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Solution Chemistry of Cobalt(III) Porphyrins in Water and Nonaqueous Solvents. Axial Ligation by Solvent and Counterion

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Improved preparations of cobalt(III) tetrakis(*N*-methylpyridiniumyl)porphyrin (Co(TMpyP(4)) derivatives were developed to avoid Co(II) contaminants produced by the standard precipitant, iodide. Careful oxidation of solutions containing TMpyP(4), $CoCl_2$, and HCl followed by precipitation with ClO_4^- gave a product, compound I, with an acceptable elemental analysis for a formula containing ClO_4^- as the only source of Cl. However, the ^1H NMR spectrum in DMSO-d_6 has signals for two nearly equally abundant species (**a** and **b**). Signals for only one of these species (**a**) are present in the new product $[Co(TMpyP(4))Cl(H_2O)](PF_6)_4$. Therefore, species **a** of compound **I** is a monochloro derivative; the elemental analysis of compound **I** did not readily distinguish between ClO_4^- and Cl^-/H_2O combinations. Solvent suppression NMR of the methyl signal of DMSO (natural abundance) by techniques that do not lead to signal saturation showed that this monochloro species **a** has one bound DMSO signal at a shift (−0.55 ppm) consistent with a DMSO bound through oxygen (DMS*O*). At 30 °C, this signal was broad; it was most readily observed at lower temperatures, indicating that the DMS*O* is in relatively fast exchange. Solvent suppression experiments showed that **b** was $[Co(TMpyP(4))(DMSO)_2]^{5+}$ and that DMS*O* exchange was slow. This $(DMSO)_2$ species was formed nearly exclusively from $[Co(TMpyP(4))(H_2O)_2](ClO_4)_5$, which was best prepared in the absence of Cl^- or NO_3^-. In water, $[Co(TMpyP(4))X(H_2O)]^{4+}$ ($X = Cl^-$ and NO_3^-) were not formed appreciably, but these 4+ species were precipitated preferentially over the 5+ diaqua species. Undeuterated DMSO was titrated into $CDCl_3$ solutions of cobalt(III) chloro complexes of tetraphenylporphyrin (Co(TPP)Cl), octaethylporphyrin (Co(OEP)Cl), and tetrakis(4-(trifluoromethyl)phenyl)porphyrin (Co(TCF_3PP)Cl). At 1:1 to 2:1 ratios of DMSO:Co(III) porphyrin, the DMSO signal was observed from −0.7 to 1 ppm. Further addition of DMSO shifted the DMSO signals downfield for all three porphyrins, but no separate free DMSO signal was observed. The pyrrole signals shifted downfield but gave no evidence of two slowly exchanging species. These results demonstrated that for these porphyrins the DMSO was in fast exchange. The downfield shift of the pyrrole signal indicated that, at ratios of DMSO to porphyrin >2, the Cl,DMS*O* species were fully formed. In 100% DMSO-d_6, both Co(TPP)Cl and Co(TCF_3PP)Cl have two species. Solvent suppression experiments as a function of temperature and added LiCl showed that one had $(DMSO)_2$ and the other Cl,DMS*O* axial ligation. As found for Co(TMpyP(4)), the DMS*O* exchange rate was slower for the $(DMSO)_2$ than for the Cl,DMS*O* species. The preference for Cl^- binding was found to be Co(TMpyP(4)) > Co(TCF_3PP) > Co(TPP).

Introduction

Derivatives of tetrakis(*N*-methyl-4-pyridiniumyl)porphyrin (TMpyP(4)) are of interest because they exhibit activity against HIV-1, the virus responsible for AIDS.[1−5] Numerous porphyrin compounds exhibit such activity, but the mechanism of action is not known. The axial ligands in metalloporphyrins influence the binding to biomolecules.[5−9] However, there has been little systematic study of the effect of axial ligation on biomolecule binding and hence potential therapeutic mechanisms. This paucity of data results in part from the lability of porphyrin complexes compared to complexes with the same metal center but with different equatorial ligands. We have decided to investigate Co(III) porphyrin complexes. Past studies of such complexes have in part been motivated by their use as models for B_{12} species such as coenzyme B_{12}.[10,11] The axial ligation of such species by amino acids has also been studied.[12]

We describe the synthesis of TMpyP(4) complexes containing Co(III). Cations containing the $[Co^{III}(TMpyP(4))]^{5+}$ moiety are expected[5,6] to have two axial ligands, since the porphyrin is relatively electron poor (Figure 1). One or both may be the counterion. We use the designation Co(TMpyP(4)) when the axial ligation is not specified or not known. In this study, we have elucidated the nature of Co(TMpyP(4)) species in nonaqueous solvents useful for preparative purposes or for studying interactions with ligands which are not water soluble. We discovered that NMR spectra were particularly revealing in DMSO-d_6 compared with those recorded in D_2O. These findings led us to make a careful study of the preparations of Co(TMpyP(4)) derivatives and of some of the interactions of anions with the $[Co^{III}(TMpyP(4))(H_2O)_2]^{5+}$ cation in water. In order to gain insight into the Co(TMpyP(4)) chemistry, we also

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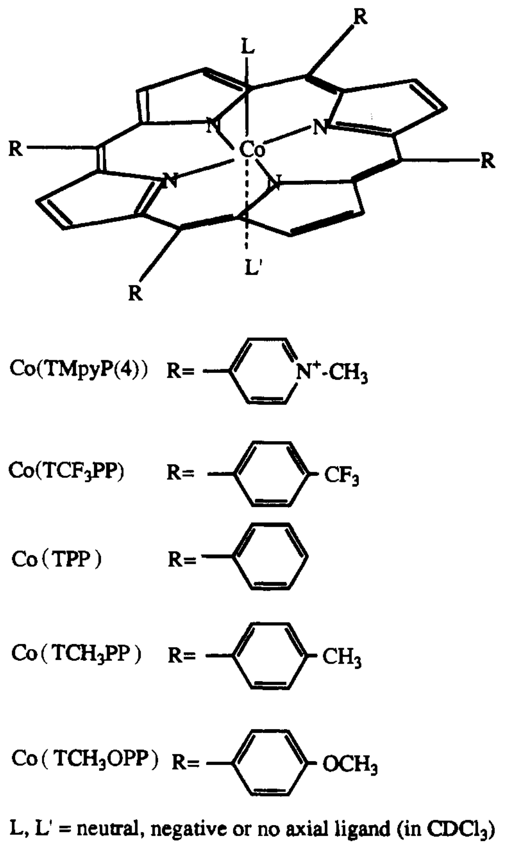

Figure 1. Structures of porphyrins referred to in this study.

examined other porphyrin species (Figure 1) for interactions with common solvent molecules in $CDCl_3$ solution as well as for axial ligation in DMSO-d_6.

