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^{1}H NMR Studies of Iron(III) Porphyrins with Axial Phenoxide or Thiophenoxide Ligands†

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The proton NMR spectra of five-coordinate, high-spin iron(III) complexes of protoporphyrin IX dimethyl ester and tetraphenylporphyrin with axial *p*-nitrophenoxy and *p*-nitrothiophenoxy ligands have been obtained and analyzed. Differences between S and O coordination included an upfield bias for the heme methyls in the phenoxy complexes by ca. 5 ppm and a more sizable upfield shift (by ca. 10 ppm) for the porphyrin meso protons in thiophenoxy complexes. Resonances due to the axial phenoxy ligands have been assigned by methyl and methoxy substitution. Analysis of relaxation properties yields two anomalous results. The axial ligand differential relaxation does not parallel the relative distances from the metal, suggesting that line widths cannot be used to make assignments when a large degree of π spin delocalization is present. The axial ligand and porphyrin resonances give conflicting indexes of the metal-centered relaxivity. The spectrum of the low-spin, six-coordinate complex with axial *p*-nitrophenoxide and imidazole ligands has been recorded. It differs from that of the bis(imidazole) adduct. Low-field resonances observed in the ^{1}H NMR spectrum of the mutant hemoglobins Iwate and Boston can now be assigned to the methylene and/or meta protons of the axial tyrosinate ligands in high-spin complexes.

Introduction

Modification of the axial ligation of the heme prosthetic group is one of the major means of altering the heme behavior in the heme enzymes. This study is concerned with obtaining ^{1}H NMR spectral data on iron(III) porphyrins with phenoxide or thiophenoxide as the axial ligand. These serve as models for two important classes of heme proteins. Phenoxide ligands, in the form of tyrosinate, are found in the heme enzyme catalase[1] and arise in one of the subunits in the mutant hemoglobins, designated HbM, for which either the proximal (F8) or distal (E7) sites have been substituted by tyrosinate.[2] Thus, both HbM Boston (α E7 His → Tyr) and HbM Iwate (α F8 His → Tyr) possess a high-spin ferric ion with a bound tyrosinate.[3,4] In the former HbM, the structure is known to be five-coordinate,[3] while, for the latter protein, it has been suggested[4] that a histidine may also be bound to the high-spin ion. While thiophenoxides, as such, do not occur in proteins, the ligand allows an assessment of the influence of -SR versus -OR′ bonding on the magnetic and electronic properties of the bound heme in a relatively stable five-coordinate ferric complex and serves as a model for the thiolate ligand, which is responsible for many of the unique properties of the cytochromes P450.[5] NMR studies of such model complexes for cytochromes P450 have been restricted largely to high-spin ferrous species.[6]

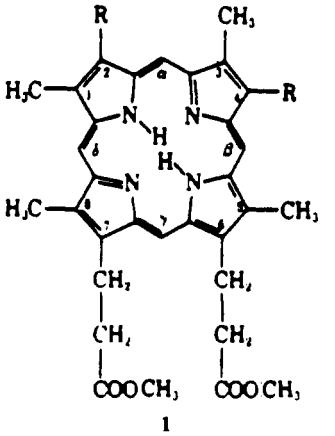
We are concerned with both high-spin, five-coordinate complexes, (P)Fe^{III}(OAr)[7] and (P)Fe^{III}(SAr),[8] as well as low-spin, six-coordinate complexes, (P)Fe^{III}(OAr)(Im), where an imidazole ligand occupies the sixth coordination site.[8] While the basic resonance patterns expected for iron(III) porphyrins with these spin and ligation states are reasonably well established,[9,10] we are involved here with identifying specific features in the ^{1}H NMR spectra of the porphyrin resonances that may be useful in identifying and differentiating the axial ligands present in both heme proteins and in model systems. Specifically, can axial Fe–O versus Fe–S ligation effects on the heme electronic properties be readily differentiated by ^{1}H NMR spectroscopy? Additionally, the axial ligands themselves contribute to the spectrum, and we are concerned with identifying these axial ligand resonances and with assigning them to specific protons within the ligands. With axial phenolate ligands, assignments of these resonances have been made[11,12] and complementary information is available from Que and co-workers' studies on five-coordinate complexes with salen as the equatorial ligand.[13,14]

Complexes considered here include those of protoporphyrin IX dimethyl ester ((PP)H$_2$) (**1**), R = CHCH$_2$, and of synthetic *meso*-tetraarylporphyrins.

