

Water-Soluble Lanthanide Porphyrins: Shift Reagents for Aqueous Solution

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Abstract: Water-soluble lanthanide complexes of tetra-*p*-sulfonatophenylporphyrin (TPPS) with the general formula $\text{Ln}^{\text{III}}\text{TPPS}(\text{OH})(\text{imidazole})_x$ ($x \leq 2$), stable in neutral and highly basic solutions, have been synthesized for Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu. Well-resolved NMR spectra are observed for the TPPS protons of Yb(III) and Tm(III) complexes in 95% v/v DMF-*d*₇-5% v/v D₂O solution. The phenyl proton resonance shifts are mostly downfield and are consistent with a dominant dipolar interaction with the metal atom situated significantly out of the porphyrin plane. The resonance shifts in the Yb(III) complex increase with increasing temperature with a dependence on *T* roughly linear in the 230–300 K range studied. The TPPS complexes of the latter lanthanides (Ho–Yb) serve as potent aqueous solution shift reagents (particularly the Tm derivative) for nuclei of neutral and cationic substrates (e.g., the 4-picoline molecule and *N*-methylpyridinium cation examined in the present study) and, to a lesser extent, for the water proton resonance and anionic substrates like the *p*-toluidate anion studied here. Sizable upfield (Er, Tm, Yb) and downfield (Ho) shifts are observed in both the 4-picoline and *N*-methylpyridinium cation. The water and *p*-toluidate proton resonances experience much smaller shifts whose signs differ from the pattern observed in 4-picoline or *N*-methylpyridinium cation. Upfield shifts are also observed for the diamagnetic LuTPPS systems. The LnTPPS complexes are more effective as shift reagents than the corresponding LnEDTA complexes or aquo ions. Contact contributions to the observed shifts are larger in LnTPPS complexes than in systems involving oxygen donor ligands.

Introduction

The recent synthesis^{1,2} in this laboratory of lanthanide porphyrin complexes and those of thorium and yttrium³ has provided a potential new class of metal-centered probe for the study of biological systems. The successful insertion of the ytterbium complex of mesoporphyrin IX into apomyoglobin⁴ demonstrates the feasibility of introducing lanthanide and related ions into hemoproteins by this method. Initially, our interest centered on the NMR shifting characteristics of these paramagnetic species and we studied the action as shift reagents^{5,6} of the organic solvent-soluble tetraphenylporphyrin (TPP) lanthanide derivatives toward organic substrates.² Other properties of lanthanide porphyrins, such as their fluorescence characteristics,^{7,8} may eventually prove useful.

For NMR shift studies of most biological molecules or other water-soluble substrates a reagent suitable for use in aqueous solution is necessary. The simple aquo lanthanide ions, Ln^{3+} , formed upon dissolution of simple salts (chlorides, nitrates, etc.) have been used in this capacity.^{9–13} Their use, however, is restricted to the acidic side of neutral pH owing to hydrolysis and precipitation of hydroxides at higher pH values. This limitation can be overcome by complexation of the lanthanide ions as has recently been done with EDTA.^{11,14–16} It has been found, however, that the shifts induced by LnEDTA^- complexes are relatively inferior to those induced by the aquo ions.¹⁶

In the present study we have synthesized water-soluble lanthanide complexes of the tetra-*p*-sulfonatophenylporphyrin (TPPS) and studied their action as proton resonance shift reagents toward water, anionic, neutral, and cationic substrates. The complexes of the latter lanthanides (Ho–Lu) are stable at pH values as high as 13 and induce shifts which are generally greater than those caused by the corresponding LnEDTA^- chelates. In the case of the water proton resonance only the HoTPPS complex produces shifts significantly larger than those produced by the free ion. LnTPPS complexes are quite soluble in water (concentrations of up to 0.4 M can be obtained) and are stable at pH values ≥ 6.0 . Owing to the lack of stability of complexes of the earlier lanthanides to our chromatographic purification procedures, and to the serious signal broadenings produced by the Gd(III), Dy(III), and

Tb(III) complexes, the present study concentrates on the heavier member of the series (Ho–Lu).

Experimental Section

Preparation and Purification of the Complexes. The synthesis of TPPS is begun with the synthesis of tetraphenylporphyrin (TPP) free base by a literature method.^{17–19} The TPP is then sulfonated using the method of Winkelmann et al.²⁰ as further developed by Srivastava and Tsutsui,²¹ except that the TPP-sulfuric acid mixture was heated on a steam bath for 8 h and then allowed to stand at room temperature for 2 days. This period of sulfonation ensures that the tetrasulfonated tetraphenylporphyrin is the major product. Purification of the crude product was effected by column chromatography to eliminate the mono-, di-, and trisulfonated tetraphenylporphyrins. The column was packed with basic alumina (Brockman activity 1, 80–200 mesh) using a water-methanol-acetone solvent system in the volume ratios 7:2:1, respectively. The major component gave an elemental analysis consistent with it being a tetrasulfonated product. Anal. Calcd for $\text{C}_{44}\text{H}_{26}\text{N}_4\text{S}_4\text{O}_{12}\text{Na}_4 \cdot 7\text{H}_2\text{O}$: C, 45.99; H, 3.48; N, 4.88, S, 11.12. Found: C, 45.71; H, 3.08, N, 5.09; S, 11.32.

The method of synthesis of the lanthanide TPPS complexes was derived from the metalloporphyrin synthesis of Treibs²² and Buchler,²³ who employed the metal acetylacetonates as the metal source. A 100-mL Schlenk tube containing approximately 5 g of imidazole was initially purged by melting the imidazole and flushing the tube with dry nitrogen for 15 min. TPPS (0.1 g) and 0.2 g of tris(acetylacetonato)lanthanide(III), $\text{Ln}(\text{acac})_3$, were added and a temperature range between 230 and 240 °C was maintained by immersing the Schlenk tube in a sand bath. Lanthanide salts (e.g., chlorides, nitrates, etc.) may equally well be employed as reactants. The course of the reaction was followed by examining the UV-visible absorption spectra of periodically withdrawn aliquots. Completion of the reaction, which generally occurs within 0.5 h, is indicated by the complete disappearance of the four visible absorption bands of the free base TPPS at (relative intensities indicated) 510 > 555 > 575 > 625 nm and the appearances of bands characteristic of the metalloporphyrin with relative intensities at the indicated wavelengths 510 << 545 >> 575 nm (see Figure 1 for a comparison of the UV-visible spectra of YbTPPS and free base TPPS). Immediately upon completion of the reaction, the mixture was cooled and transferred to a sublimation apparatus. The bulk of the imidazole was sublimed under vacuum while heating on a steam bath. The purple residue contained mostly metalloporphyrin but also traces of free base TPPS and $\text{Ln}(\text{acac})_3$. Unreacted free base TPPS and $\text{Ln}(\text{acac})_3$ were separated from the metalloporphyrin by column chromatography. The lighter lanthanide porphyrin