Experimental Section

Materials. The TMpyP(4) tosylate salt from Aldrich was used without further purification. The chloro derivatives of (tetraphenylporphyrinato)cobalt(III) (Co(TPP)Cl), (tetratolylporphyrinato)cobalt(III) (Co(TCH$_3$PP)Cl), (tetrakis(4-methoxyphenyl)porphyrinato)cobalt(III) (Co(TCH$_3$OPP)Cl), (octaethylporphyrin, cobalt(III) (Co(OEP)Cl), and (tetrakis(4-(trifluoromethyl)phenyl)porphyrinato)cobalt(III) (Co(TCF$_3$PP)Cl) were obtained from Mid-Century. 1,5,6-Trimethylbenzimidazole (Me$_3$Bzm) was prepared as reported.[13] Deuteriated solvents were obtained from Cambridge.

Cobalt(III) Tetrakis(*N*-methyl-4-pyridiniumyl)porphyrin Syntheses. A pH 11 solution of TMpyP(4) tosylate (100 mg, 0.073 mmol) in water (25 mL) was degassed and treated (under N_2) with a solution of $CoCl_2 \cdot 6H_2O$ (34 mg, 0.14 mmol) in water (5 mL). The reaction mixture was stirred under N_2 overnight, and the reaction was followed by UV–vis spectroscopy. Usually the pH had dropped to ~9–10 the following day and the reaction was not complete. The pH was readjusted to 11 and the reaction allowed to continue until the visible spectrum showed no change with time. The Soret band shifted from 424 to 437 nm at a final pH of ~8. The filtered reaction mixture was adjusted to pH 1.3 with HCl (concentrated), and air was bubbled through the solution for 1 h. The solution was filtered again, and the filtrate was reduced in volume to ~15 mL. This solution (solution I) was treated with 2 M $NaClO_4$ (~1 mL). The resulting precipitate (compound I) was washed with dilute $NaClO_4$ solution. Anal. Calcd for Co(TMpyP(4))$(ClO_4)_5 \cdot 2H_2O$, $C_{44}H_{36}Cl_5CoN_8O_{20} \cdot 2H_2O$: C, 41.64; H, 3.18; Cl, 13.97; N, 8.83. Anal. Calcd for Co(TMpyP(4))$Cl_{0.6}(ClO_4)_{4.4} \cdot 4H_2O$, $C_{44}H_{36}Cl_5CoN_8O_{17.6} \cdot 4H_2O$: C, 41.72; H, 3.50; Cl, 14.00; N, 8.85. Found: C, 41.56; H, 3.42; Cl, 13.99; N, 8.89. *Caution! Perchlorate salts may be explosive and should be handled in small quantities with appropriate precautions.* The hexafluorophosphate salt, compound **II**, was prepared by treating solution I with sodium hexafluorophosphate (1 M, 1.5–2 mL). The precipitate was collected and washed with dilute $NaPF_6$ solution. Anal. Calcd for $C_{44}H_{36}ClCoF_{24}N_8P_4 \cdot H_2O$: C, 38.60; H, 2.80; Cl, 2.59; N, 8.19. Found: C, 38.72; H, 2.89; Cl, 2.52; N, 8.04. Compound **III** was obtained as above for compound I but with $Co(NO_3)_2 \cdot 6H_2O$ and HNO_3. Anal. Calcd for Co(TMpyP(4))$(ClO_4)_{3.2}(NO_3)_{1.8} \cdot 5H_2O$, $C_{44}H_{36}Cl_{3.2}CoN_{9.8}O_{18.2} \cdot 5H_2O$: C, 42.08; H, 3.69; Cl, 9.04; N, 10.93. Found: C, 42.16; H, 3.75; Cl, 9.27; N, 11.01. The chloride salt, compound IV, was obtained by passing compound I through an AG-1X ion exchange column in the chloride form, and the product was obtained by lyophilization. The purity of compound IV was checked by gel electrophoresis (one band observed) and ^{1}H NMR (UV–vis 434, 550, 592 nm). Anal. Calcd for Co(TMpyP(4))$Cl_5 \cdot 8H_2O$, $C_{44}H_{36}Cl_5CoN_8 \cdot 8H_2O$: C, 50.00; H, 4.96; Cl, 16.77; N, 10.80. Found: C, 50.16; H, 4.91; Cl, 16.68; N, 10.69. Compound V was obtained as above for compound I but in a half-scale reaction with $Co(CH_3CO_2)_2$. After the visible spectrum showed no change with time (λ_{max} 437 nm), the filtered reaction mixture was adjusted to pH ~2.6 by adding chloroacetic acid (250 mg). Air was bubbled through the solution for 2 h. Then the reaction solution was treated with 2 M $HClO_4$ (~1 mL). The resulting precipitate was washed with a dilute $NaClO_4$ solution. Anal. Calcd for Co(TMpyP(4))$(ClO_4)_5 \cdot 6H_2O$, $C_{44}H_{36}Cl_5CoN_8O_{20} \cdot 6H_2O$: C, 39.40; H, 3.60; Cl, 13.22; N, 8.36. Found: C, 39.25; H, 3.48; Cl, 13.42; N, 8.23.

Physical Measurements. Electronic absorption spectra were recorded with a Cary 3 spectrophotometer equipped with a thermostated cell compartment.

NMR Spectroscopy. ^{1}H NMR studies were carried out with a Nicolet NB 360 spectrometer, typically with ~15 mM cobalt(III) porphyrin, unless described otherwise. In D_2O, the HOD signal at 4.8 ppm was used as a reference since the TSP shift was influenced by the porphyrin complex. Chemical shifts for solutions in organic solvents were relative to internal TMS.

Results and Discussion

Co^{III}(TMpyP(4)) Synthesis. The ^{1}H NMR spectrum of one commercial [Co(TMpyP(4))Cl_2]Cl_3 sample in D_2O showed some impurity signals between 8 and 10 ppm, as well as one at higher field, ~4.4 ppm. The spectrum of a second sample had broad impurity peaks both in D_2O (NCH_3, 5.7 ppm; pyridinium, 9.7 ppm; pyrrole (very broad), ~13.7 ppm) and in DMSO-d_6 (NCH_3, 5.20 ppm; pyridinium, 9.77 ppm; pyrrole (very broad), ~13.7 ppm). The ^{1}H NMR spectrum of a third commercial Co(TMpyP(4)) sample (tosylate salt) showed a small amount of impurities, as evidenced by small peaks in the 8.8–9.5 ppm and 0–3 ppm regions; also, two other peaks at 1.95 and 2.19 ppm were observed (probably due to acetic acid and acetone). Therefore, an effort was made to obtain a pure Co(TMpyP(4)) derivative. Although a few references briefly describe the preparation of Co(TMpyP(4)) derivatives, unfortunately little detail was provided as to concentration and pH.[14–18] We first followed the most cited published preparation,[14] in which an aqueous solution of an excess (~10 times) of $CoCl_2 \cdot 6H_2O$ and TMpyP(4) was heated at reflux overnight at pH ~8–9. Then the product was precipitated with NaI. However, impurities were found in the product, as evidenced by some broad NMR peaks at 9–11 and ~13.7 ppm in D_2O (Figure 2) and a smeared electrophoresis band. Therefore, a modified preparation was developed.

