMA was studied over the concentration ranges used in the stopped-flow runs, and no indication of ion association was detected. With the two selected thiophenoxides, the k_{obs} values are close to saturation above 1×10^{-3} M, while the conductances grow almost linearly at least up to 1×10^{-2} M. The Kohlrausch plots of Λ vs $c^{1/2}$ gave Λ_o values of 42.4 ± 0.3 and 43.7 ± 0.6 Ω^{-1} cm^2 mol^{-1} at 25 °C for C_6H_5SNa and 4-Cl$-C_6H_4SNa$, respectively, and the slopes close to the theoretical values (see the plots in Supporting Information).

Because of the instability of dilute thiophenoxide solutions, saturated k_{obs} values (k_2/K in Table 2) are clearly the most accurately determined kinetic parameters for the reactions promoted by the most basic thiophenoxides. The observed concentration dependence of the rates (Figure 4) is consistent with the previously proposed mechanism involving a prior equilibrium leading into a cul-de-sac (Scheme 1). The second-order rate constant for methyl transfer, k_2, and formation constant for the inert $CH_3Co^{III}Pc(SR)$ complex, K, can be found from a double reciprocal plot,[7] eq 2 (Figure 5B).

$$\frac{1}{k_{obs}} = \frac{1}{k_2[RS^-]} + \frac{K}{k_2} \qquad (2)$$

The relatively small variance of the saturated k_{obs} (the k_2/K column in Table 2) is conspicuous. While it could raise suspicions that mechanisms other than S_N2 are involved, it can also be explained by almost proportional changes of k_2 and K. Besides, the apparent invariance cannot be readily accommodated into other mechanisms as well. An OSET mechanism (Scheme 3) predicts that the demethylation rates for all of the thiolates be equal at infinite thiolate concentration (saturation) and similar to the rate of $[CH_3CoPc]^-$ decay obtained from cyclic voltammetry. It would also explain the atypical transient spectra, which are similar over a range of various substituents. However, a 10-fold change in k_2/K between **2,6-Cl_2** and **3,4-Cl_2** reactions does not agree with this mechanism, whereas the large value for the **2,6-Cl_2** reaction is consistent with significant steric hindrance to ligand binding by the cobalt center.[7] Furthermore, if the reaction indeed were to follow an OSET mechanism, the fast rates for assumed uphill electron-transfer reactions, k_1 in Scheme 3 and in Table 2, would be unreasonably insensitive to electronic factors. It is worth nothing that the rate for decay of the electrochemically generated $[CH_3CoPc]^-$ is (incidentally) close to the k_2/K values. The difference in redox potentials between $CH_3Co^{III}Pc/[CH_3CoPc]^-$ and $RS^\bullet/RS^-$ couples,[33] >0.9 V, is too large for an OSET mechanism, especially with the electron-withdrawing substituents onto thiophenoxide.

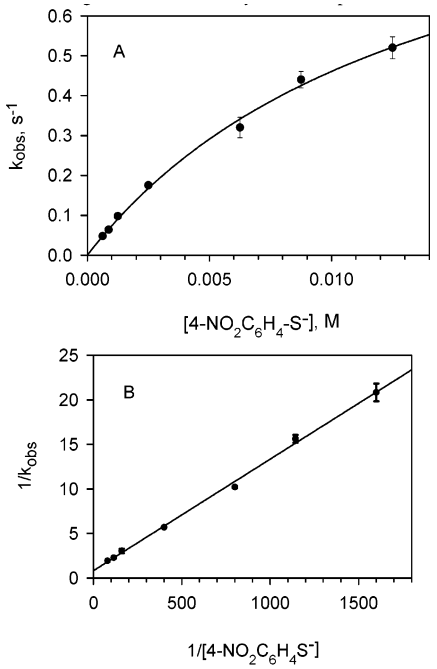
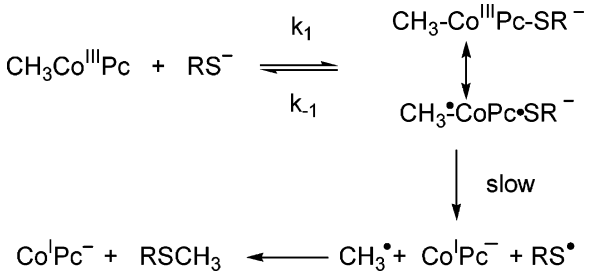


Figure 5. Kinetics of $CH_3Co^{III}Pc$ with 4-$NO_2C_6H_4SNa$ in DMA (25 °C) (A) and a double-reciprocal plot, eq 2 (B). Error bars are at 2σ.

Given the versatile chemistry of thiolates, the possibility that the demethylation follows a mechanism in which the thiolato adduct is the reactive species (Scheme 4) should also be considered, although with other nucleophiles the six-coordinate species proved to be inactive.[7] The rate-limiting homolytic cleavage of the Co$-$C bond in $CH_3CoPc(SR)^-$ would be seemingly consistent with observed concentration dependencies of the rates. The rate constant for the homolytic fission step would again be represented by the k_2/K values

Scheme 4. Homolytic Cleavage of $CH_3CoPc(SR)^-$



of Table 2. The Co−C bond rupture is probably not fast unless charge transfer to the antibonding σ^* orbital along this bond occurs,[27] which would depend, in turn, on the electron donation properties of substituents onto the trans axial ligand. Strong acceptor groups such as NO_2 are known for their significant bond strengthening/radical destabilizing effect.[35] Hence, similar k_2/K values for **4-NO$_2$** and **4-MeO** reactions are at odds with the homolytic mechanism.