complexes are very susceptible to hydrolysis, the middle lanthanide porphyrin complexes are moderately stable, and the heavier lanthanide porphyrin complexes are, relatively, quite stable to hydrolysis. For the purification of TPPS complexes of the elements Gd through Lu a basic aluminum oxide column was prepared and saturated with water. A small volume of methanol was then applied to the column. The crude lanthanide TPPS product was dissolved in a minimum volume of methanol, filtered, and then applied to the column. The column was then eluted with methanol until the remaining imidazole had been removed from the column. The unreacted free base TPPS and finally the lanthanide TPPS complex were eluted with water. The unreacted Ln(acac)₃ and a considerable quantity of the lanthanide TPPS complex remain trapped in the column. The trapped portion was recovered by the addition of the minimum volume of 2 M sodium carbonate solution required to cause the trapped lanthanide TPPS band to begin to move down the column. The metalloporphyrin band was then eluted with water. The two portions of the metalloporphyrin were then combined, concentrated on a steam bath, and then recycled on a new column of basic aluminum oxide saturated with water. The metalloporphyrin was recovered from the water by evaporation on a steam bath to give a product which was dried in an oven at 100 °C for 1 h. It is important to note that care must be taken to avoid overloading the column, which results in the apparent loss of crystallinity in the product. Addition of a minimum amount of 2 M sodium carbonate solution to the concentrated solution of the noncrystalline metalloporphyrin (pH 9–10) and then evaporating to dryness gives rise to a product crystalline in appearance. Elemental analyses and NMR spectra presented below indicate that imidazole remains bound to the LnTPPS complex throughout the purification process. We have found that the Yb(III) complex binds two molecules of imidazole per molecule of the metalloporphyrin while the Tm(III) complex binds less than one molecule of imidazole per molecule of metalloporphyrin.

Characterization of the Complexes. Elemental analyses (Galbraith Laboratories, Knoxville, Tenn.) and the metal oxide content (Chemalytics, Inc., Tempe, Ariz.) for Na₄YbTPPS·OH·(C₃H₄N₂)₂·3H₂O were obtained. Anal. Calcd for Yb-C₅₀H₄₁N₈S₄Na₄O₁₃·3H₂O: C, 42.80; H, 2.92; N, 7.99; S, 9.13; Yb, 14.05. Found: C, 42.85; H, 2.88; N, 8.19; S, 9.40; Yb, 12.93.

The extinction coefficients of the LnTPPS complexes at 415 (Soret band), ~510, ~545, and ~575 nm were determined by quantitative conversion to the dication²⁴ of the free base, H₄TPPS₄²⁺, by treatment with aqueous HCl (pH 3.8). The 435- (ε 41.5 × 10⁴ M⁻¹ cm⁻¹) and 645-nm (ε 3.95 × 10⁴ M⁻¹ cm⁻¹) bands of H₄TPPS₄²⁺, resulting from conversion of weighed amounts of LnTPPS complexes to the diacid cation, were used in this determination. Satisfactory agreement between the concentrations of metalloporphyrin determined from UV-visible spectra and those determined from the known weights of metalloporphyrin is obtained. The molar extinction coefficients ((M⁻¹ cm⁻¹) × 10⁻⁴) are given for the four bands in order of increasing wavelength: Gd (59.55, 0.40, 1.70, 0.31); Tb (55.42, 0.38, 1.72, 0.36); Dy (57.56; 0.34, 1.75; 0.36); Ho (46.42; 0.41, 1.73, 0.37); Er (56.2, 0.42, 1.91, 0.39); Tm (62.75; 0.35, 1.85, 0.35); Yb (61.20, 0.32, 2.10, 0.37); Lu (57.34, 0.35, 2.21, 0.40).

NMR spectra of lanthanide TPPS complexes in 95% v/v deuteriodimethylformamide (DMF-d₇)–5% v/v D₂O solution were obtained using a JEOL-PFT 100 instrument equipped with a variable temperature accessory and employing (CH₃)₄N⁺ as an external standard with the appropriate correction for bulk susceptibility shifts being made (vide infra).

Results and Discussion

Search for an Internal Standard. In any NMR study the use of a particular molecule as an internal standard requires that the molecule undergo no association or specific interaction with the species under investigation. For solubility reasons NMR studies in aqueous solution usually employ as internal reference molecules which are either charged or are polar with groups capable of coordinating to a metal ion. Our initial choice of an internal standard in our NMR studies of LnTPPS complexes was the tetramethylammonium cation, (CH₃)₄N⁺ or TMA⁺, since it cannot coordinate to the positive metal center in LnTPPS complexes. We found that TMA⁺ is a good internal standard for the lanthanide free ion, as evidenced by the values of the Evans' method²⁵ susceptibilities we obtained

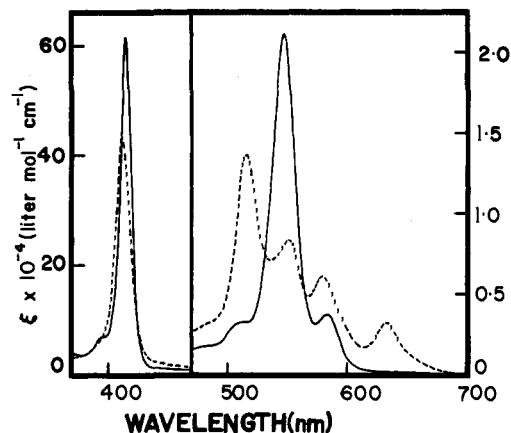


Figure 1. Electronic spectra of YbTPPS (—) and TPPS (---) in water at room temperature.