Three factors (temperature, pH, and precipitating anion) were found to be important for avoiding impurities. Since heating was found to generate impurities that were difficult to remove, we eliminated the reflux step by careful pH control at different

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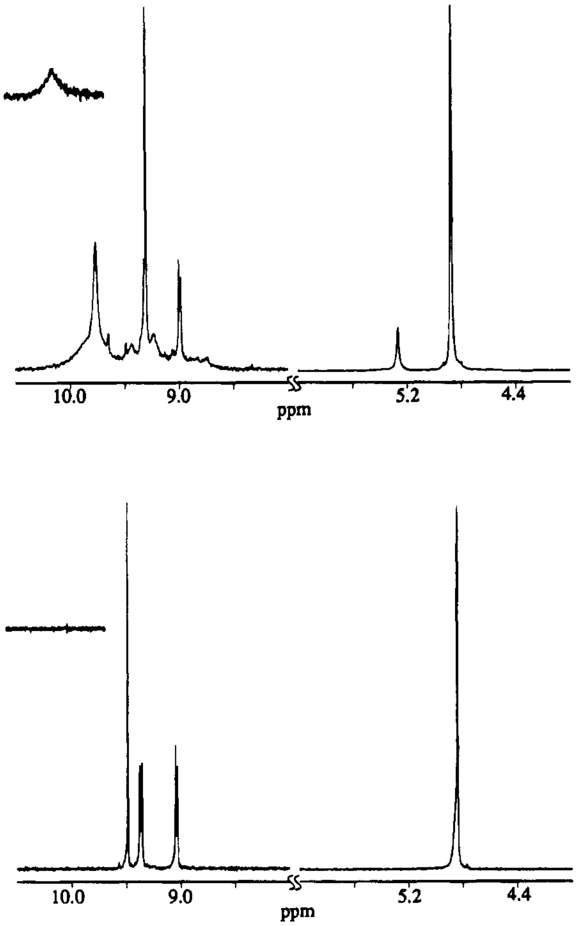

Figure 2. ^{1}H NMR spectra of [Co^{III}(TMpyP(4))Cl$_2$]Cl$_3$ (15 mM in D$_2$O) at room temperature of typical samples prepared with I$^-$ as precipitant (top) and by new procedures (bottom). The upper left insert in each covers the region from 14.8 to 12.8 ppm.

stages of the preparation. Because insertion of a metal into a porphyrin releases two protons, the cobalt(II) insertion reaction was conducted at high pH, in order to ensure complete conversion. N$_2$ was used in order to prevent the oxidation of Co(II) at this stage. The aerial oxidation of Co^{II}(TMpyP(4)) requires low pH; therefore, after the formation of Co^{II}(TMpyP(4)), the pH was lowered. Finally, extra, broad downfield-shifted ^{1}H NMR signals were observed when I$^-$ was used as a precipitant. We did investigate the species that gave these extra, broad signals. However, no effort was made to identify the impurities that gave the sharper signals in literature preparations.

To determine the cause of the extra signals, the reaction solution from a typical preparation using CoCl$_2$ was divided into two portions. One portion was treated with NaPF$_6$, giving the precipitate [Co(TMpyP(4))Cl(H$_2$O)](PF$_6$)$_4$ (compound **II**). The complex in the other portion was precipitated with NaI. In DMSO-d_6, the ^{1}H NMR spectrum of the iodide salt showed the extra broad downfield-shifted signals, while that of compound **II** lacked these signals. Addition of I$^-$ to the compound **II** DMSO-d_6 solution, however, induced the broad signals in the spectrum. These broad signals were also observed in spectra of material isolated after less exhaustive oxidation. We attribute these signals to Co^{II}(TMPyP(4)), and the shifts and the broadness of the pyrrole signal are of the magnitude expected for Co(II) porphyrins.[19] To verify these conclusions, the reducing agent NaBH$_4$ was added to Co^{III}(TMpyP(4)) derivatives in DMSO-d_6 and D$_2$O solutions. In both cases, BH$_4^-$ reduced the Co(III) to the Co(II) TMpyP(4) species, as evidenced by broad downfield-shifted signals similar to those found when I$^-$ was added. These results suggest that iodide can reduce Co^{III}(TMpyP(4)). Therefore, it is best to precipitate the product with hexafluorophosphate or, in a small-scale synthesis, perchlorate. These precipitants gave an essentially Co(II)-free product as evidenced by ^{1}H NMR in D$_2$O but particularly by ^{1}H NMR in DMSO-d_6. The results are summarized in Chart 1.

Chart 1. Axial Ligands after Oxidation of Co(TMpyP(4)) Species with Key Counterions in Solution, Solids Obtained with Various Precipitants, and Major Species Favored When the Solid is Dissolved in DMSO[a]

water soln (+counterion)	precipitant	solid	DMSO soln
Co(H$_2$O)$_2$ + Cl$^-$	ClO$_4^-$	Co(H$_2$O)$_2$ + Co(H$_2$O)Cl	CoCl,DMS*O* + Co(DMS*O*)$_2$
Co(H$_2$O)$_2$ + Cl$^-$	PF$_6^-$	Co(H$_2$O)Cl	CoCl,DMS*O*
Co(H$_2$O)$_2$ + NO$_3^-$	ClO$_4^-$	Co(H$_2$O)NO$_3$	Co(DMS*O*)$_2$
Co(H$_2$O)$_2$ + CH$_3$CO$_2^-$	HClO$_4$	Co(H$_2$O)$_2$	Co(DMS*O*)$_2$
Co(H$_2$O)N$_3$	ClO$_4^-$	Co(H$_2$O)N$_3$	
Co(H$_2$O)$_2$ + Cl$^-$	I$^-$	Co(III,II) mixture	Co(II) + CoCl,DMS*O* + Co(DMS*O*)$_2$

[a] The oxidation state is III unless specified as II.