Small but detectable amounts of light hydrocarbons (Table 1) indicate that some mechanisms other than S_N2 , either concurrent or follow up, must be operating. It is noteworthy that somewhat larger hydrocarbon yields were found in product studies with other nucleophiles such as phosphines or thiocyanate.[7] Thus, with this respect, thiolate reactions, in which transients of atypical spectra are observed, are no different from dealkylations promoted by other nucleophiles,[7,36] which are usually not suspected of diversified chemistry. In the $CH_3CH_2Co^{III}Pc$ system, if ethylene is formed by a concerted β-elimination, the concurrent reaction can be neglected, since the organocobalt substrate decay would follow the main S_N2 path in at least 98%. The ethylene could also be formed by a cage reaction within the $CH_3CH_2^{\bullet}$,$Co^{II}Pc(SR)^-$ geminate radical pair,[37] which is the possible intermediate in the mechanism of Scheme 4. If we assume that the presence of a trans-thiolato ligand does not qualitatively change the nature of the homolytic process, and disregard the 40−50 °C difference in temperature ranges between the thermolysis and thiolate reaction studies, then judging by 21% and ∼70% yields of ethylene found on thermolysis of $CH_3CH_2Co^{III}Pc$ in DMA[38] in the presence and in the absence of radical trap TEMPO, respectively, the upper limit of the homolytic process in the unsubstituted thiophenoxide reaction can be roughly estimated at 9 or 3%. The former estimate (1.8% of Table 1 multiplied by 100 divided by 21) is based on the assumption that there is no recombination of free ethyl radicals with the cobalt center; that is, they are all intercepted by H-donors, thiyl radicals, or trace disulfide impurities or they dimerize.[39] The latter value is obtained when we allow recombination to the extent observed in thermolysis (with no trap added). This estimate is less plausible because $Co^{II}Pc(SR)^-$ is unstable. Disproportionation of free ethyl radicals is unlikely, since it would give approximately equimolar amounts of ethane and ethylene.

Methane in a few percent yield could indicate a competition from H donors present in the solvent for methyl radicals formed by the mechanisms of Schemes 3 or 4 but ethylene as the main gaseous byproduct of the $CH_3Co^{III}Pc$ reactions,[40] and surprisingly low yields of methane, whereas thermolysis in DMA gives methane in >90% yield,[38] is incompatible with this proposal. Faced with a methane/ethane ratio of 50 observed on the thermolysis,[38] sharply contrasting with the ratio of 0.015 for the thiophenoxide assay (Table 1), we are forced to state that, in the latter case, ethane could not be formed by the self-trapping of methyl radicals. The results of product studies, especially for methyl system, do not support a significant contribution of homolytic mechanisms to the overall rate of disappearance of the organocobalt substrate. The distribution of hydrocarbon products is also incompatible with chain mechanisms initiated by the reaction of Scheme 4, where hydrocarbons would be formed either on self-trapping chain termination or on scavenging of alkyl radicals by H donors. Other reasons to refute chain mechanisms have been given earlier.[12] Now, it can be also argued that, because of the presence of H donors in DMA, the chains, if any, would not be long, as witnessed by the high methane/ethane ratios obtained on the thermolysis of CH_3-CoPc. Because of the large size of the phthalocyanine planar system, cage recombination of $CH_3^{\bullet}$ and thiyl radicals (Scheme 4) is unlikely.[12] Hence, large yields of thioethers formed in a moderately trapping solvent DMA are in support of a simple S_N2 mechanism.

In our original paper,[12] considerations of a typical S_N2 behavior of the reactions of Co^IPc^- with alkyl halides, in terms of the microreversibility principle, led us to indirect evidence for S_N2 mechanism of the demethylation of CH_3-CoPc. It was also argued that the ratio of PhS^-/I^- with CH_3-CoPc is similar to those observed with other methyl donors (in aprotic solvents). An important point is that, contrary to the notion that methylcobalt complexes are inert, CH_3Co^{III}-Pc is a reasonably good methyl donor in aprotic solvents, merely an order of magnitude slower than CH_3I. The CH_3I/CH_3CoPc second-order rate constant ratio for methyl transfer to PPh_3 is $1.2 \times 10^{-2}/4.8 \times 10^{-4} \approx 25$ (in propylene carbonate[41] and DMA,[7] respectively), while for the iodide reaction in DMA the ratio is equal $11.8/0.492 \approx 24$.[42] Rapid demethylation of CH_3I by thiophenoxide at 43 °C in sulfolane[43] is three times faster than the reaction of CH_3-$Co^{III}Pc$ with thiophenoxide in DMA (Table 2). The rate for the latter reaction clearly falls into the range of expected values, especially if the fact that typical methyl transfers in sulfolane are an order of magnitude slower than those in