Table I. Chemical Shifts (ppm) for Fe^{III} Five-Coordinate and Six-Coordinate Complexes

complex	1,3,5,8-CH$_3$	*m*-H	β-vinyl
	Five-Coordinate		
Fe(PP)(OC$_6$H$_4$-*p*-NO$_2$)[a]	45.28[b]	-38.7	-0.88
	44.16		
	43.14		
Fe(PP)(OC$_6$H$_4$-*p*-NO$_2$)[c]	43.26[b]	-39.6	*h*
	41.46		
	39.81		
Fe(PP)(SC$_6$H$_4$-*p*-NO$_2$)[c]	51.04[b]	-49.6	-1.39
	48.12		
	46.87		
	Six-Coordinate		
Fe(PP)(OC$_6$H$_4$-*p*-NO$_2$)(Im)[a,d]	20.16	0.83	-5.34[e]
	19.79	-0.2	-5.88
	16.93	-1.8	-6.51
	15.20	-2.2	-7.14
Fe(PP)(Im)$_2^+$[a,d]	18.08	1.7	-5.27[f]
	17.59	0.4	-5.92[g]
	17.08	-0.5	-6.53
	14.93	-1.7	

[a] In $CDCl_3$ at 24 °C referenced to TMS through the residual $CHCl_3$ signal at 7.26 ppm. [b] Corresponds to two overlapping methyl proton resonances. [c] In toluene-d_8 at 24 °C referenced to TMS via residual toluene methyl protons at 2.09 ppm. [d] At -60 °C. [e] α-vinyl: 12.64, 11.86 ppm. [f] α-vinyl: 12.99, 12.08 ppm. [g] Corresponds to two overlapping vinyl proton resonances. [h] Buried in the diamagnetic region.



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† Abbreviations: TPP, tetraphenylporphyrin dianion; TTP, tetra-*p*-tolylporphyrin dianion; protoporphyrin IX dimethyl ester dianion; Ar, aryl group; salen, ethylenebis(salicylideneamine) dianion; Im, imidazole; P, generic porphyrin dianion; TMS, tetramethylsilane.

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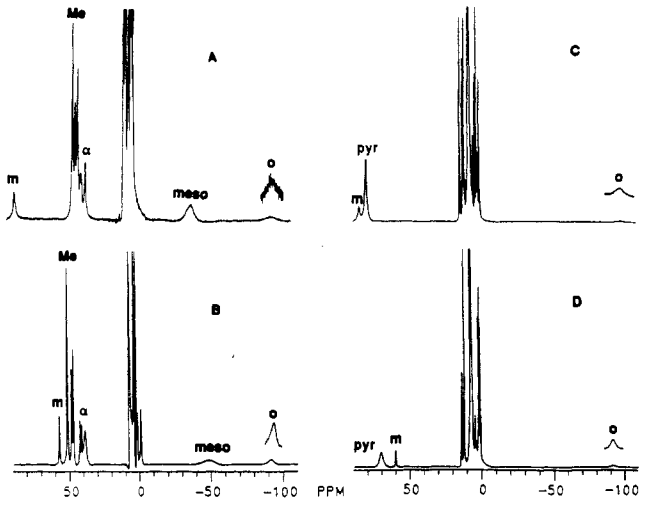