Table 1. ^{1}H NMR Chemical Shifts (ppm) of Co(III) Porphyrin Species (15 mM) in DMSO-d_6 at 25 °C and vs TMS, Except As Noted

compd/ species	axial ligands	pyrrole	α-H	β-H	NCH$_3$	DMSO[a]
I/a	Cl, DMS*O*	9.28	8.91	9.45	4.73	−0.55 (5 °C)
I/b	(DMS*O*)$_2$	9.49	9.01	9.50	4.75	−0.65
II/a	Cl, DMS*O*	9.28	8.91	9.45	4.72	
III/b	(DMS*O*)$_2$	9.49	9.01	9.51	4.76	−0.65
IV/a	Cl, DMS*O*	9.29	8.93	9.54	4.76	
IV/Cl$_2$	Cl$_2$	9.11	8.83	9.46	4.73	
III/a, 1 equiv of LiCl	Cl, DMS*O*	9.29	8.91	9.46	4.73	
III/a	Cl, DMS*O*	9.29	8.93	9.54	4.76	
IV/Cl$_2$, 10 equiv of LiCl	Cl$_2$	9.11	8.82	9.47	4.73	
IV/(D$_2$O)$_2$[b]	(D$_2$O)$_2$	9.48	9.03	9.36	4.82	
III/N$_3$,D$_2$O[b]	N$_3$ D$_2$O	9.35	8.99	9.34	4.85	
III/(N$_3$)$_2$[b]	(N$_3$)$_2$	9.29	8.98	9.33	4.85	
III/Br[b]	Br, D$_2$O	9.49	9.01	9.32	4.84	

compd/ species	axial ligands	pyrrole	β-H	α-H	γ-H	DMSO[a]
Co(TCF$_3$PP)/**a″**	Cl, DMS*O*	8.99	8.20	8.38		∼−0.5[c]
Co(TCF$_3$PP)/**b″**	(DMS*O*)$_2$	9.20	8.26	8.45		−0.62
Co(TPP)/**a′**	Cl, DMS*O*	8.98	7.83	8.14	7.83	
Co(TPP)/**b′**	(DMS*O*)$_2$	9.18	7.88	8.21	7.88	−0.61

[a] 90% DMSO/10% DMSO-d_6, 30 °C. [b] D$_2$O, TSP reference, 10 mM solution. [c] 60% DMSO/40% CDCl$_3$, 0 °C.

Solutions of Co(TMpyP(4)). The coordination chemistry of Co(TMpyP(4)) complexes has been studied mainly in aqueous solution, where [Co(TMpyP(4))Cl$_2$]Cl$_3$ is known to be a diaqua complex.[20] Preparations in which care was taken to avoid Co(II) gave products with multiple species in DMSO-d_6.

Therefore the axial ligation of Co(TMpyP(4)) in DMSO was studied by ^{1}H NMR. We began with the more soluble perchlorate salt prepared from CoCl$_2$ (compound **I**), which had two species (**a** and **b**) in DMSO-d_6 (cf. Table 1 and Figure 3). There are six possible solvated forms of Co(TMpyP(4)) in DMSO: First, Co(TMpyP(4)) might have two DMSO's bound as axial ligands. Each DMSO could bind through either oxygen

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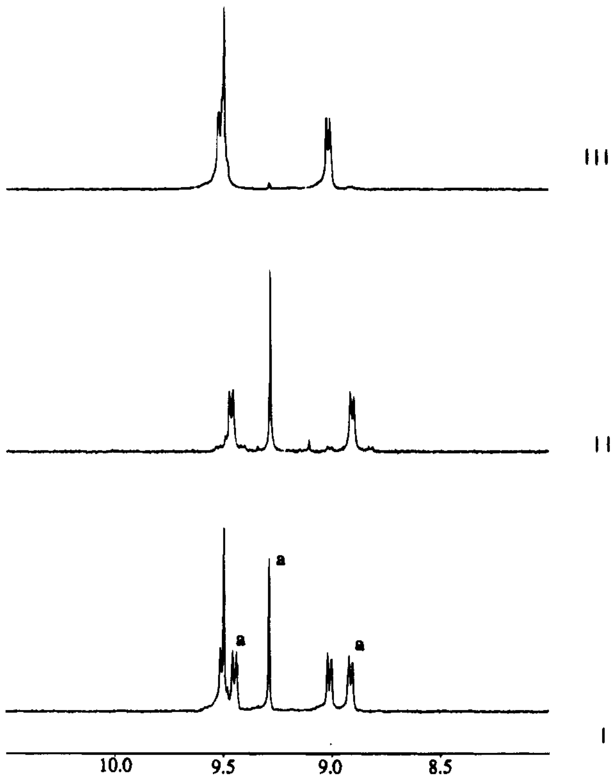

Figure 3. Downfield region of ^1H NMR spectra of Co^{III}(TMpyP(4)) derivatives (15 mM) in DMSO-d_6 at 25 °C: (I) compound **I**; (II) compound **II**; (III) compound **III**.

or sulfur. There are three possible species: both bound through oxygen (DMS*O*−Co−DMS*O*), both through sulfur (DM*S*O−Co−DM*S*O), or one through sulfur and the other through oxygen (DMS*O*−Co−DM*S*O). Second, water present in the solvent could give three possible species: H_2O−Co−H_2O, DM*S*O−Co−H_2O, and DMS*O*−Co−H_2O. There are fifteen possible combinations of two species. Furthermore, the counterion could be bound.

In order to address these issues, a water titration of compound **I** was performed. Details are available in the supplementary material (Table S1). These water titration results indicated that none of the species, H_2O−Co−H_2O, DM*S*O−Co−H_2O, and DMS*O*−Co−H_2O, were present in 100% DMSO-d_6 solution.

The ^1H methyl signal of DMSO (not DMSO-d_6) will be shifted upfield upon binding due to the shielding effect of the porphyrin. Upon N-binding of amino acids to Co(TMpyP(4)), ~3 and ~7 ppm upfield shifts for the β-H and α-H signals, respectively, resulted from the shielding effect.[12] The methyl group of DM*S*O will be in a position similar to that of the α-H. Therefore, an ~7 ppm upfield shift should be observed. The methyl group of DMS*O* will be at a similar distance from cobalt as the β-H, and the methyl signal should have an ~3 ppm upfield shift. To evaluate these possibilities, compound **I** was dissolved in 90% DMSO/10% DMSO-d_6. The methyl signals were examined with 1−1 solvent suppression experiments.[21] However, only one DMS*O* signal, at −0.65 ppm, was clearly observed in these experiments conducted at 30 °C. This signal is ~3 ppm upfield from the solvent DMSO shift, indicating oxygen binding.

A similar titration experiment was conducted with compound **I** in *N,N*-dimethylformamide-d_7 (DMF-d_7). Unlike DMSO, which has two possible binding sites, DMF has only one binding site. Four species were observed over the course of the titration (supplementary Table S2). Since a maximum of three solvato species is possible, these results indicate that there must be axial ligation by the counterion. These results for DMF-d_7 led us to suspect that in DMSO solution the counterion might also be bound.