(35) (a) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc*. **1991**, *113*, 1736. (b) Bordwell, F. G.; Zhang, X.-M.; Satish, A. V.; Cheng, J.-P. *J. Am. Chem. Soc*. **1994**, *116*, 6605. (c) Chandra, A. K.; Nam, P.-C.; Nguyen, M. T. *J. Phys. Chem. A* **2003**, *107*, 9182.
(36) Note that some of these nucleophiles, especially triphenylphosphine and bromide, are very weakly bound, in contrast to thiophenoxides.
(37) Halpern, J. *Acc. Chem. Res*. **1982**, *15*, 238.
(38) Galezowski, W.; Kubicki, M. Unpublished work.
(39) The yields of butane, the dimerization product, are negligible.
(40) Note that ethylene appears to be the main hydrocarbon byproduct of the reaction of $CH_3Co^{III}Pc$ with bromide (Table 1).
(41) McCortney, B. A.; Jacobson, B. M.; Vreeke, M.; Lewis, E. S. *J. Am. Chem. Soc*. **1990**, *112*, 3354.
(42) Galezowski, W.; Ibrahim, P. N.; Lewis, E. S. *J. Am. Chem. Soc*. **1993**, *115*, 8660.
(43) Lewis, E. S.; Vanderpool, S. H. *J. Am. Chem. Soc*. **1978**, *100*, 6422.

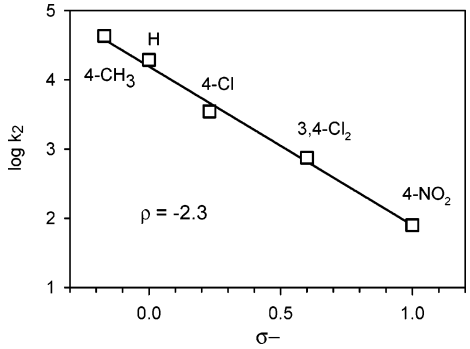


Figure 6. Hammett plot for methyl transfer from $CH_3Co^{III}Pc$ to thiophenoxides in DMA (25 °C). The σ value for 4-NO_2 is modified as explained in the text.

DMA is accounted for. Hence, rapid rates of methyl transfer from a good methyl donor, CH_3CoPc, to an excellent nucleophile, such as thiophenoxide, could be predicted, and they are in agreement with the normal S_N2 mechanism.

After due correction of the σ^- value for the 4-NO_2 group,[44] the rate constants, k_2, fit the Hammett equation adequately (Figure 6) yielding $\rho = -2.3 \pm 0.1$. The kinetics ρ values are usually compared with those for the equilibrium, ρ_{eq}, which in the present case are not accessible. A rare example of $\rho_{eq} = -3.8$ (or -6.6 after far extrapolation to 25 °C) for a methyl transfer to arenethiolates has been determined in protic EtOH at elevated temperatures.[45] The reaction constant for protonation of thiophenoxides in an aprotic solvent, a process in which the formal negative charge on sulfur is also entirely reduced, is not likely to be much different from that for methyl-transfer equilibria. The ρ value determined from pK_a values for thiophenols in polar aprotic DMSO is -4.84.[46] There is a reason to believe that the ρ value in DMA will not be much different, since a close correspondence exists between the pK_a values, including those for thiophenols, in DMSO and DMF.[47] Given that, a 50% negative charge outflow from sulfur in the transition state could be concluded. The $\rho = -2.3$, similar to the values determined for the reaction of butyl chloride with thiolates in DMSO[46] and DMF,[34] or other thiophenoxide promoted displacement reactions,[43,45,48] is clearly consistent with the S_N2 mechanism.

Lability of $CH_3Co^{III}Pc(SR)^-$. The rates for the initial fast step can be measured by stopped flow, albeit with difficulty, in dilute thiophenoxide solutions. A striking feature of the rough second-order rate constants for thiophenoxide binding, k_1, is that they are invariant within experimental error (Table 2), while the amplitude of the initial drop in the Q-band intensity decreases markedly from **4-MeO** to **3,4-Cl_2** (Tables S1−S5, Supporting Information). Rough equilibrium constants determined from the amplitudes are consistent with the values obtained from deconvolution of k_{obs} for the methyl-transfer step via eq 2. All of this is in agreement with a limiting dissociative mechanism of ligand exchange in CH_3-$Co^{III}Pc$(DMA). However, rapid thiophenoxide reactions are slower than aromatic amine ligation by $CH_3Co^{III}Pc$ in DMA.[7] A search for other ligands that bind to cobalt at a measurable rate led to determination of the rate constant of 261 000 ± 6000 M^{-1} s^{-1} for possibly the strongest binding cyanide ligand, $K = 2.1 \times 10^6$ M^{-1} [42] (see Figure S7, Supporting Information).