which are in good agreement with those measured by other means (Yb³⁺ at 309 K; $M_{\chi}^{\text{Evans}} = 7242 \text{ VV k mol}^{-1}$ and $M_{\chi}^{\text{lit}} = 7761 \text{ VV k mol}^{-1}$).²⁶ An examination of the literature values of the susceptibilities of Yb(III) complexes shows that they lie within the range $M_{\chi} = 6920\text{--}8465 \text{ VV k mol}^{-1}$, at temperatures between 298 and 309 K.^{26–29} The value of the susceptibility we obtained for YbTPPS at 309 K using the Evans' method ($M_{\chi} = 56\,080 \text{ VV k mol}^{-1}$) shows that TMA⁺ is not a suitable internal reference for the LnTPPS systems. The extremely large separation between the resonances of internal and external TMA⁺ observed in the Evans' experiment clearly results from a sizable upfield isotropic shift of the internal TMA⁺ resonance resulting from a specific interaction with the paramagnetic metalloporphyrin. This upfield isotropic shift of the internal TMA⁺ methyl resonance augments the smaller upfield bulk susceptibility shift. If the entire observed signal separation is attributed to the latter cause this results in an anomalously large calculated magnetic susceptibility, as is observed. These unexpectedly large observed resonance shifts induced in the protons of organic cations are discussed in a later section. Other molecules which have been used as internal standards in aqueous solution include dioxane and *tert*-butyl alcohol. These molecules were tested for their suitability as internal standards in the present LnTPPS systems. Evans' method susceptibilities of $M_{\chi} = 13\,050$ and $290 \text{ VV k mol}^{-1}$, at 309 K, were obtained for YbTPPS using 2% v/v dioxane and 0.1% v/v *tert*-butyl alcohol, respectively, based on the separation of the internal and external signals for these molecules. Clearly these molecules are not suitable internal references for LnTPPS systems.

Additional evidence that TMA⁺, dioxane, and *tert*-butyl alcohol undergo specific interactions with the LnTPPS complexes comes from the observation of different shift magnitudes for nonequivalent protons in analogous compounds (tetraethylammonium cation (TEA⁺), 3-methyltetrahydrofuran, dimethylacetone, and *tert*-amyl alcohol). For example, the ratio of the CH₂ to CH₃ shifts induced by YbTPPS in TEA⁺ is 1.91. For a good internal standard this ratio should be unity. Similar observations were made for *tert*-amyl alcohol, 3-methyltetrahydrofuran, and dimethylacetone. In view of the above-mentioned observations we abandoned the search for an internal standard and chose to use TMA⁺ as an external standard. A correction for the bulk susceptibility shift, taken to be that of the corresponding aqueous Ln³⁺ ion at the same concentration ($\Delta\nu$ (ppm) (0.1 M Ln³⁺) Yb = 1.57, Tm = 4.49, Er = 6.05, and Ho = 7.86 at 309 K), was made with each measurement. This bulk susceptibility shift was assumed to be linearly dependent on the concentration and inversely proportional to the absolute temperature. It is reasonable to assume that the estimated $\Delta\nu$ (ppm) values quoted above are

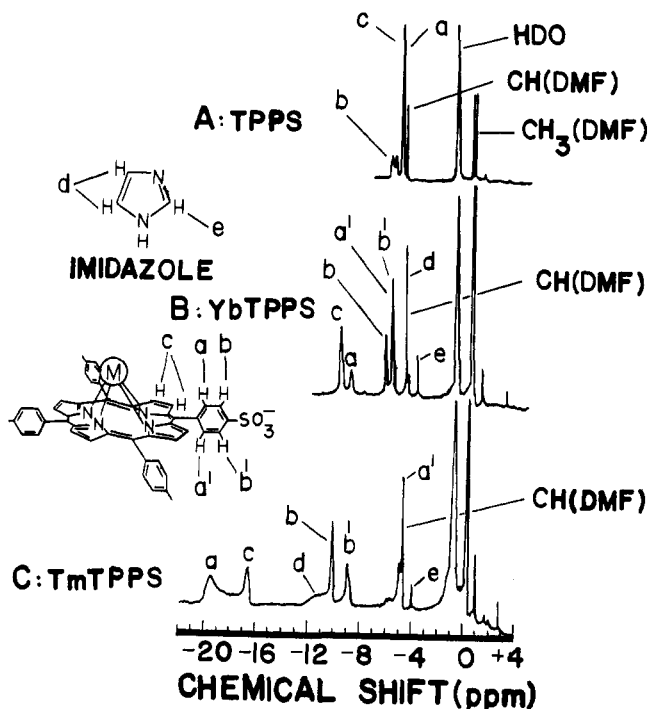


Figure 2. ^1H NMR spectra of TPPS (A), YbTPPS(imidazole) (B), and TmTPPS(imidazole) (C), taken in 95% v/v deuteriodimethylformamide ($\text{DMF-}d_7$)-5% v/v D_2O solution, at -20°C . Chemical shift in parts per million from $(\text{CH}_3)_4\text{N}^+$ as an external standard.

uncertain to the extent of $\pm 10\%$; thus the chemical shift scale in our experiments may be in error by as much as a tenth of the quoted values, e.g., Yb, ± 0.16 ppm; Tm, ± 0.45 ppm; Er, ± 0.61 ppm; Ho, ± 0.79 ppm. Errors of these magnitudes are insufficiently large to affect any of our conclusions. Our finding that none of several ions and molecules previously used as internal standards in aqueous solution is suitable in the presence of paramagnetic lanthanide porphyrin complexes should provide an important caution to investigators studying new systems. We propose that a combination of Evans' method and the requirement that nonequivalent nuclei of potential internal standards experience identical bulk susceptibility shifts be applied before adoption of an internal standard.