To determine if ClO_4^- was bound, $LiClO_4$ (10 equiv) was added to compound **I** in DMSO-d_6. Neither the ratio nor the shifts of the two species (**a** and **b**) changed. Addition of the same amount of LiCl, however, gave two sets of peaks with the same shifts found in solutions of compound IV {[Co(TMpyP(4))Cl_2]Cl_3}, which had two species in DMSO-d_6 (Table 1). One set of these peaks has the same chemical shifts as species **a** of compound **I** prior to the addition of 10 equiv of LiCl. Although the material isolated as the perchlorate salt was obtained from water (a solvent in which the NMR spectrum showed no evidence for bound chloride at chloride concentrations higher than that used in the preparations), the NMR results led us to recalculate the analytical data. A good fit was obtained for a formula with approximately one Cl^- per two Co species.

To evaluate anion binding further, a PF_6^- salt ([Co(TMpyP(4))Cl(H_2O)]$(PF_6)_4$, compound **II**) was synthesized with $CoCl_2$ and HCl. Analytical data demonstrated the presence of one chloride per Co in the product. The ^1H NMR spectrum in DMSO-d_6 (Table 1, Figure 3) showed mainly the one set of signals characteristic of species **a** of compound **I**.

Likewise, a preparation of a perchlorate salt was carried out with chloride excluded. The preparation utilized $Co(NO_3)_2$ and HNO_3. The spectrum of the product (compound **III**) in DMSO-d_6 also gave only one set of peaks, which agree with species **b** of compound **I** in DMSO-d_6 (Table 1, Figure 3). In 90% DMSO/10% DMSO-d_6, the spectrum of compound **III** showed a single DMS*O* signal at −0.65 ppm. These results indicate that, of the two species of compound **I** originally present in DMSO, the axial ligands for **a** are Cl^- and possibly water (but more likely DMSO) and for **b** are two DMS*O* molecules.

A careful titration of compound **III** with LiCl showed that addition of a small amount (1 equiv) induced formation of the monochloro species (**a** in compounds **I** and **II**) as the major species present. Continued addition of LiCl gave a second new species with signals at 4.73 (s, Me), 8.82 and 9.46 (d, pyridinium), and 9.11 (s, pyrrole) ppm. Some signals of **a** shift slightly (Table 1). At 10 equiv, ~50% of the second new species was present. These results indicate that the second new species has two axial chlorides. The signals of the dichloro species matched those of the two species present in DMSO solutions of compound IV {[Co(TMpyP(4))Cl_2]Cl_3} (Table 1). Therefore, the axial ligation of the two species is Cl−Co−Cl and Cl−Co−(D_2O or DMSO).

Combined DMSO solvent suppression and water titration NMR experiments were conducted with compounds **II** and **III** to determine the number of DMS*O*'s bound to **a** and to determine if **b** (the monochloro species) has a bound DMS*O*. This determination required a knowledge of signal intensity. The excitation profiles of pulses in the solvent suppression experiments do not allow meaningful comparisons of signal intensity unless shifts are <~0.5 ppm. In order to assess which species were formed, comparisons were made between signals in the same regions of the spectrum in a water titration experiment of compound **III**. The results (supplementary material) indicate that (i) **b** has two DMS*O* molecules, (ii) the monoaqua species has one DMS*O*, (iii) ClO_4^- cannot be bound to species **b**, (iv) both DMSO molecules are bound in the same way, and (v) the diaqua species identified earlier has no DMS*O* signal, as expected.

Since a fast-exchange DMSO was observed for Co(TPP)Cl and Co(TCF_3PP)Cl (see below), an effort was made to determine

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[21] Clore, G. M.; Kimber, B. J.; Gronenborn, A. M. *J. Magn. Reson.* **1983**, *54*, 170–173.

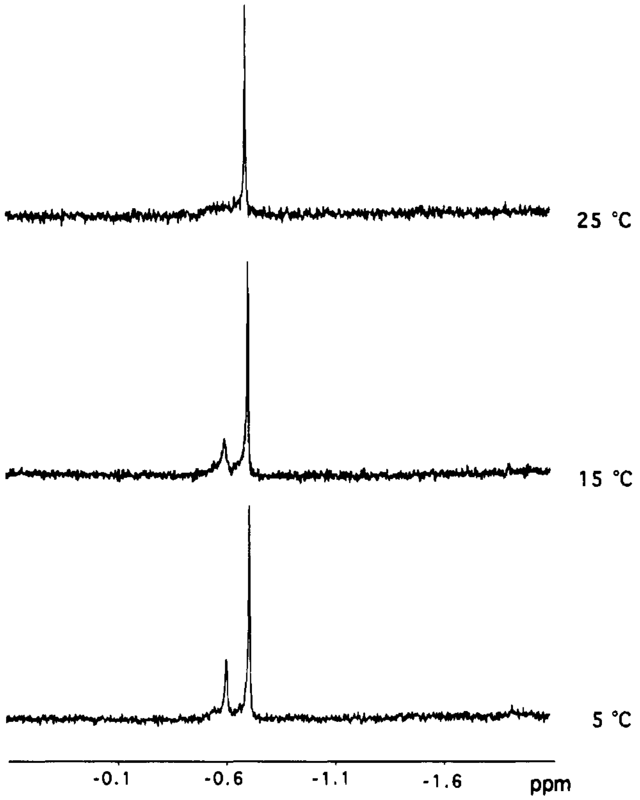

Figure 4. Upfield region of 1−1 solvent suppression NMR spectra of compound **I** (15 mM) in 75% DMSO/25% $CDCl_3$ at different temperatures.

if the monochloro apecies has a bound DMSO. The 1−1 solvent suppression experiment was conducted at different temperatures. In order to keep the solution from freezing at low temperature, 25% $CDCl_3$ was added. In spectra at 25 °C, the porphyrin signals of both the monochloro **a** and the $(DMSO)_2$ species **b** of compound **I** were observed, as found in 100% DMSO-d_6. A sharp, clearly observed signal at −0.65 ppm is from the $(DMSO)_2$ species. There is probably a very weak broad signal in the same upfield region (Figure 4). At 15 °C, a broad signal at −0.55 ppm was clearly observed, and it was sharper at 5 °C. This signal, which must be for the monochloro species **a**, had half the intensity of the $(DMSO)_2$ signal. The corresponding porphyrin signals retain the same intensity ratio (~1) as found at 30 °C, indicating that species **a** has one DMS*O*,Cl. Therefore, at room temperature, the DMS*O* in **a** is in fast exchange with free DMSO.

In water titration experiments (supplementary material) it was found that the Cl,DMS*O* species (**a**) is disfavored by addition of water. This result may be attributed to the solvation of the chloride anion by water. DMSO is not effective in solvating this anion. On addition of water, coordination of both water and DMSO became favored over chloride. At 20% D_2O/80% DMSO, the molar concentrations of these solvents are equal (~11 M). In solutions of this mixture, the ratio of $(DMSO)_2$:D_2O,DMSO:$(D_2O)_2$ was about 3:3:1, indicating that DMSO binds more strongly than D_2O. The amount of the D_2O,DMS*O* species was slightly less than that expected; statistically the ratio should be 3:4:1.