Figure 1. 200-MHz ^{1}H NMR spectra of five-coordinate iron(III) complexes at 24 °C in toluene-d_8: (A) (PP)Fe^{III}(OC_6H_4-*p*-NO_2); (B) (PP)Fe^{III}(SC_6H_4-*p*-NO_2); (C) (TPP)Fe^{III}(OC_6H_4-*p*-NO_2); (D) (TPP)-Fe^{III}(SC_6H_4-*p*-NO_2). Resonance assignments: Me = heme 1,3,5,8-methyls; α = propionate α-CH_2; β = propionate β-CH_2; meso = meso porphyrin; *o*, *m* = ortho, meta of axial ligand. Axial ligand proton line widths: (PP)Fe^{III}(OC_6H_4-*p*-NO_2), *o*-H 1.9 kHz, *m*-H 0.49 kHz; (PP)-Fe^{III}(SC_6H_4-*p*-NO_2), *o*-H 1.2 kHz, *m*-H 0.10 kHz; (TPP)Fe^{III}-(OC_6H_4-*p*-NO_2), *o*-H 1.8 kHz, *m*-H 0.29 kHz; (TPP)Fe^{III}(SC_6H_4-*p*-NO_2), *o*-H 0.77 kHz, *m*-H 0.12 kHz.

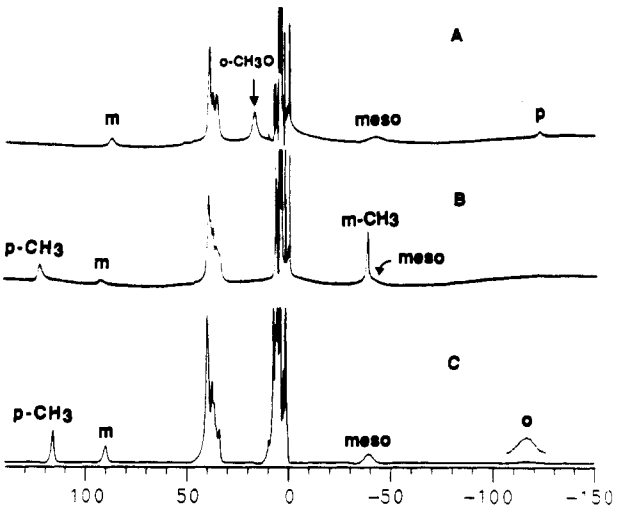

Figure 2. NMR spectra of five-coordinate complexes, (PP)Fe^{III}(OAr), in chloroform-*d* at 24 °C: (A) Ar = *o*,*o*-dimethoxyphenyl at 200 MHz; (B) *m*,*p*-dimethylphenyl at 200 MHz; (C) *p*-tolyl at 300 MHz. Resonance assignments: *o*, *m*, *p* = ortho, meta, para phenoxy protons; *p*-CH_3, *m*-CH_3 = *p*-, *m*-methyl protons of phenoxy ligands; *o*-CH_3O = *o*-methoxy protons of phenoxy; meso = meso porphyrin protons.

Results

The ^{1}H NMR spectra of the five-coordinate complexes are gathered in Figure 1 for ready comparison. Numerical values for selected resonances are listed in Table I. The basic pattern of chemical shifts of these four complexes follows the pattern seen for other five-coordinate complexes like (P)Fe^{III}Cl, and the resonance assignments given in the figure caption follow those made earlier.[10]

Axial ligand resonances are clearly seen in these spectra for the phenolate and thiophenolate ligands. To facilitate assignment of these resonances, Figure 2 offers a comparison of the spectra of (PP)Fe^{III}(OAr) with three different aryl groups chosen to allow identification of individual resonances. The assignments made here agree with those of Goff and co-workers on synthetic porphyrins.[12] Table II contains information for the axial ligand resonances of these complexes, information for some tetraarylporphyrins, and corresponding data for some salen complexes.[13]

Figure 3 shows ^{1}H NMR spectra relevant to the formation of low-spin, six-coordinate, mixed-ligand species. Trace A shows the spectrum in chloroform-*d* at −60 °C of (PP)Fe^{III}($Im)_2$, which has been obtained previously.[9] Trace B shows the spectrum