Assignment of the Porphyrin Resonances. The ^1H NMR spectra of Yb(III)- and Tm(III)TPPS complexes in water do not yield readily to a detailed interpretation. The spectrum of the Yb(III) complex, for example, is comprised of 33 peaks spread over 80 ppm (-49 to $+31$ ppm from the external standard $(\text{CH}_3)_4\text{N}^+$). This is likely due to the formation of aggregates. A number of studies have shown that the addition of polar organic solvents like alcohols, *N,N*-dimethylformamide (DMF), or dimethyl sulfoxide (Me_2SO) favors the formation of the monomeric species by the participation of these solvent molecules in axial interactions which are thought to play an essential role in the aggregation process.³⁰⁻³² Addition of dimethylformamide to a water solution of LnTPPS induces changes in the NMR spectra, an effect which reaches its maximum when the solvent contains $\sim 90\%$ by volume of dimethylformamide. Under these conditions the spectra consist of the expected numbers of peaks. Figure 2 shows the ^1H NMR spectra of the free base TPPS, the Yb(III) and Tm(III) complexes taken in 95% v/v deuteriodimethylformamide ($\text{DMF-}d_7$)-5% v/v D_2O solution at -20°C . The tentative signal assignments shown were made on the basis of relative line widths and areas, temperature dependencies, and degree of agreement with calculated dipolar shift ratios.

All of the porphyrin proton resonances of YbTPPS(imidazole) are shifted downfield. The ortho and meta aryl proton

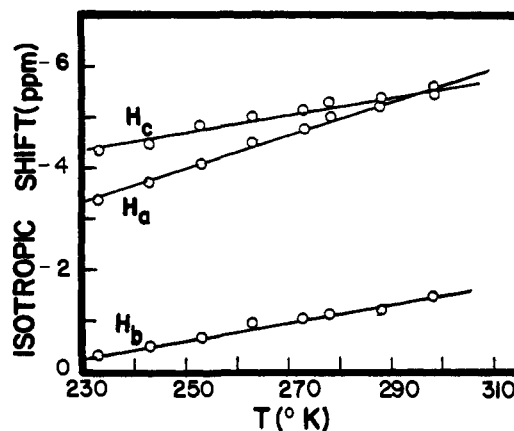


Figure 3. Plot of the isotropic shifts (ppm) vs. T for the porphyrin proton resonances of YbTPPS(imidazole) in deuteriodimethylformamide- D_2O solution.

resonances, equivalent in the free base, become nonequivalent in the complex owing to the out-of-plane position of the metal ion. One of the two imidazole proton resonances (Im-d) is shifted downfield while the other (Im-e) experiences a small upfield shift with respect to free imidazole. For TmTPPS(imidazole) the shift magnitudes are much larger than for the corresponding resonances in the Yb(III) complex. In the Tm(III) complex the endo-ortho proton resonance (a) experiences a larger shift than the pyrrole proton resonance (c) and the exo-meta proton resonance (b') appears to be shifted slightly upfield. Both the imidazole proton resonances are shifted downfield.

For TmTPPS the normalized ($H_a = 10.00$) shifts for protons H_a , H_b , H_a' , H_b' , and pyrrole (c) are 10.0, 3.09, -0.14 , 2.34, and 8.04, respectively, which compare roughly with those calculated² (10.0, 3.17, -0.14 , 1.00, 6.41) using an axial model with the Ln(III) ion 1.6 \AA out of the porphyrin plane along the C_4 axis. The agreement is not exact and additional evidence (vide infra) suggests that we do not have a simple, well-behaved, monomeric system even under these conditions. The indicated assignments must thus remain tentative. The assignment of individual peaks to imidazole resonances was confirmed experimentally by observing an increase in intensity of these resonances upon addition of this ligand to the solution.

Temperature Dependencies of the Porphyrin Resonances. Unlike the organic solvent soluble LnTPP complexes studied by us earlier,² which exhibited resonance shifts linear in T^{-1} , the shifts observed for YbTPPS in 95% v/v $\text{DMF-}d_7$ -5% v/v D_2O solution actually increase with increasing temperature as shown in Figure 3. The shifts dependence on T is roughly linear in the 230-300 K range studied for the phenyl H_a , H_b , and pyrrole (c) protons. One of us³³ has recently examined in some detail the experimental and theoretical bases of the temperature dependencies of lanthanide-induced shifts. The main conclusion of this work³³ is that for purely dipolar shifts the temperature dependence of the resonance shifts, which results from the temperature dependence of the magnetic susceptibility anisotropy, is not expected to exhibit a simple T^{-2} dependence as predicted by Bleaney³⁴ nor is a simple T^{-1} dependence to be expected. However, no theory based on the variation of magnetic anisotropy alone could account for an increase in anisotropy (and hence in shifts) with increasing temperature. Furthermore, antiferromagnetic interactions, which might produce such an observation, are unknown for lanthanide ions at elevated temperatures. The present results are thus persuasive evidence that the YbTPPS system is not simple, but that temperature-dependent structural rearrangements are occurring in solution. Such rearrangements,

Table I. Comparison of Shift Reagent Capabilities of LnTPPS and Ln(EDTA)⁻ Complexes and Ln³⁺ Ions toward the Water Proton Resonance at 36 °C

Ln	LnTPPS Obsd water proton shift, ^{a,c,d} ppm	Ln(EDTA) ⁻ Obsd water proton shift, ^{a,c} ppm	Ln ³⁺ Obsd water proton shift, ^{a-c} ppm
Ho	-2.05 ± 0.79	-0.15	-0.488
Er	-0.65 ± 0.61	+0.20	+0.383
Tm	-1.13 ± 0.45	+0.13	+0.929
Yb	-0.48 ± 0.16	+0.10	+0.252

^a Interpolated values for 0.1 *m* solutions. ^b Shifts for 0.1 *m* solutions, obtained from the 1 *m* shifts taken from ref 35 and verified in our laboratory. ^c The Ln(EDTA)⁻, LnTPPS, and Ln³⁺ shifts were studied at pH values 8–9, 9–10, and 6, respectively. ^d Corrected for diamagnetic shift taken to be that of the Lu(III) complex (LuTPPS, +0.05 ppm; Lu(EDTA)⁻, 0.0 ppm; Lu³⁺, 0.0 ppm).

by affecting the coordination geometry of the metal, will affect the magnitude of the magnetic anisotropy and hence the dipolar shifts. Furthermore, any changes in the structure will affect the shift magnitudes by changing the time-averaged geometrical position of the resonating nuclei with respect to the metal ion and the axes of the susceptibility tensor. The pyrrole protons (c) appear to exhibit a smaller dependence on *T* than do the phenyl protons (a and b). This may be due to a significant contact contribution to the shift of these protons which will, in general, have a different temperature dependence than dipolar shifts. A more detailed interpretation of the observed temperature dependencies is impossible at the present time.