For a purely dissociative ligand exchange in CH_3CoPc-(DMA) proceeding via the five-coordinate $CH_3Co^{III}Pc$ intermediate, a steady-state approach yields the familiar eq 3

$$k_{obs} = \frac{k_{-S}k_L[L] + k_S k_{-L}[solv]}{k_S[solv] + k_L[L]} \qquad (3)$$

where k_{-S} and k_S refer to desolvation/solvation of CH_3Co^{III}-Pc and k_L and k_{-L} refer to ligation of (five-coordinate) RCo^{III}-Pc by L. Saturation predicted by eq 3 is not reached in dilute solutions of incoming ligand, in which the stopped-flow studies are viable. Then, in the denominator, k_S[solv] must be much larger than k_L[L], a condition that in view of [solvent] ≫ [L] is likely to be fulfilled. The slopes of k_{obs} vs [L] can be interpreted as a combination of three rate constants, k_{-S}, k_S[DMA], and k_L. The ratio $k_{-S}/(k_S$[DMA]) represents a fraction of the five-coordinate species in DMA, which has been estimated to be of the order of 0.01.[7] Consequently, k_L would be $\sim 10^8$ M^{-1} s^{-1}, which is still an order of magnitude smaller than the value predicted by the Smoluchowski equation for a diffusion-controlled reaction in DMA. Given the equation was derived for spherical reagents, perhaps ligation by thiolates could be diffusion controlled, which would account for the rates nearly equal for all of the thiophenoxides studied. On the other hand, a preassociation mechanism would allow for the differences in the rates between pyridine, *N*-MeIm, thiophenoxide, and cyanide ligation. The association constant for the spectator mechanism would be the largest for incoming ligands that can favorably interact with the phthalocyanine macrocycle. This would explain the relatively slow cyanide ligation compared to aromatic amines. Pressure effect on the rates would be helpful for establishing the mechanism with a reasonable confidence. Whatever the mechanism for the ligand exchange, this study underlines the amazing kinetic lability of the electron-deficient $CH_3Co^{III}Pc$ model.[7]

The order of the rates for dissociation of $CH_3Co^{III}Pc(SR)^-$, k_{-1}, calculated from k_1 and K (Table 2), is consistent with a limiting dissociative or I_d mechanism. The rate for thiolate ligand liberation from $CH_3Co^{III}Pc(4\text{-}CH_3O{-}C_6H_4{-}S^-)$ is only about 140 times larger than $k_{-1} = 0.124$ s^{-1} for dissociation of possibly the most stable cyanide complex.[49] Faster rates for dissociation of pyridine than for thiolate

(44) Previous LFER studies of the reaction of butyl chloride with thiophenoxides in DMSO (ref 46) clearly showed that the σ^- for the 4-NO_2 substituent, which was determined in hydroxylic solvents, is unsuitable for correlations in aprotic solvents. It appeared that an effective substituent constant of 1.0, that is, the intermediate between σ and σ^-, would place the 4-NO_2 point on the line determined by the data for non-R+ substituents. The same seems to be true in the present case.

(45) Lewis, E. S.; Kukes, S. *J. Am. Chem. Soc.* **1979**, *101*, 417.

(46) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224.

(47) Maran, F.; Celadon, D.; Severin, M. G.; Vianello, E. *J. Am. Chem. Soc.* **1991**, *113*, 9320.

(48) Westaway, K. C.; Ali, S. F. *Can. J. Chem.* **1978**, *57*, 1089.

(49) Calculated from the stability constant for $CH_3Co^{III}Pc(CN)^-$ from ref 42 and the rate constant for cyanide binding by cobalt.

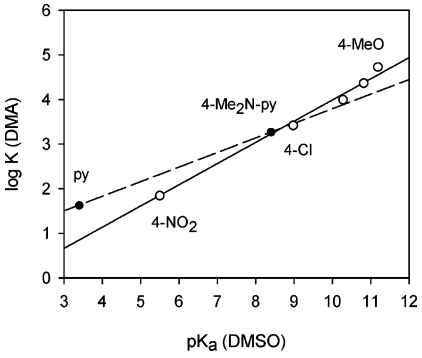


Figure 7. Dependence of equilibrium constants for ligation of X-py (●) and thiophenoxides (○) by $CH_3Co^{III}Pc$ in DMA (25 °C) upon basicity of the ligand. The *K* values for X-py from ref 7, pK_a values for thiophenols from ref 46, and pK_a of 4-bromothiophenol was adopted for **4-Cl**. For pK_a values for X-pyH$^+$, see ref 51.

complexes are in agreement with the behavior of analogous methylcobaloxime complexes.[50]

A reasonable comparison of thiolate and N-donor binding by $CH_3Co^{III}Pc(L)$ is possible only when ligands of similar basicity are compared. It is customary to use aqueous pK_a values for protonated ligands, but in the present case, it would be inappropriate especially for thiophenoxides, of which the basicity changes with remote substitution much faster in aprotic solvent, such as in DMSO rather than in water.[46] In Figure 7,the basicities of protonated ligands are either those determined in DMSO (thiolates) or those determined in acetonitrile and recalculated (pyridines). It can be roughly estimated that, in DMSO, the basicity of 4-chlorothiophenoxide should be similar to that of 4-Me_2N-py.[51] The corresponding ligand association constants of these two ligands with CH_3CoPc in DMA are not much different, 2600 ± 100 (Table 2) and 1840 ± 70 M^{-1},[7] respectively. However, the response to changes in ligand basicity, represented by β_{eq} = d(log *K*)/d(pK_a), is significantly stronger for thiophenoxide than X-py ligands, 0.48 ± 0.02 and 0.33,[52] respectively (Figure 7). Hence, in the low pK_a range thiophenoxides are weaker binding ligands than X-py, whereas in the high pK_a range, where alkanethiolates belong, the reverse would be true if only pyridines basic enough existed. This is contrary to the methylcobaloxime model, which shows significantly stronger affinity for binding by thiolates than X-py over the whole range of practical pK_a values, and the β_{eq} values for both types of complexes are small. A larger value, $\beta_{eq} = 0.38$, for coordination of aliphatic amines to methylcobaloxime, than β_{eq} (X-py) = 0.21 and β_{eq} (RS^-) = 0.18, was used as an argument for a strong back π bonding of thiolates, stronger than that of X-py. Accordingly, by the criteria adopted by Brown et al.,[50] the reverse would be true for the phthalocyanine model: X-py ligands would exhibit significantly stronger π bonding to CH_3Co^{III}-Pc than that of thiophenoxides. It is not clear, though, whether a qualitative change in π-bonding properties occurs between methylcobaloxime and $CH_3Co^{III}Pc$ or the comparison is not reliable because of the different types of thiols and solvents used.