Although the Co(TMpyP(4)) compounds **I**−**III** all exhibit different spectra in DMSO-d_6, all give the same spectrum in D_2O. A chloride titration was conducted on a compound **III** (0.01 M) D_2O solution. Compound **III** was prepared from Co$(NO_3)_2$ in the absence of Cl^-. Addition of Cl^- (from 0.01 to 0.2 M) did not induce any new signals, and only very small shifts of the signals (0.01 ppm) were observed, suggesting that Cl^- binding is not favored at low Cl^- concentration. The chloride concentration in the solutions from which compounds **I** and **II**, $Co(TMpyP(4))Cl_{0.6}(ClO_4)_{4.4}\cdot 4H_2O$ and $[Co(TMpyP(4))Cl(H_2O)](PF_6)_4$, respectively, were precipitated is <0.1 M; therefore, Cl^- is not likely to be extensively bound to cobalt before ClO_4^- or PF_6^- is added. Small shoulders on pyridinium signals, which emerged at higher Cl^- concentration (>0.2 M), indicated the formation of a new species. The new species increased slightly as Cl^- concentration increased. Similarly, addition of Br^- to a compound **III** D_2O solution did not give new species until the concentration of Br^- reached 0.1 M, when a small amount of new species started to emerge. The new species was clearly observed when $[Br^-] > 0.5$ M. The signals (Table 1) for the new species were broader than those for the diaqua species, suggesting that Br^- is probably in fast exchange with water. The amount of the new species obtained with Br^- is larger than that obtained with Cl^-. In contrast, addition of $NaNO_3$ to a compound **III** D_2O solution did not induce any new species even in 1 M $NaNO_3$ solution, confirming that the spectral shoulders observed at high Cl^- or Br^- concentrations resulted from anion binding.

Monoazido and diazido species can be formed by addition of 1 or 2 equiv of N_3^- to the $[Co(TMpyP(4))Cl_2]Cl_3$ solution (Table 1). The signals of the azido species remained sharp, indicative of slow exchange of azide. Precipitation was readily observed upon addition of a small amount of N_3^- (0.5 equiv) to a 10 mM compound **III** D_2O solution containing ClO_4^- as the counterion. The NMR spectrum of this Co(TMpyP(4)) solution showed the formation of monoazido species. Addition of more azide formed the diazido species, and more precipitation was observed. The reduction of the charges of the porphyrin complex on binding of anions to cobalt induced the precipitation. N_3^- is a better ligand than Cl^- and Br^-; therefore, the precipitation can be induced readily even at N_3^- concentrations as low as 5 mM. The precipitate was also observed on addition of Br^- or Cl^-, but at much higher concentration (>100 mM). These results suggest that, in the preparative solution, a small amount of chloride was probably bound to cobalt. Addition of a salt of a large counterion precipitated the monochloro-bound species preferentially.

The best way to obtain the $[Co(TMpyP(4))(H_2O)_2]^{5+}$ salts is to use cobalt(II) acetate as the starting material, chloroacetic acid to adjust the pH for air oxidation, and, finally, $HClO_4$ to simultaneously protonate the carboxylic acids (preventing coordination) and to precipitate the product. The product prepared in this way gave a very clean spectrum in DMSO-d_6; in which only species **b** was observed, and no acetate signal was present. The results of both the preparative and solution studies on Co(TMpyP(4)) derivatives are summarized in the Chart 1.

Solutions of Other Co(III) Porphyrins. In order to gain insight into Co(TMpyP(4)) chemistry, cobalt porphyrins soluble in both noncoordinating ($CDCl_3$) and coordinating (DMSO) solvents were studied. It is well-known that the so-called five-coordinate forms of Co(TPP)Cl, Co(TCF_3PP)Cl, and Co(OEP)-Cl give broad ^1H NMR signals in $CDCl_3$.[22−24] The unusual broadening has been suggested to be a result of paramagnetism arising from the formation of a small amount of a π radical cation/cobalt(II) porphyrin species. It has also been reported that six-coordinate Co^{III}(TPP) complexes formed in the presence of a good ligand or in a coordinating solvent do not form π radical cations and do not give broad ^1H NMR signals.[22] In an alternative interpretation, it has been suggested that high-spin

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(23) Yamamoto, K.; Uzawa, J.; Chigimatsu, T. *Chem. Lett.* **1979**, 89−92.

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Table 2. ^1H NMR Chemical Shifts (ppm vs TMS) of H_2O in Co(III) Porphyrin−$CDCl_3$ Solutions[a]

porphyrin	H_2O shift[b]	H_2O:porphyrin (10 mM) ratio	H_2O shift[c]	H_2O:porphyrin (2 mM) ratio
Co(TCF_3PP)Cl	1.06	3.6	1.50	9.0
Co(TPP)Cl	1.34	1.5	1.51	11.0
Co(TCH_3PP)Cl	1.30	1.0		
Co(TCH_3OPP)Cl	1.32	1.5		

[a] The H_2O shift in $CDCl_3$ is 1.54 ppm. [b] 10 mM porphyrin. [c] 2 mM porphyrin.

Co(III) accounts for broadening in spectra of the five-coordinate forms.[23] However, we feel the report that molar susceptibilities of the complexes are too low for any substantial population of high-spin Co(III) is most reliable.[22] Therefore, the broadening could be the result of a spin equilibrium, with the low-spin form favored.

The issue of whether the π radical cation or the spin equilibrium accounts for the broadening is tangential to our studies. We were interested primarily in the nature of the DMSO complexes of these porphyrins. These are six-coordinate and diamagnetic. However, in the course of our investigation, we made several observations about the $CDCl_3$ solutions that are worth mentioning.

We noted that spectra of $CDCl_3$ solutions of Co(TPP)Cl and Co(TCF_3PP)Cl have extra signals at ~1.34 and 1.06 ppm, respectively. Addition of H_2O (1 μL) to these two solutions increased the signal intensities and shifted the signals downfield to 1.4 and 1.34 ppm, respectively. In the absence of porphyrin, $CDCl_3$ has a signal at ~1.54 ppm which increases in size and shifts downfield to 1.60 ppm on H_2O saturation by addition of 5 μL of H_2O. In the porphyrin solutions, no separate water signals were observed, suggesting that these signals at ~1.0−1.4 ppm were water signals. Addition of 1 μL of water sharpened the pyrrole signal, especially for Co(TCF_3PP)Cl. Other solutions were prepared, and most of the water was removed by using $CaCl_2$. The intensity of the water signal was just above the noise. However, the porphyrin signals did not change upon removal of H_2O, probably because the amount of water in the system is so small (fewer than two and four H_2O's per Co(TPP)Cl and Co(TCF_3PP)Cl, respectively; Table 2) that little H_2O was coordinated in solutions prepared without precaution taken to dry the solution. Since the H_2O signals of Co(TPP)Cl and Co(TCF_3PP)Cl $CDCl_3$ solutions are upfield shifted from the normal free H_2O shift, some water must be bound. The upfield shift of the bound H_2O is only ~0.5 ppm, indicating that only a small amount of H_2O was bound to the porphyrins. It was also observed that sample dilution shifted the H_2O signal downfield. In the 2 mM Co(TPP)Cl solution, the H_2O signal was observed at 1.51 ppm, which is closer to the normal free H_2O shift. Addition of coordinating solvents such as DMSO or DMF or ligands such as Me_3Bzm to $CDCl_3$ solutions of these two porphyrins shifted the H_2O signals downfield toward ~1.55 ppm. No separate free- and coordinated-H_2O signals were observed in any case.