Shifting Abilities across the Series, Gd–Lu. Before surveying the behavior of the paramagnetic lanthanide complexes of TPPS as shift reagents toward various classes of substrates, it is worthwhile to assess the action of a diamagnetic analogue. The proton resonances of water, the *p*-toluidate anion, 4-picoline, and the *N*-methylpyridinium cation are all shifted upfield in the presence of LuTPPS. In the case of 4-picoline and the *N*-methylpyridinium cation, shifts of up to approximately 1.5 ppm can be observed for the readily obtainable *R_p* value (metalloporphyrin to substrate concentration ratio) of 0.3. Quantitative shift data for the LuTPPS systems can be found in the footnotes of Tables I–IV. LuTPPS thus represents a new class of diamagnetic, water-soluble shift reagent. The diamagnetic shift effect will be present in the paramagnetic LnTPPS reagents, augmenting the shifts of the upfield reagents and decreasing the shifts of downfield reagents. The diamagnetic shift is, however, considerably smaller than the paramagnetic effect in the latter half of the lanthanide series (Tb–Yb), *vide infra*.

In our survey of the shifting abilities of LnTPPS complexes across the series Tb–Yb, we observed the Tb(III) and Dy(III) complexes to produce the largest shifts; however, because the extremely severe line broadenings hampered a detailed analysis, data for these two complexes are not presented. The shifting ability of GdTPPS has not been assessed because the line broadenings are already extremely severe at *R_p* values below 0.02. For complexes with the least objectionable line broadenings in this series (Ho–Lu), the magnitudes of the observed shifts are unaffected by pH changes within the range 8–11. At lower pH values these reagents cannot be used effectively for NMR studies because their solubilities decrease considerably, owing to protonation of the sulfonate groups of the TPPS ligand. At high pH values (11–14) the shift magnitudes decrease and serious line broadenings occur.

Action as Shift Reagents for the Water Proton Resonance. The paramagnetic contribution to the proton resonance shifts of water produced by the LnTPPS complexes may be com-

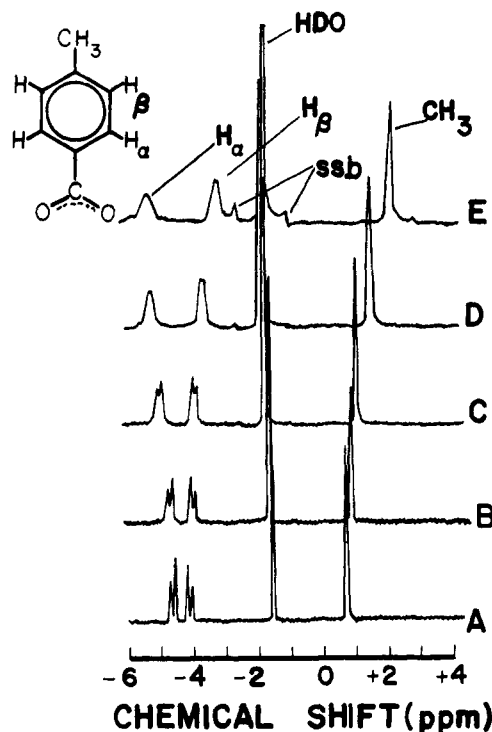


Figure 4. Effect of increasing concentrations of TmTPPS on the ¹H NMR spectrum of the *p*-toluidate anion in D₂O (pH 9–10) at 36 °C: A, *R_p* = 0.0; B, *R_p* = 0.039; C, *R_p* = 0.096; D, *R_p* = 0.175; E, *R_p* = 0.230.

pared with those observed for the corresponding LnEDTA⁻ complexes or aquo ions as shown in Table I. There is a linear dependence of the LnTPPS-induced shifts on the solute concentration as is observed with shifts arising from the aquo ions (not shown). For 0.1 M solutions of the Yb(III), Tm(III), and Er(III) complexes, the shifts are of opposite sign to those of the corresponding LnEDTA⁻ complexes or aquo ions. The magnitudes of these LnTPPS-induced shifts are much larger than those observed for the LnEDTA⁻ complexes and roughly the same as those induced by the aquo ions. In the case of HoTPPS the water proton resonance experiences a downfield shift; this also occurs for solutions of the HoEDTA⁻ complex and the aquo ion, with the HoTPPS shift being the largest. The finding that the signs of the shifts for the triad (Er, Tm, Yb) are the same as that of the Ho(III) complex is not consistent with a predominant dipolar contribution to the observed shifts. Nor do the relative magnitudes of the LnTPPS-induced water proton shifts correspond with those caused by the LnEDTA⁻ complexes or aquo ions (Table I). This observation strongly supports the suggestion that the downfield water proton resonance shift in the LnTPPS aqueous solutions are dominated by a Fermi contact interaction which would be of like sign for all of the latter lanthanides. The larger water resonance shift produced by HoTPPS may well find application in the study of resonances normally obscured by this peak.

Action as Shift Reagents toward Anionic and Neutral Substrates. In order to assess the capabilities of LnTPPS complexes as shift reagents toward anionic ligands we chose to study the rigid *p*-toluidate anion. Of the reagents studied, TmTPPS appears to be the most useful in that it produces the largest shifts with line broadenings no more severe than for YbTPPS. The spectra of the *p*-toluidate anion in the pH range 9–10 at various values of the metalloporphyrin to substrate ratio, *R_p*, are shown in Figure 4. TmTPPS induces downfield shifts in the α protons and upfield shifts in both the β and -CH₃ protons. Plots of the chemical shift vs. *R_p* are shown in Figure 5. These are linear over the range studied and extrapolate to very close to the diamagnetic positions of the various resonances at