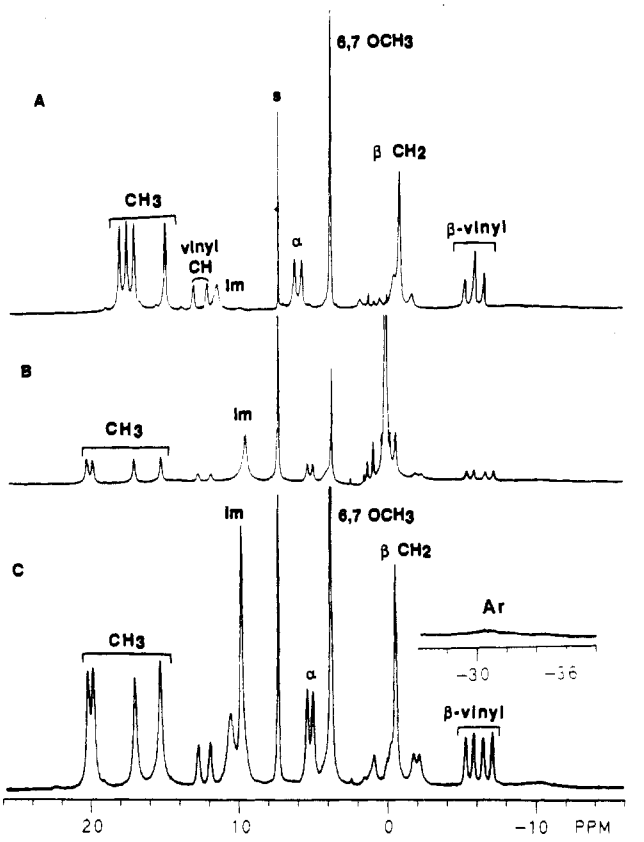

Figure 3. 200-MHz ^{1}H NMR spectra of low-spin, six-coordinate iron-(III) complexes in chloroform-*d* solution at −60 °C: (A) (PP)Fe^{III}(Cl) and 2.2 equiv of imidazole; (B) (PP)Fe^{III}(OC_6H_4-*p*-NO_2) and 1.1 equiv of imidazole; (C) (PP)Fe^{III}(OC_6H_4-*p*-NO_2) and 1.5 equiv of imidazole. The principal species in spectrum A is (PP)Fe^{III}($Im)_2^+$; the principal species in spectra B and C is (PP)Fe^{III}(OC_6H_4-*p*-NO_2)(Im). Resonance assignments follow those in Figure 1. Ar denotes a resonance probably arising from the axial phenolate.

obtained at −60 °C in chloroform-*d* from (PP)Fe^{III}(OC_6H_4-*p*-NO_2) in the presence of 1.1 molar equiv of imidazole, while trace C shows the spectrum in the presence of 1.5 molar equiv of imidazole. Note that in both traces B and C none of the bis-(imidazole) complex is present. Attempts to prepare a similar mixed-ligand complex with a thiophenolate ligand were thwarted by both precipitation when imidazole was added to (PP)Fe^{III}-

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Table II. Axial Phenolate and Thiophenolate Resonance Assignments (ppm)

complex	ortho (X)	meta (X)	para (X)
Fe(PP)(OC_6H_4-4-NO_2)[a]	-96 (H)	84.1 (H)	
Fe(PP)(SC_6H_4-4-NO_2)[a]	-93 (H)	57.1 (H)	
Fe(PP)(OC_6H_4-4-NO_2)[b]	-89 (H)	73.0 (H)	
Fe(PP)(OC_6H_4-2,6-$(OCH_3)_2$)[b]	17 (OCH_3)	85.8 (H)	-118.4 (H)
Fe(PP)(OC_6H_4-3,4-$(CH_3)_2$)[b]	-117 (H)	-37.1 (CH_3)	121.3 (CH_3)
Fe(PP)(OC_6H_4-4-CH_3)[b]	-116 (H)	89.9 (H)	116.1 (CH_3)
Fe(TPP)(OC_6H_4-4-NO_2)[a,f]	-98 (H)	85.0 (H)	
Fe(TPP)(SC_6H_4-4-NO_2)[a,g]	-91 (H)	59.8 (H)	
Fe(TTP)(OC_6H_4-4-CH_3)[a,c]	-143 (H)	111.0 (H)	144.2 (CH_3)
Fe(TPP)(OC_6H_5)[a,d]	-149 (H)	117.0 (H)	-137.5 (H)
Fe(salen)(SC_6H_5)[e]	-76 (H)	57 (H)	-79 (H)
Fe(salen)(SC_6H_4-4-CH_3)[e]	-76 (H)	58 (H)	95 (CH_3)
Fe(salen)(OC_6H_5)[e]	-94 (H)	87 (H)	-94 (H)
Fe(salen)(OC_6H_3-3,5-$(CH_3)_2$)[e]	-96 (H)	-31 (CH_3)	-96 (H)
Fe(salen)(OC_6H_4-4-CH_3)[e]	-101 (H)	89 (H)	110 (CH_3)
Fe(salen)(OC_6H_3-2,5-$(CH_3)_2$)[e]	84 (CH_3)	102 (H) 32 (CH_3)	-102 (H)