All of these results suggest that H_2O is involved in weak binding to Co(TPP)Cl and Co(TCF_3PP)Cl in $CDCl_3$ and that the bound water is in fast exchange with free water. Therefore, Co(TPP)Cl and Co(TCF_3PP)Cl in $CDCl_3$ are mixtures of five- and six-coordinate forms. The result is consistent with a crystal structure study of Co(TPP)Cl indicating that there is a cobalt-bound water.[25] One can expect that the H_2O binding is stronger for Co(TCF_3PP)Cl than for Co(TPP)Cl because of more electron-withdrawing substituents in Co(TCF_3PP)Cl. This greater binding of water to Co(TCF_3PP)Cl is manifested as a more upfield-shifted H_2O signal and sharper porphyrin signals compared to those of Co(TPP)Cl. Supporting this conclusion, the H_2O signals for Co(TCH_3PP)Cl and Co(TCH_3OPP)Cl were downfield from that for Co(TCF_3PP)Cl, although the H_2O:porphyrin ratio was smaller. At DMSO:Co(TCF_3PP)Cl = ~3, the H_2O signal was close to that of free H_2O, whereas even at DMF:Co(TCF_3PP)Cl = 3, the H_2O signal was slightly upfield shifted. The binding preference was clearly DMSO > DMF > H_2O.

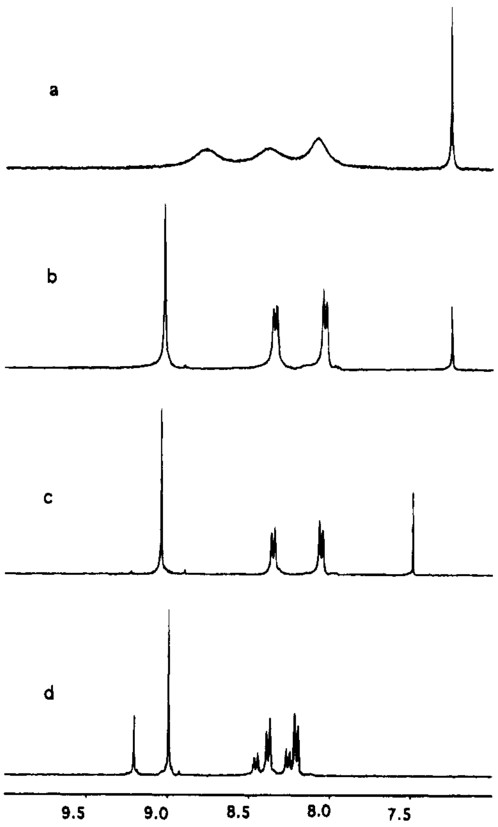

Figure 5. Downfield region of ^1H NMR spectra of Co(TCF_3PP)Cl (10 mM) solutions at room temperature: (a) in $CDCl_3$, no DMSO; (b) in $CDCl_3$, 2 equiv of DMSO; (c) in 90% $CDCl_3$/10% DMSO-d_6; (d) in 100% DMSO-d_6.

$CDCl_3$ Solutions. DMSO (natural abundance) was titrated into Co(TPP)Cl, Co(TCF_3PP)Cl, and Co(OEP)Cl $CDCl_3$ solutions. Upon addition of DMSO, the broad porphyrin signals became sharper, indicating that DMSO coordinated to form six-coordinate complexes. For Co(TPP)Cl, Co(TCF_3PP)Cl, and Co(OEP)Cl solutions, at DMSO:Co(III) porphyrin ratios of 1:1 and 2:1, DMSO signals were observed at 0.07, −0.203, and −0.72 ppm and at 1.08, 1.07, and 1.06 ppm, respectively. Further addition of DMSO shifted the DMSO signals downfield for all three cobalt porphyrins, but no free-DMSO signal was observed. The pyrrole signals shifted downfield but gave no evidence of two slowly exchanging species. These results demonstrate for these species that the DMSO is in fast exchange. The downfield shift of the pyrrole signal of Co(TPP)Cl and Co(TCF_3PP)Cl occurred only up to a 2:1 ratio, indicating that the diamagnetic Cl,DMS*O* complexes (**a′** for Co(TPP)Cl and **a″** for Co(TCF_3PP)Cl) were fully formed.

Addition of DMSO-d_6 to Co(TCF_3PP)Cl was studied in depth (supplementary Table S5). Even in the presence of 10% DMSO-d_6, only one Co(TCF_3PP)Cl species (**a″**, the Cl,DMS*O* species) was observed (Figure 5). At 20% DMSO-d_6, a small amount of a second species (**b″**, $(DMSO)_2$) with more downfield-shifted signals was observed. The intensity of the **b″** signals increased with increasing DMSO-d_6 percentage. At 20−

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50% DMSO-d_6, only **a″** and **b″** were observed; the porphyrin signal line widths of these two species remained unchanged. When the titration was extended to 100% DMSO-d_6 (Table S5), the signals of **a″** and **b″** we assigned to the Cl,DMS*O* and the (DMS*O*)$_2$ species, respectively, correlated with those assigned to these species in 100% DMSO-d_6 (see below). Furthermore, in a related solvent suppression experiment at 30 °C on Co(TCF$_3$PP)Cl, the spectrum in CDCl$_3$/10% DMSO did not show a DMS*O* signal in the upfield region; but when DMSO was increased to 25%, a sharp DMS*O* signal was observed at −0.61 ppm, consistent with a (DMS*O*)$_2$ species.

Although the presence of the (DMS*O*)$_2$ species for Co(TCF$_3$PP) was not observed until ≥20% DMSO-d_6, the Co(TPP)(DMS*O*)$_2$ (**b′**) species (~30%) was observed in the presence of only 10% DMSO-d_6 (supplementary Table S6). The porphyrin signals of the (DMS*O*)$_2$ species were sharper than those of the Cl,DMS*O* (**a′**) species. Solvent suppression experiments on Co(TPP)Cl in CDCl$_3$/10% DMSO at 30 °C showed a DMS*O* signal (the signal is broader than that observed for Co(TCF$_3$PP)Cl). The DMS*O* signal increased and became sharper with an increase in DMSO. At 25% DMSO, the sharp signal (at −0.60 ppm) is assigned to **b′**; it has a broad weak shoulder assigned to **a′**.