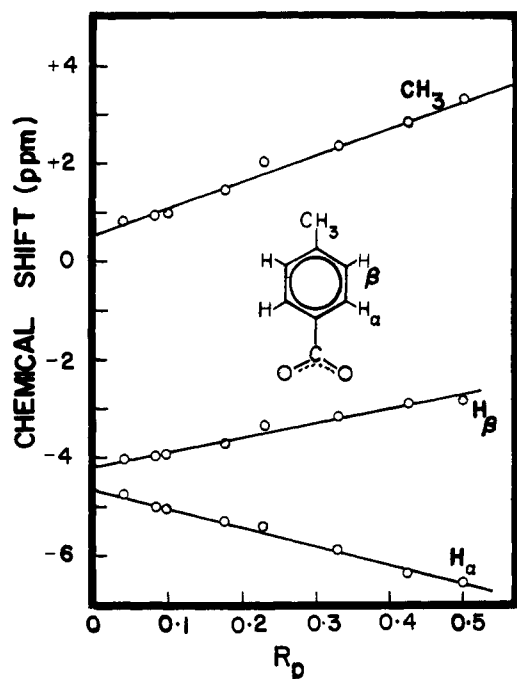


Figure 5. Plot of chemical shift (ppm from $(\text{CH}_3)_4\text{N}^+$) of proton resonances of the *p*-toluidate anion (0.244 M) in the presence of TmTPPS vs. R_p in D_2O (pH 9-10) at 36°C .

Table II. Comparison of Shift Reagent Capabilities of LnTPPS and $\text{Ln}(\text{EDTA})^-$ Complexes toward the Proton Resonances of the *p*-Toluidate Anion in D_2O at 36°C

Ln	LnTPPS shift, ppm ^{a-c}			$\text{Ln}(\text{EDTA})^-$ shift, ppm ^a		
	α	β	CH_3	α	β	CH_3
Ho	-1.35	-1.98	-1.88	-0.33	-0.27	-0.15
Er	-1.11	+0.37	+0.87	+0.40	+0.28	+0.17
Tm	-1.86	+0.52	-1.47	+0.55	+0.33	+0.19
Yb	-0.66	+0.02	+0.27	+0.24	+0.17	+0.11

^a Interpolated value for a metal complex; *p*-toluidate molar ratio of 0.3, pH 9-10. ^b Yb, ± 0.12 ppm; Tm, ± 0.33 ppm; Er, ± 0.45 ppm; Ho, ± 0.58 ppm. ^c Corrected for diamagnetic shift taken to be that of the Lu(III) complex (LuTPPS: α , +0.26 ppm; β , +0.38 ppm; CH_3 , +0.43 ppm. $\text{Lu}(\text{EDTA})^-$: α , 0.0 ppm; β , 0.0 ppm; CH_3 , 0.0 ppm).

$R_p = 0$. In Table II is presented a comparison of the paramagnetic contributions to the shifting abilities of several LnTPPS complexes with those of the corresponding EDTA complexes. The shifts induced by the Yb(III), Tm(III), and Er(III) EDTA complexes are upfield while those induced by the Ho(III) reagent are downfield. In contrast, for the LnTPPS species the α proton shifts are downfield for all four complexes (Ho, Er, Tm, Yb). These findings lead us to suggest that there is a significant contact contribution to the α proton shift, as observed for the water proton resonance shifts, while the β and the $-\text{CH}_3$ proton shifts are dominated by dipolar contributions. While ErTPPS induces shifts comparable in magnitude to those of TmTPPS, the concomitant broadening is quite severe, as it is with the Ho(III) reagent. Also apparent from an inspection of Table II is the fact that the paramagnetic shifts induced by the metalloporphyrin reagents are significantly larger than those produced by the EDTA complexes.

We have established the suitability of the LnTPPS complexes as aqueous shift reagents for neutral ligands by examining the proton chemical shifts of 4-picoline in the presence of varying amounts of the LnTPPS complexes. The effects of successive additions of TmTPPS on the proton spectrum of 4-picoline, in the pH range 9-10, are shown in Figure 6. Considerable lanthanide-induced upfield shifts are observed

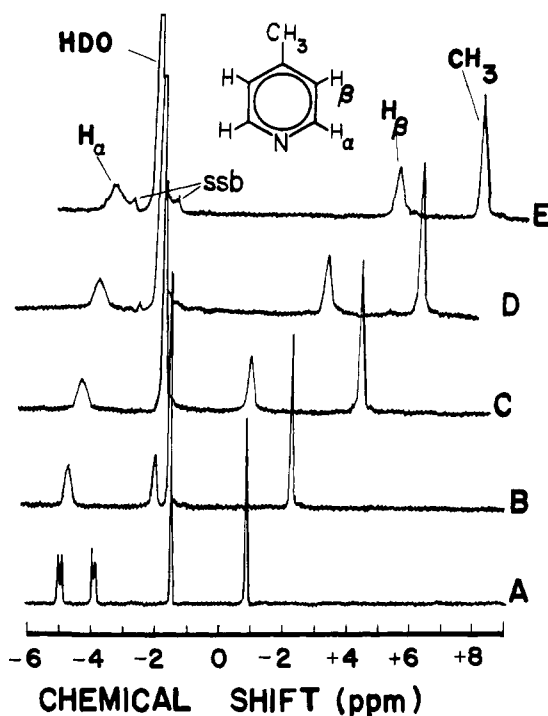


Figure 6. Effect of increasing concentrations of TmTPPS on the ^1H NMR spectrum of 4-picoline in D_2O (pH 9-10) at 36°C : A, $R_p = 0.0$; B, $R_p = 0.032$; C, $R_p = 0.083$; D, $R_p = 0.131$; E, $R_p = 0.185$.

Table III. Isotropic Shifts of 4-Picoline Induced by the LnTPPS Complexes ($R_p = 0.3$) at 36°C

LnTPPS	Shift, ppm ^{a,b}		
	α	β	CH_3
Ho	-3.30	-7.05	-5.85
Er	+2.00	+8.45	+4.85
Tm	+1.90	+12.55	+9.55
Yb	-0.90	+2.15	+1.65

^a Yb, ± 0.12 ppm; Tm, ± 0.33 ppm; Er, ± 0.45 ppm; Ho, ± 0.58 ppm. ^b Corrected for diamagnetic shift taken to be that of the Lu(III) complex (LuTPPS: α , +1.20 ppm; β , +1.45 ppm; CH_3 , +1.45 ppm).

for all of the protons with the α protons experiencing the smallest shift but largest broadening. Plots of the observed chemical shift vs. the TmTPPS to substrate ratio (R_p) for 4-picoline are shown in Figure 7. The shifts of the α protons are quite linear in R_p while those of the β and $-\text{CH}_3$ protons are nonlinear. As expected, the shifts extrapolate back to very close to their diamagnetic positions at $R_p = 0$.