[a] In toluene-d_8 at 24 °C referenced to TMS via the residual methyl protons at 2.09 ppm. [b] In $CDCl_3$ at 24 °C referenced to TMS via the residual $CHCl_3$ at 7.26 ppm. [c] At -10 °C. [d] At -30 °C. [e] Data from ref 13. [f] pyr: 79.8 ppm. [g] pyr: 70.4 ppm.

(SC_6H_4-*p*-NO_2) in toluene and the instability of (PP)Fe^{III}(SC_6H_4-*p*-NO_2) in chloroform. In chloroform, (PP)Fe^{III}(SC_6H_4-*p*-NO_2) is readily converted into (PP)Fe^{III}(Cl).

Discussion

Response of Porphyrin Resonances to Axial Ligation. As seen in Figure 1, the resonance patterns for the phenolate or thiophenolate complexes are grossly similar and follow the pattern seen for other five-coordinate, high-spin species.[9,10] In searching for distinctive variations between the spectra resulting from S^- versus O^- axial ligation, it is clear that the largest difference comes in the location of the broad meso resonance. For the phenolate complexes these occur at ca. -39 ppm, while for the thiophenolate complexes they are shifted to ca. -50 ppm. There is also a detectable difference in the location of the 1,3,5,8-methyl resonances between the two ligation modes. For the phenolate complexes the group of four methyl resonances is shifted to higher field than is the group of methyl resonances for the thiolate analogues. This is best seen by comparing the average resonance position shown in Table I. For (PP)Fe^{III}(OC_6H_4-*p*-NO_2) this is 42 ppm, while for (PP)Fe^{III}(SC_6H_4-*p*-NO_2) it is 49 ppm. Finally, it is apparent in Figure 1 that axial ligand resonances are readily observed. Moreover, the resonances assigned to the meta phenolate protons (vide infra) are very significantly downfield of their thiophenolate counterparts. Also the line widths of the axial ligand resonances are greater for the phenolates than for the thiophenolates. This follows the trend seen for similar ligand pairs in salen complexes[13] and in iron-sulfur clusters.[15]

Axial Phenolate Resonances. The general pattern of phenolate resonances follows that observed by Que for complexes of the type (salen)Fe^{III}OAr[13,14] and by Goff for synthetic porphyrins.[12] As can be seen in Table II, the ortho and para protons in these salen complexes have upfield shifts of similar magnitudes while the meta protons have a somewhat smaller, downfield shift. The magnitude of the actual hyperfine shifts of the phenolate groups for the salen complexes are smaller than those observed for the porphyrin complexes.

The six-coordinate (PP)Fe^{III}(OC_6H_4-*p*-NO_2)(Im) complex[7] has spectral features similar to those of the bis(imidazole) complex. However, it is clearly a distinct species and an excess of imidazole at -60 °C does not displace the axial phenolate ligand. An upfield resonance at ca. -31 ppm may be due to the protons of the phenoxy ligand.