Table 3. Kinetic Data for Methyl Transfer from $CH_3Co^{III}Pc$ to 2,6-Dichlorothiophenoxide in DMA

temp, °C	[2,6-Cl_2−$C_6H_3S^-$], M	k_{obs}, s^{-1}	k_2, M^{-1} s^{-1} [a]	*K*, M^{-1}
15	0.002−0.02	0.198−0.840	115 ± 3	79 ± 8
20	0.002	0.247 ± 0.006		
20	0.003	0.365 ± 0.005		
20	0.004	0.479 ± 0.006		
20	0.006	0.64 ± 0.01		
20	0.01	0.851 ± 0.009		
20	0.02	1.275 ± 0.009	139 ± 4	77 ± 7
25	0.00125−0.1	0.283−2.91	255 ± 4	69 ± 7
30	0.002−0.02	0.856−3.78	490 ± 20	65 ± 10
35	0.002−0.02	1.26−6.16	730 ± 20	63 ± 7

[a] $\Delta H^{\ddagger}$ = 16.4 ± 1.3 kcal/mol, $\Delta S^{\ddagger}$ = 7.6 ± 4.2 cal mol^{-1} K^{-1}.

A reasonable prediction can be made, using trends shown in Figure 7, that strongly basic alkanethiolates (pK_a ~17 in DMSO) will coordinate to CH_3CoPc stronger than to pyridine, and such strong binding is indeed observed (vide infra). These two ligands have been invoked here, because in aqueous solution a change in the order of ligand affinity for coordination to the Co center is observed on going from methylcobaloxime, RS^- > X-py, to $MeCbi^+$, where pyridine binding is measurable but thiolate coordination has not been observed.[10] The behavior of $CH_3Co^{III}Pc$, alkanethiolate > py, is consistent with its electron-deficient character, which positions this model closer to methylcobaloxime than to $MeCbi^+$.[7] The fact that the formation constants for $CH_3Co^{III}Pc(SR)^-$, determined indirectly from kinetic data, are comparable to those for the pyridine adduct stands in support of the mechanistic assignments of this work. This is of some importance for a system in which thiolate binding cannot be directly studied because of rapid demethylation.

Alkyl Group and Axial Base Effects. It has been demonstrated that the alkyl group effect Me > Et is one characteristic feature of S_N2 alkyl transfer from $CH_3Co^{III}Pc$ to nucleophiles.[7] In the present work, the **2,6-Cl_2** reaction, which can be most conveniently studied, has been scrutinized. The data of Tables 3 and 4 demonstrate that, in accordance with alkyl transfers to other nucleophiles, CH_3-$Co^{III}Pc$ is considerably faster than $CH_3CH_2Co^{III}Pc$. The Me/Et second-order rate constants ratio of ca. 10 is similar to those determined by Norris and Pratt for slow alkyl transfer from $MeCbi^+$ to alkanethiolates.[3] The $\Delta S^{\ddagger}$ values for both methyl and ethyl transfer are moderately positive:[7] 8 ± 4 and 2 ± 3 cal mol^{-1} K^{-1}, respectively, which seems to be the rule for methyl transfers from $CH_3Co^{III}Pc$ to anionic

(50) Brown, K. L.; Chernoff, D.; Keljo, D. J.; Kallen, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 6697.

(51) This estimate is based on the following: (i) pK_a values for X-pyH$^+$ in acetonitrile from Kaljurand, I.; Rodima, T.; Leito, I.; Koppel, I. A.; Schwezinger, R. *J. Org. Chem.* **2000**, *65*, 6202 and *Tables of Rate and Equilibrium Constants of Heterolytic Organic Reactions*; Palm. V., Ed.; VINITI: Moscow-Tartu, Russia, 1975−1985. (ii) Assumed parallel shift of pK_a values between acetonitrile, DMSO, and DMA, the pK_a shift $-8.94 = pK_a(pyH^+)^{DMSO} - pK_a(pyH^+)^{MeCN}$. (iii) The p$K_a$ value for pyridine in DMSO from Izutsu, K. *Acid−Base Dissociation Constants in Dipolar Aprotic Solvents; IUPAC Chemical Data*; Series No. 35; Blackwell Scientific: Oxford, U.K., 1990. (iv) pK_a values for thiols in DMSO from ref 46.

(52) This slope is very similar to that of 0.30 ± 0.03, determined in toluene using four X-py ligands (ref 7). Similar sensitivity of X-py binding to methylcobaloxime in DMSO or DMSO/H_2O to changes in X can be seen in Tables 21 and 50 in Bresciani-Pahor, N.; Forcolin, M.; Marzilli, L. G.; Randaccio, L.; Summers, M. F.; Toscano, P. J. *Coord. Chem. Rev.* **1985**, *63*, 1.