These results suggest that addition of a small amount of DMSO to Co(TPP)Cl or Co(TCF$_3$PP)Cl in CDCl$_3$ solution gives the Cl,DMS*O* species. The formation of the six-coordinate species caused the sharpening of the porphyrin signals. The (DMS*O*)$_2$ species formed only in the presence of large amounts of DMSO. The DMS*O* trans to chloride is in fast exchange with free DMSO, whereas exchange is slower for DMS*O* trans to another DMS*O*.

100% DMSO-d_6. In DMSO-d_6, both Co(TPP)Cl and Co(TCF$_3$PP)Cl gave sharp signals; furthermore, both have two species (**a′** and **b′** for Co(TPP)Cl, **a″** and **b″** for Co(TCF$_3$PP)Cl; Table 1). Solvent suppression and LiCl titration experiments (supplementary material) showed that these were the Cl,DMS*O* (**a′**, **a″**) and (DMS*O*)$_2$ (**b′**, **b″**) species.

Further Comparisons and Summary

The Co^{III}(TMpyP(4)) moiety has five positive charges. In the DMSO solutions of [Co(TMpyP(4))Cl(H$_2$O)](PF$_6$)$_4$, compound **II**, at equilibrium, the ratio Cl,DMS*O*:(DMS*O*)$_2$ was ~20:1. Compared to Co(TMpyP(4)), Co(TCF$_3$PP) has lower charge (one plus); therefore, the chloride binding is expected to be less favorable. The ratio Cl,DMS*O*:(DMS*O*)$_2$ was only ~2:1. Co(TPP), which has the same charge but is a more electron-rich porphyrin, has an even lower ratio (~1:1). In all three cases, the DMS*O* trans to Cl is in relatively fast exchange.

In DMSO-d_6, even in the presence of 0.2 M LiCl, only about 60% of [Co(TMpyP(4))Cl$_2$]$^{3+}$ was formed. To assess the affinity for Cl$^-$ further, we searched for dichloro species of Co(TCF$_3$PP) and Co(TPP) in DMSO-d_6. A pyrrole signal at 8.82 ppm for Co(TCF$_3$PP) was observed at 0.1 M LiCl (Figure 6). The intensity of this signal (6%) increased to 17% in 0.4 M LiCl. In contrast, for Co(TPP), no signals attributable to dichloro species were observed even in 0.4 M LiCl. The preference for Cl$^-$ binding is thus Co(TMpyP(4)) > Co(TCF$_3$PP) > Co(TPP) for both mono- and dichloro species.

It is commonly believed[22] that it is difficult to obtain satisfactory elemental analyses for porphyrin complexes. We found two sources of problems with Co(TMpyP(4)) derivatives. First, iodide can lead to Co(II) impurities. Second, lower charged acido complexes precipitate preferentially. In water, the order of affinity of common anions for the [Co^{III}(TMpyP(4))(H$_2$O)$_2$]$^{5+}$ cation was N$_3^-$ > Br$^-$ > Cl$^-$ > NO$_3^-$.

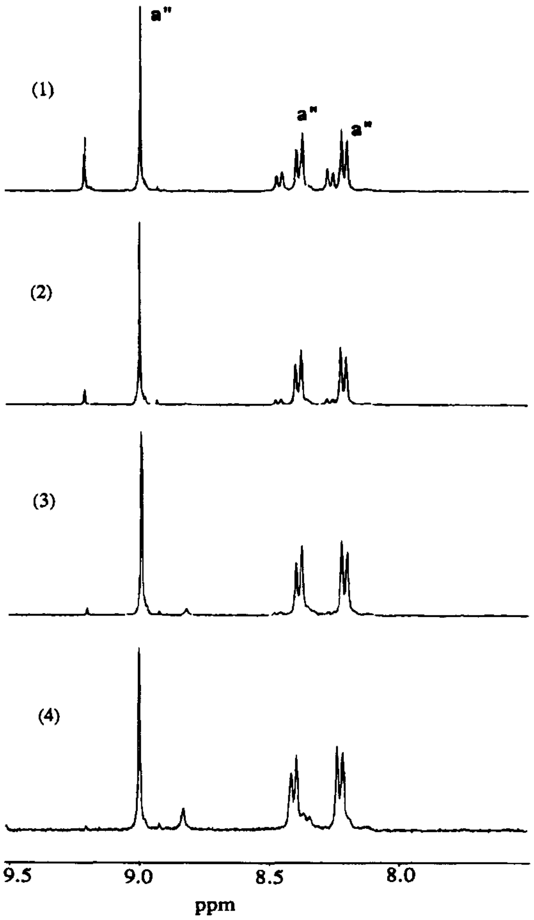

Figure 6. Downfield region of ^{1}H NMR spectra of Co(TCF$_3$PP)Cl (10 mM) in DMSO-d_6 at 25 °C with (1) no LiCl, (2) 0.01 M LiCl, (3) 0.1 M LiCl, and (4) 0.4 M LiCl.

It has been generally assumed that Co(TPP)Cl and related species are five-coordinate in both solid and solution.[22,23,26] Our NMR results clearly show that the species are preferentially five-coordinate in CDCl$_3$ solution but that the solids contain water. An X-ray structure[25] showing that Co(TPP)Cl is six-coordinate with coordinated water agrees with this assessment. We accept the assessment that these species have only a small degree of paramagnetism (due to either high to low spin equilibria or porphyrin to Co redox processes). Such paramagnetism can explain the line broadening observed.

For all species studied, the NMR data suggest oxygen binding by DMSO and that the exchange rate on the NMR time scale depends on the trans ligand. The DMS*O* exchange is slower when the trans ligand is an oxygen donor (DMS*O* or H$_2$O) than when the trans ligand is Cl$^-$. Compared to the case of Co(TPP)Cl, the electron-withdrawing CF$_3$ substituents in Co(TCF$_3$PP)Cl decrease electron donation to Co, favoring water binding in CDCl$_3$ and decreasing DMS*O* exchange rates in DMSO. For the Co(III) porphyrins, the data suggest the following order of preferential binding by solvent molecules: DMSO > DMF > H$_2$O. However, Cl$^-$ binds relatively strongly in DMSO-d_6 compared to H$_2$O solutions.

Acknowledgment. This work was supported by NIH Grant AI 27196 to L.G.M.

Supplementary Material Available: Text giving details of various titrations and tables of ^{1}H NMR data for titrations in nonaqueous solvents (9 pages). Ordering information is given on any current masthead page.

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