Relaxation Properties. Relative line widths have been used to make assignments of resonances with the assumption of dominant metal-centered paramagnetic relaxation[16] (line width $\propto R_i^{-6}$) using estimated distances (R_i). The line widths for ring protons of the phenolates follow the pattern *o*-H > *m*-H $\gtrsim$ *p*-H (2.8 kHz, 0.6 kHz, 0.65 kHz for *o*-H, *m*-H, *p*-H of (TPP)Fe^{III}(OC_6H_5) at -30 °C). While the broadest line is for *o*-H and indicates dominant contribution from metal-centered dipolar relaxation[16] for the *o*-H, the comparable line widths for *m*-H and *p*-H, in spite of the greater distance from the metal for the latter, demonstrate that ligand-centered dipolar relaxation is important.[17] A similar discrepancy is seen for (PP)Fe^{III}(OC_6H_3-3,4-$(CH_3)_2$), as shown in spectrum B of Figure 2, where the more remote *p*-methyl resonance (0.37 kHz) exhibits 1.8 times the line width of the *m*-methyl resonance (0.21 kHz). In order to ascertain that these anomalous line widths do not come from exhange phenomena, we determined the T_1 values and line widths of the resonances of the *p*-H (1.21 ms, 0.31 kHz) and *m*-H (0.70 ms, 0.39 kHz) for (PP)Fe^{III}(OC_6H_2-2,6-$(OMe)_2$). The ratio T_1^{-1}(*m*-H)/T_1^{-1}(*p*-H) = 1.7, which is comparable to the line width ratio of 1.3. The difference in T_1 data dictates that π spin delocalization is important in determining the relaxation properties and that neither differential line broadening nor T_1 values can be used alone to make resonance assignments when a large degree of spin delocalization is present. This is in contrast with similar line width data on salen complexes where the same functional group yields a narrower line in the para than in the meta positions.[18] The basis for the different manifestations of metal-versus ligand-centered dipolar relaxation in otherwise structurally similar salen and porphyrin complexes is not understood, but underscores the danger of misassignments based solely on this analysis of differential paramagnetic line widths or relaxation time contribution.

Differential relaxivity has been used to assess electronic structural information (i.e. zero-field splitting) by comparing related five-coordinate, high-spin compounds.[19] Other anomalous features that demonstrate the danger of overinterpretation of line width data concern the relative relaxivities of the porphyrin versus the axial ligand as seen in traces C and D of Figure 1. With similar chemical shifts, the pyrrole resonance is 2.8 times as broad for the thiolate relative to the phenolate, while the axial ligand resonances are broader for the phenoxide than for the thiophenoxide. Since the chemical shifts for comparable groups are similar, this discrepancy cannot be rationalized by simple differences of ligand- versus metal-centered relaxation. Hence, in this case we cannot determine which of the pair has the shorter electron spin relaxation and therefore the largest zero-field splitting.

Comparisons with Proteins. The results obtained on these model systems offer insight into the structure of the mutant hemoglobins with axial tyrosinate ligands. The NMR spectra of the five- and six-coordinate model complexes are clearly distinguishable, with

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the five-coordinate form having heme methyls at ca. 50 ppm (Figure 1), while the six-coordinate form with imidazole coordination has no resonances below ca. 15 ppm (Figure 3) (extrapolated to 23 °C). Published spectra[20] for native HbM Iwate and HbM Boston in the state where only the mutated (tyrosine-containing) subunits are oxidized reveal a series of intense peaks in the region 30–45 ppm, consistent with their origin in heme methyls of high-spin ferric subunits. The unmutated reduced high-spin ferrous subunits are known not to exhibit hyperfine shifted peaks downfield of 25 ppm.[21] This suggests that the mutated α subunits of both HbM Iwate and HbM Boston are high-spin, and hence five-coordinate. The latter protein is known[3] to have a five-coordinate ferric α subunit, but the preliminary X-ray data have suggested[22] that the former has both tyrosinate and histidine coordination. In view of the fact that both phenoxide and imidazole coordination leads to a clear low-spin derivative with a characteristic NMR spectrum with heme methyls upfield of 30 ppm, we conclude that either the histidine E7 is not coordinated in the α chain of HbM Iwate in solution or the interaction is so weak as to leave the iron high-spin. ESR measurements also detect a high-spin species.[4]

The extreme low-field, nonexchangeable single-proton signals at 78, 91, and 122 ppm for HbM Iwate and at 80 and 105 ppm for HbM Boston (both at 35 °C) are very unlikely to arise from the ferric heme, but are consistent with assignments to the coordinated tyrosinate meta hydrogens and/or the two nonequivalent protons of the *p*-CH_2 (β-CH_2 in amino acid terminology). It is thus clear that the observations of several nonexchangeable single-proton peaks in the far downfield region of ferric heme systems can be used as strong indicators for tyrosinate coordination.