Table 4. Kinetic Data for Ethyl Transfer from $CH_3CH_2Co^{III}Pc$ to 2,6-Dichlorothiophenoxide in DMA

temp, °C	[2,6-Cl_2−$C_6H_3S^-$], M	k_{obs}, s^{-1}	k_2, M^{-1} s^{-1} [a]	K, M^{-1}
15	0.002−0.02	0.0111−0.061	6.0 ± 0.2	46 ± 10
20	0.002−0.02	0.0224−0.107	12.4 ± 0.5	73 ± 12
25	0.002	0.0358		
25	0.003	0.0504		
25	0.004	0.0641		
25	0.006	0.0846		
25	0.01	0.118		
25	0.02	0.199	20.0 ± 0.4	63 ± 6
35	0.002−0.02	0.080−0.495	44 ± 2	51 ± 14
40	0.002−0.02	0.129−0.880	71 ± 5	50 ± 20

[a] $\Delta H^{\ddagger} = 16.4 \pm 1.0$ kcal/mol, $\Delta S^{\ddagger} = 2.4 \pm 3.2$ cal mol^{-1} K^{-1}.

Table 5. *N*-Methylimidazole Inhibition of Methyl Transfer from $CH_3Co^{III}Pc$ to 2,6-Dichlorothiophenoxide in DMA (25 °C)

[2,6-Cl_2−$C_6H_3S^-$], M	k_{obs} s^{-1}		k_{calcd} s^{-1} [a]
	[*N*-MeIm] = 0	[*N*-MeIm] = 0.0125 M	[*N*-MeIm] = 0.0125 M
0.002	0.44 ± 0.1	0.023 ± 0.001	0.020
0.003	0.63 ± 0.1	0.036 ± 0.002	0.029
0.004	0.81 ± 0.1	0.045 ± 0.002	0.039
0.006	1.08 ± 0.2	0.059 ± 0.001	0.058
0.01	1.53 ± 0.2	0.092 ± 0.002	0.095

[a] Calculated using eq 4, $K_{N-MeIm} = 2000 \pm 20$ M^{-1} from ref 7.

nucleophiles in coordinating polar solvents.[7] Even though **2,6-Cl_2** is the weakest of the thiolate nucleophiles[24,28] studied, the $\Delta H^{\ddagger} = 16 \pm 1$ kcal/mol appears to be the lowest among methyl transfers from $CH_3Co^{III}Pc$ to anionic nucleophiles in DMA determined so far.[7] The activation parameters for methyl and ethyl transfer are indistinguishable within experimental error. Experimental error in the K values is larger yet, not allowing any reasonable determination of reaction parameters for **2,6-Cl_2** binding by cobalt. It transpires, however, that $-\Delta H$ must be very small. The alkyl group effect is not restricted to weak thiolate nucleophiles since a similar Me/Et rate constant ratio of 10 ± 2 has been determined also for the thiophenoxide reaction (data for the ethyl derivative, $k_2 = 900 \pm 100$ M^{-1} s^{-1}, $K = 1900 \pm 300$ M^{-1}).

Homolytic cleavage of the Co−C bond is usually faster for ethyl than the methyl σ-bonded group. This was observed for electrochemically generated anions and cations of σ-bonded alkyl porphyrins. Also in this study, $[CH_3CoPc]^-$ was found to be more stable than $[CH_3CH_2CoPc]^-$ (the first reduction of CH_3CH_2CoPc is still irreversible when that of CH_3CoPc reaches quasi-reversibility). Faster rates for the methyl derivative are against any mechanism in which the homolytic fission is rate limiting. With attention to the mechanisms of Schemes 3 and 4, larger k_2/K values for methyl than ethyl transfer to **2,6-Cl_2** are noteworthy.

Another familiar feature of methyl transfers from Co(III), axial base inhibition,[7] is also found for thiolate reactions as can be seen in Table 5. Given all sorts of experimental error, the fit of experimental data to eq 4,[7]

$$k_{calcd} = \frac{k_2[\text{thiolate}]}{1 + K[\text{thiolate}] + K_{N-MeIm}[N\text{-MeIm}]} \qquad (4)$$

where K_{N-MeIm}, the formation constant of CH_3CoPc(*N*-MeIm), 2000 ± 20 M^{-1},[7] appears satisfactory. Similar inhibition was also observed for the unsubstituted thiophenoxide reaction. The *N*-MeIm inhibition, while consistent with mechanisms of Schemes 1 and 4, allows us to rule out the OSET mechanism, since *N*-MeIm has little impact on the reduction potential.[7]