Several features become apparent when examining the shifts induced in 4-picoline by the LnTPPS complexes in Table III. The shifts of the α protons are the smallest in each case, with the β protons experiencing the largest shifts. The signs of the paramagnetic contribution to the Er(III) and Tm(III) α -proton shifts differ from those of the Yb(III) and Ho(III) complexes. This finding does not agree with the theoretically predicted variation of magnetic anisotropy with f-electron configuration across the series and provides evidence for a combination of a contact and dipolar contribution to the observed α -proton shifts. The smaller magnitudes of the α -proton shifts as compared to the β and $-\text{CH}_3$ protons can be attributed in large measure to the contact contributions to the α -proton shifts. Comparing these shifts with those induced by LnEDTA^- complexes reveals that, for a given value of R_p , the shift magnitudes are much larger in the LnTPPS systems. For instance, at $R_p = 0.3$ the TmTPPS complex induces paramag-

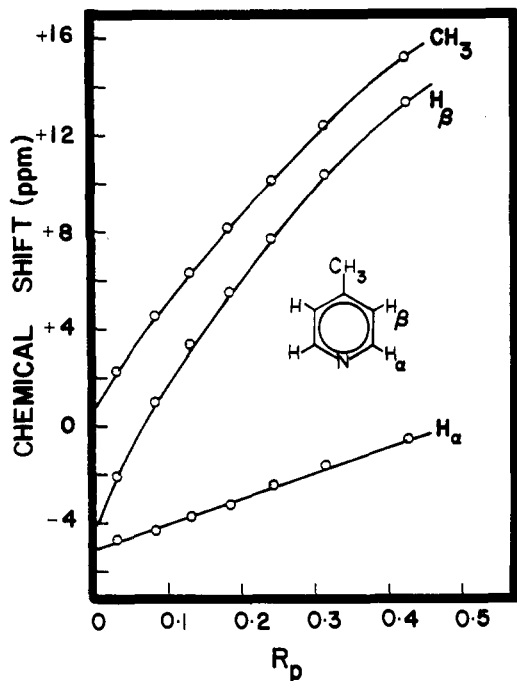


Figure 7. Plot of chemical shift (ppm from $(\text{CH}_3)_4\text{N}^+$) of proton resonances of 4-picoline (0.243 M) in the presence of TmTPPS vs. R_p in D_2O (pH 9–10) at 36 °C.

netic shifts in α , β , and $-\text{CH}_3$ protons of 4-picoline whose magnitudes are, respectively, +1.90, +12.55, and +9.55 ppm while those induced by the TmEDTA⁻ complex at the same R_p value are +0.20, +0.10, and +0.05 ppm, respectively. It may be that the much larger shifts observed for the 4-picoline compared to the *p*-toluidate anion can be explained in terms of structural rearrangements such as depolymerization induced by the heterocyclic base which are absent in the case of the anionic substrate. Such rearrangements affect the coordination geometry of the metal and metalloporphyrin–substrate equilibria.

The fact that the water proton resonance and the α -proton resonances of 4-picoline and the *p*-toluidate ion show significant contact contributions, contrasts with the results for other lanthanide systems including the aquo ions and the tris- β -diketonate class of organic solvent soluble shift reagent³⁶ where contact shifts are quite often negligible (or at least not dominant). Insofar as contact shifts may be associated with covalency, the coordination of a porphyrin moiety to a Ln(III) ion appears to cause it to act more covalently toward other ligands. Consistent with this is the surprising affinity of LnTPPS complexes for nitrogen donor ligands, e.g., picoline and imidazole, even in the presence of the abundant oxygen donor solvent, water. The Ln(III) metal center in a porphyrin complex is clearly much “softer” than it is in a complex containing only oxygen donor ligands.

The presence of a significant contact contribution of course eliminates any possibility of using the observed shift ratios to draw structural inferences. The ratios of substrate resonance shifts as one proceeds across the LnTPPS series (Yb–Ho) vary markedly (Tables II and III) and contrast with the relative constancy of these ratios in the tris- β -diketonate shift reagent series.³⁶ The apparent adherence of the shift ratios to effective axial symmetry in the latter systems has recently been rationalized by one of us.³⁷ As a consequence of the stereochemical nonrigidity of these complexes, the effects of magnetic nonaxiality are averaged out, thus preserving in some cases a semiquantitative relationship between substrate geometry and the observed shifts. Such fluctuation is expected

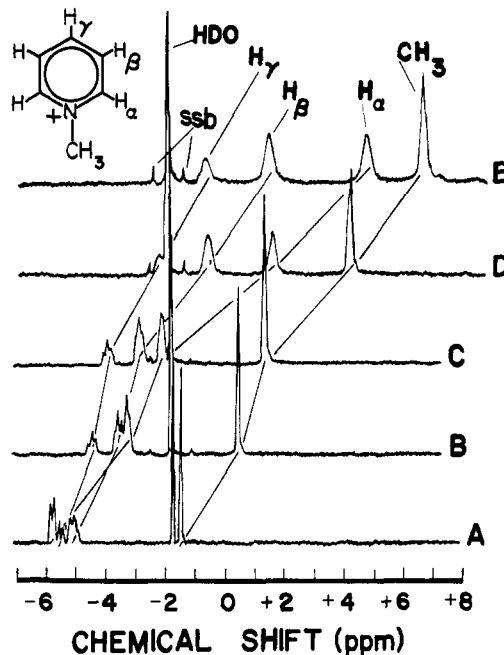


Figure 8. Effect of increasing concentrations of TmTPPS on the ^1H NMR spectrum of the *N*-methylpyridinium cation in D_2O (pH 9–10) at 36 °C: A, $R_p = 0.0$; B, $R_p = 0.036$; C, $R_p = 0.055$; D, $R_p = 0.111$; E, $R_p = 0.148$.

Table IV. Isotropic Shifts of the *N*-Methylpyridinium Cation Induced by the LnTPPS Complexes ($R_p = 0.3$) at 36 °C

LnTPPS	Shift, ^{a,b} ppm			
	CH ₃	α	β	γ
Ho	-11.27	-11.97	-7.90	-5.67
Er	+9.86	+12.81	+8.07	+6.6
Tm	+14.85	+19.15	+11.93	+9.33
Yb	+2.83	+3.78	+2.55	+1.95

^a Yb, ± 0.11 ppm; Tm, ± 0.32 ppm; Er, ± 0.43 ppm; Ho, ± 0.56 ppm.