Experimental Section

Preparation of Samples. The iron complexes, (PP)Fe^{III}(OAr),[4] (PP)Fe^{III}(SAr),[5] (TPP)Fe^{III}(OAr),[4] and (TPP)Fe^{III}(SAr),[5] were prepared by established routes. Because of the sensitivity of the thiolate complexes to moisture and dioxygen, all handling and measurements of these were performed under an atmosphere of purified dinitrogen.[5] The solvents for NMR measurements were distilled from phosphorus pentoxide ($CDCl_3$) or sodium (toluene-d_8) and stored over molecular sieves. The six-coordinate imidazole adduct was obtained by adding measured quantities of imidazole to the solution of (PP)Fe(OC_6H_4-*p*-NO_2) via a microliter syringe.

NMR Measurements. ^1H NMR spectra were recorded on a Nicolet NT200 or GE QE300 FT NMR spectrometer operating in the quadrature mode (^1H frequencies 200 or 300 MHz). Typically, 1000 transients were accumulated by using a 7-μs 90° pulse and 8K data points. The peaks were referenced against tetramethylsilane. T_1 measurements were made by the standard inversion recovery technique.

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Registry No. (TPP)Fe^{III}(OC_6H_5), 76282-28-5; (PP)Fe^{III}(OC_6H_3-3,4-$(CH_3)_2$), 126460-00-2; (PP)Fe^{III}(OC_6H_4-*p*-NO_2), 54959-23-8; (PP)Fe^{III}(SC_6H_4-*p*-NO_2), 54959-22-7; (PP)Fe^{III}(OC_6H_4-*p*-NO_2)(Im), 126460-02-4; (PP)Fe^{III}(OC_6H_4-4-CH_3), 126460-03-5; (TPP)Fe^{III}(OC_6H_4-4-NO_2), 83486-39-9; (TPP)Fe^{III}(SC_6H_4-4-NO_2), 126460-04-6; (TPP)Fe^{III}(OC_6H_4-4-CH_3), 84893-13-0.

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μ-Oxo-Bis(oxo) Dinuclear Complexes of Technetium(V) with Amine Phenol Ligands: Syntheses, Characterization, and X-ray Crystal Structures

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Technetium(V) complexes of three amine phenol ligands prepared by reducing Schiff bases derived from salicylaldehyde and 1,3-diaminopropane, 2,2-dimethyl-1,3-diaminopropane, and 1,4-diaminobutane have been synthesized. ^1H and proton-decoupled ^{13}C nuclear magnetic resonance spectra of the complexes have been recorded and compared with those of the parent ligands. The complexes have been characterized by infrared spectroscopy, visible-UV spectrophotometry, and X-ray crystallography. X-ray crystal structures show all three complexes are dinuclear with a μ-oxo-bis(oxo) (O=Tc—O—Tc=O) backbone. The distorted octahedral coordination of Tc(V) is completed by a tetradentate diamine diphenolate ligand. Neutrality of the complexes is achieved by deprotonation of the phenols and by terminal and bridging oxo ligands. The technetium complexes have either a true crystallographic center of symmetry or an approximate center at the bridging oxygen.

Introduction

The widespread application of ^{99m}Tc in nuclear medicine has initiated extensive studies on the coordination chemistry of this man-made element. This in turn has contributed to the development of a large number of custom-tailored ligands for possible application in such specialized areas of nuclear medicine as brain and heart perfusion studies. Fair et al.[1] and Jurisson et al.[2,3] have earlier reported the synthesis and characterization of several neutral, lipophilic ^{99}Tc complexes of the amine oxime class of ligands. The ^{99m}Tc complex of one such ligand, *dl*-HMPAO, is now widely used as an effective cerebral blood flow agent.[4-6] We have been continuing the search in this area for the development of more such neutral, lipophilic Tc complexes for likely application in nuclear medicine. Bandoli et al.[7] have reported the synthesis and crystal structure of Tc(V) complexes of tetradentate Schiff base ligands derived from salicylaldehyde and alkanediamines.

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