Methyl Transfer to Aliphatic Thiolates. As is apparent from Table 2, the more powerful a thiolate nucleophile, the less accurate the k_2 value. The value for the **4-MeO** reaction could not be determined with any reasonable accuracy. On the basis of the results of Bordwell's study of thiolate attack on butyl chloride, where strongly basic aliphatic thiolates ($pK_a \sim 17$ in DMSO)[46] were faster than thiophenoxide ($pK_a = 10.3$ in DMSO),[46] a prediction could be made that, in the present case, determination of k_2 for reactions with aliphatic thiolates (similar to homocysteine thiolate) would not be possible. There is another hurdle, an extreme instability of basic aliphatic thiolates in DMA. Nevertheless, it seems important to demonstrate that methyl transfers from $CH_3Co^{III}Pc$ to alkanethiolates, similar to homocysteine thiolate, are rapid. A DMA solution of the organocobalt substrate is stable in the presence of 0.3 M *t*-BuSH or *n*-BuSH in the spectrophotometric cell under argon. Subsequent injection of an equimolar amount of Bu_4NOH results in the instantaneous formation of $Co^{I}Pc^-$. Stopped-flow runs of the *n*-BuS^- reaction were not attempted because of the extreme instability of the thiolate in DMA. For the *t*-BuS^- reaction, two exponential kinetic curves, similar to those of basic thiophenoxide reactions, are observed in the stopped flow. Rough second-order rate constants for the preequilibrium process are within experimental error indistinguishable from the k_1 values listed in Table 2. The initial drop in 660 nm absorbance is as large as that observed with basic thiophenoxides. Hence, although complete reaction spectra have not been obtained, it is plausible that they are similar to those of Figure 2. The k_{obs} values for the methyl transfer step of 2.2 ± 0.1 s^{-1} were observed for [*t*-BuS^-] > 0.0008 M at 25 °C. There is no compelling reason to believe that there is any qualitative difference between the reactions of basic thiophenoxides and the methyl transfer to the considerably more basic *t*-BuS^-. They are likely to follow the mechanism of Scheme 1.

Is the "Extremely Reactive" $CH_3Co^{III}Pc$ Consistent with Inert Methylcobaloxime? In our work, we have been trying to show that Co(I) nucleophiles, although very powerful, are consistent with other ordinary nucleophiles.[42] Conversely, CH_3Co^{III} complexes should be consistent with other methyl donors. In fact, in polar aprotic solvents, $Co^{I}Pc^-$ is 2 orders of magnitude faster a nucleophile than I^-, while CH_3CoPc is approximately a 10-fold slower methyl donor than CH_3I. All of the CH_3Co^{III} complexes known are considerably weaker methyl donors than methyl iodide; they are also weaker than $CH_3Co^{III}Pc$. Methyl transfers from $CH_3Co^{III}Pc$ to a variety of nucleophiles, not only thiolates, are "unusually fast".[7] Hence, there is nothing special about the fast methyl transfer from $CH_3Co^{III}Pc$ specifically to thiolates. Rather, the phthalocyanine model appears uncharacteristically

reactive. This reactivity stems from the "electron-poor" nature of $CH_3Co^{III}Pc$ combined with a considerable lability of trans axial ligands compared with other electron-deficient alkylcobalt complexes.[7] The association constant of pyridine with methylcobaloxime in DMSO is about 200 times larger than that obtained with $CH_3Co^{III}Pc$.[7] The increased demand of methylcobaloxime for six coordination[11] alone makes CH_3-CoPc about 10^2-fold more reactive a CH_3^+ donor than methylcobaloxime (that is, if we assume for a moment equal reactivity of the reactive five-coordinate forms). Since the α carbon in the 16-electron five-coordinate species is considerably more electrophilic than that in 18-electron six-coordinate complexes, the latter complex appears inactive.[7] One should also keep in mind that nucleophilic power of thiolates in aprotic solvents such as DMA is significantly increased compared with aqueous or alcoholic solution where demethylations of methylcobaloximes and $MeCbi^+$ have been studied (or attempted). If we allow a factor of 10^4 for this effect,[53] then a methyl transfer reaction from CH_3CoPc in DMA will be overall a million times faster than that from methylcobaloxime in methanolic solution (seconds instead of a month). Thus, the apparent inertness of electron-poor methylcobaloxime or Costa-type models toward thiolates can nearly be reconciled with the reactive phthalocyanine model. The conclusion made by Brown,[5] Marzilli, and co-workers[6] that thiolate ligation is the primary process observed upon addition of a thiolate to methylcobaloxime, and that the Co−C bond remains intact, would also be true for CH_3Co^{III}-Pc if only the observation time was sufficiently short (∼10 ms). It is noteworthy that methyl transfer from methylcobaloxime to thiolates was lately attempted in the presence of very strong trans axial ligands, Me_2PhP or Me_3P.[6] This must have further reduced the already low population of the reactive species. Furthermore, because of the kinetic saturation such as observed in this work, the rate for demethylation of methylcobaloxime or a Costa-type model could not be significantly increased by raising the concentration of the nucleophile.

The electron-poor character of the phthalocyanine model is evident from the small negative reduction potential for $CH_3Co^{III}Pc$, −0.95 V vs SCE in DMA or −0.98 V in DMF,[7] compared to −1.35 V for methylcobaloxime in DMF,[54] and a small negative oxidation potential for $Co^{I}Pc^{-}$ [19] of −0.37 V in DMF[55] compared with −1.17 V for the cobaloxime Co(II)/Co(I) couple.[56] The phthalocyanine model has exceptional ability to stabilize negative charge in the transition state and in the product of demethylation. This shows in low, for a cobalt supernucleophile, thermodynamic nucleophilicity of $Co^{I}Pc^{-}$, and consequently, in an enhanced thermodynamic drive for demethylation of $CH_3Co^{III}Pc$.[42] The unique properties of the phthalocyanine model should result in larger reactivity of the five-coordinate $CH_3Co^{III}Pc$ species than that of the hypothetical five-coordinate form of methylcobaloxime. Of note, the order of trans ligand binding properties, methylcobaloxime > $CH_3Co^{III}Pc$, is contrary to what could be predicted from electrochemical data. It is striking that the methylcobaloxime model is characterized by both slow methyl transfer and slow trans ligand exchange. A simple rationale behind it would be that these different reactions have a common intermediate, the five-coordinate methylcobaloxime species, which, in contrast to CH_3Co^{III}-Pc, is extremely unstable.