^b Corrected for diamagnetic shift taken to be that of the Lu(III) complex (LuTPPS: α , +1.32 ppm; β , +1.20 ppm; γ , +1.00 ppm; CH₃, +1.27 ppm).

to be inhibited to a considerable degree in LnTPPS complexes owing to the constraints of the rigid porphyrin ligand. Even in the absence of a significant contact contribution, adherence to effective axial symmetry in the present LnTPPS shift reagents is not to be expected. Thus, while LnTPPS complexes, particularly the Tm(III) complex, can act as potent shift reagents for applications requiring spectral resolution enhancement of anionic and neutral substrates, they would not appear to be useful in the determination of substrate geometries under the assumption of axial symmetry.

Action as Shift Reagents toward Cationic Substrates. Figure 8 shows the quite remarkable effect of adding successive quantities of TmTPPS to aqueous solutions of the *N*-methylpyridinium cation. Upfield shifts are observed in the pH range 9–10, for all the proton resonances. Plots of the chemical shift vs. R_p are shown in Figure 9. These are linear over the range studied and extrapolate to very close to their diamagnetic positions at $R_p = 0$. Upfield shifts are also observed for the proton resonances of the aliphatic quaternary ammonium cation, the tetrapropylammonium ion, in the presence of TmTPPS with a linear dependence (not shown) of the chemical shift on the R_p over the range studied.

Table IV presents a summary of the data obtained from the shift reagent studies of the LnTPPS–*N*-methylpyridinium systems. Sizable upfield shifts were observed for the Er, Tm,

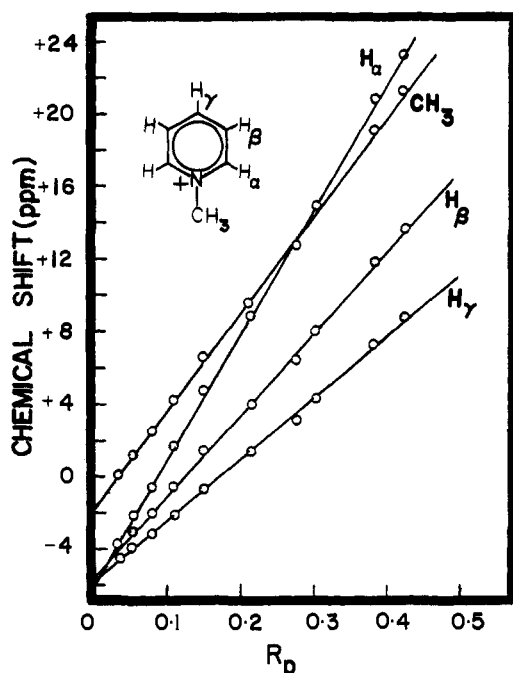


Figure 9. Plot of chemical shift (ppm from $(\text{CH}_3)_4\text{N}^+$) of proton resonances of the *N*-methylpyridinium cation (0.238 M) in the presence of TmTPPS vs. R_p in D_2O (pH 9–10) at 36 °C.

Yb triad and downfield shifts for the HoTPPS system. This finding is fully consistent with a predominant dipolar shift mechanism. The shift ratios ($\text{CH}_3/\alpha = 0.78$, $\beta/\alpha = 0.62$, and $\gamma/\alpha = 0.49$ for Tm) are relatively constant across the LnTPPS series suggesting that the LnTPPS-*N*-methylpyridinium systems are isostructural. Further confirmation of the essential dipolar nature of the observed shifts of the *N*-methylpyridinium cation proton resonances can be obtained by applying method A_2 of separating dipolar and contact shifts as described by Reilly et al.³⁸ Plots (not shown) of the $\Delta H_n^{\text{cor}}/\langle S_z^G \rangle_n$ ³⁹ ratios vs. the $C_m^{\text{D}}/\langle S_z^G \rangle_m$ ³⁹ ratios for the lanthanides Ho–Yb were constructed. With the exception of the Yb system, the data points lie on straight lines which pass very close to the origin. This behavior is to be expected for predominantly dipolar shifts.³⁸ A similar analysis of the 4-picoline proton shifts reveals that the β and $-\text{CH}_3$ proton shifts behave very similarly to those of the *N*-methylpyridinium cation, while the character of the analogous plot for the α proton is very different. This finding is consistent with our conclusion that there is a significant contact contribution to the α proton shift.

The magnitudes of the LnTPPS-induced shifts for the *N*-methylpyridinium cation and those induced by the corresponding LnEDTA[−] complexes can be compared in the following manner. For example, at identical R_p values (1.35) the PrEDTA[−] complex induces a shift of about 0.5 ppm downfield in the α protons of the pyridinium⁴⁰ cation while the corresponding paramagnetic shift in the YbTPPS-*N*-methylpyridinium system is +17.0 ppm upfield. Similarly, resonance shifts induced in the tetraalkylammonium cations are much greater for the LnTPPS than for the LnEDTA[−] systems. The present results indicate that the LnTPPS systems are much more effective in inducing shifts than the LnEDTA[−] analogues. It would appear that LnTPPS systems are potentially useful in NMR studies of water-soluble cations which exhibit complicated diamagnetic spectra.

Conclusions

The synthetic, water-soluble lanthanide complexes of tetra-*p*-sulfonatophenylporphyrin (TPPS) at the end of the

lanthanide series are stable in neutral and highly basic solutions. They are shown to serve as potent shift reagents (particularly the Tm derivative) for the proton resonances of nuclei of anionic, neutral, and cationic substrates exemplified in the present study by the *p*-toluidate anion, 4-picoline, and the *N*-methylpyridinium cation, respectively. The shifts induced by the LnTPPS systems are generally much larger than those produced by the analogous LnEDTA[−] complexes, with the advantage over the aquo ions that they may be used in basic solution. Contact contributions to the observed shifts appear to be much larger for the LnTPPS systems than for the LnEDTA[−] complexes or aquo ions where the coordination of the lanthanide is entirely through oxygen.

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