A consistent, although simplified, description of alkyl (formally cation) transfer from cobalt(III) is possible: some alkylcobalt(III) complexes are inactive because of their "electron-rich" nature; and others have an "electron-deficient" equatorial ligand but heavy trans axial ligation reduces their methyl donation power. Finally, in some models, the increased electron-deficient character of the equatorial system is only partially compensated by an enhanced demand for hexacoordination. Methyl transfer from such complexes to thiolates should be measurable in nonhydroxylic, possibly weak binding, solvents in the absence of strong axial bases.

$MeCbi^+$ has been shown to persist in a significant percentage as a five-coordinate complex in aqueous solution.[57] Accordingly, it reacts with alkanethiolates slowly but measurably.[3] The reaction should be reasonably fast in a nonhydroxylic, weakly binding, polar solvent.

Conclusions

Our original claim of normal S_N2 mechanism of methyl transfer from Co to thiophenoxide is confirmed and even extended to alkanethiolates, despite distracting atypical transient spectra and the coincidence of the rates for methyl transfer to thiolates and the rate for homolysis of $[CH_3CoPc]^-$. As demonstrated a decade ago and confirmed by this study, nonenzymatic S_N2 methyl transfers from cobalt to thiolates can be as fast as enzymatic systems demand. A prediction based on Bordwell and Hughes' work[46] yields a second-order rate constant for the reaction of $CH_3Co^{III}Pc$ with butanethiolate in DMA on the order of 10^6 M^{-1} s^{-1}, compared with 135 000 M^{-1} s^{-1} for the analogous reaction of methionine synthase fragments.[17] The increased methyl donation power of a RCo(III) complex implies a weaker nucleophilic ability of the corresponding Co(I) complex. Consequently, the phthalocyanine system probably could not replace the corrinoid because $Co^{I}Pc^{-}$ is too weak a nucleophile to attack a nitrogen-bonded methyl group.

The high reactivity of a five-coordinate electron-poor complex seems to suggest one possible mode of activation of inert MeCbl. Another lesson, not new, is that chemical precedent studies in aqueous solution are somewhat misleading because in a hydroxylic solvent, the nucleophilic power of a nucleophile is drastically lowered compared with aprotic

(53) See, for instance, a 4 order-of-magnitude faster reaction of *n*-BuBr with thiophenoxide in DMF than in MeOH in Table 4. Alexander, R.; Ko, E. C. F.; Parker, A. J.; Bronxton, T. J. *J. Am. Chem. Soc*. **1968**, *90*, 5049.

(54) Costa, G.; Puxeddu, A.; Tavagnacco, C. *J. Organomet. Chem*. **1985**, *296*, 161.

(55) Lever, A. B. P.; Milaeva, E. R.; Speier, G. In *Phthalocyanines, Properties and Applications*; Leznoff, C. C., Lever A. B. P., Eds.; Wiley-VCH: New York, 1993; Vol. 3, p 47.

(56) Elliot, C. M.; Hershenhart, E.; Finke, R. G.; Smith, B. L. *J. Am. Chem. Soc*. **1981**, *103*, 5558.

(57) Hamza, M. S. A.; Zou, X.; Brown, K. L.; van Eldik, R. *Eur. J. Inorg. Chem*. **2003**, 268 and references therein.

solvents, which probably better mimic a hydrophobic, enzymatic environment. Nucleophilic participation by cobalt, which plays an important role in the phthalocyanine model and makes the methyl transfer effectively slower, is not that important for the $MeCbi^+$ reactions with thiolates, where linear concentration dependencies of the rates are observed. Methylcobaloxime, in turn, exhibits a very strong demand for six-coordination and with this respect should be regarded as a MeCbl antimodel.[58]

Acknowledgment. This work was supported by the Polish State Committee for Scientific Research Grant 7 T09A 07421.

(58) Doll, K. M.; Finke, R. G. *Inorg. Chem.* **2004**, *43*, 2611.

Supporting Information Available: Figures showing concentration dependencies of conductances of C_6H_5SNa and 4-ClC_6H_4SNa in DMA at 25 °C and corresponding Kohlrausch plots. Figures showing typical kinetic curves and corresponding end-point plots. Tables of detailed kinetic data for methyl transfer from CH_3Co^{III}Pc to sodium thiophenoxides in DMA (25 °C). Figure showing concentration dependence of the rates for methyl transfer to 4-$CH_3C_6H_4S^-$ rates and the double reciprocal plot. An example for determination of *K* from the amplitudes of the fast step. Figure showing the concentration dependence of the rates for cyanide binding by CH_3Co^{III}Pc in DMA (25 °C). This material is available free of charge via the Internet at http://pubs.acs.org.

IC0503378