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Ion-Pair Interactions of Lanthanide(III) Complexes in Aqueous Solutions

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The formation of ion-pair adducts between the cationic complex La(THP)$^{3+}$ (THP = 1,4,7,10-tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane) and the anionic complexes Tm(DOTA)$^{-}$ (DOTA = 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetate), Tm(DTPA)$^{2-}$ (DTPA = diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetate), Tm(TTHA)$^{3-}$ (TTHA = triethylenetetraamine-*N*,*N*,*N*′,*N*″,*N*‴,*N*‴-hexaacetate), and Tm(DOTP)$^{5-}$ (DOTP = 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetrakis(methylenephosphonate)) is examined by ^{13}C NMR spectroscopy. The induced ^{13}C shifts of the La(THP)$^{3+}$ complex are followed by titration of the Tm(III) complexes of DOTA, DTPA, and TTHA at pH 7. From these data, the stability constants are calculated to be $\beta_1 = 64$ M^{-1} (1:1), $\beta_1 = 296$ M^{-1} (1:1), and $\beta_2 = 26\,000$ M^{-2} (2:1) for the ion pairs of La(THP)$^{3+}$, with Tm(DOTA)$^{-}$, Tm(DTPA)$^{2-}$, and Tm(TTHA)$^{3-}$, respectively. The La(THP)$^{3+}$,Tm(DOTP)$^{5-}$ system elicits chiral resolution of the rapidly interconverting Tm(DOTP)$^{5-}$ isomers.

Introduction

The search for more effective and specific contrast agents (CA's) for magnetic resonance imaging (MRI) continues to be an active area of research.[1] The CA's currently in use are predominantly low molecular weight chelates of Gd(III), including Gd(DTPA)$^{2-}$ (Magnevist), Gd(DOTA)$^{-}$ (Dotarem), Gd(DTPA-BMA) (Omniscan), and Gd(HP-DO3A) (Prohance). However, it is theoretically possible to obtain CA's with efficiencies much higher than those of CA's presently in use.[1] In the quest for peak efficiency, one useful approach has been to optimize inner-sphere proton relaxation by decreasing the rotational dynamics of a complex. In this case, Gd(III) complexes are bound covalently[1] or noncovalently[2] to high molecular weight conjugates or biological materials.

The formation of ion pairs between Gd(III) chelates of opposite charges is of interest to address problems associated with producing efficacious CA's. The advantages of utilizing electrostatically induced adducts include an increased effective Gd dose, reduction of solution osmolality, and the possibility of extending this approach to biopolymers of opposite charge (obtained by covalent linking of various chelates to the polymer backbone), thereby forming supramolecular adducts in solution.

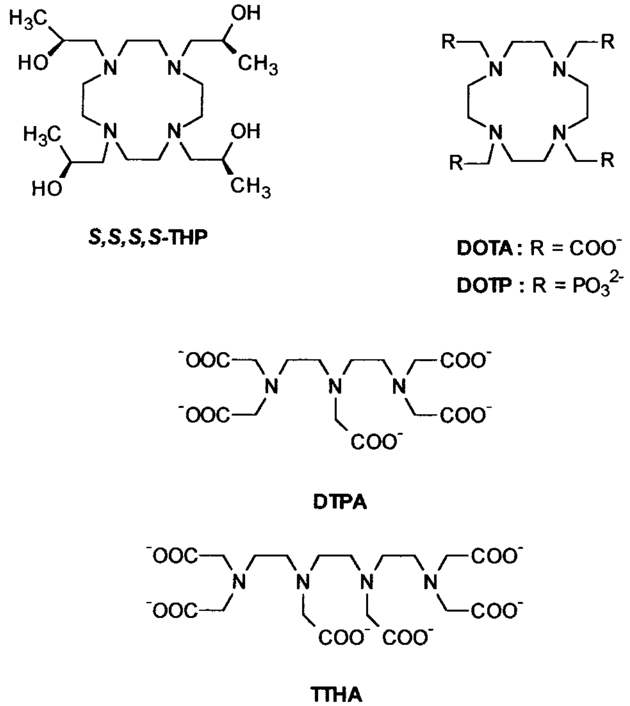

Figure 1. Structures of ligands used in the present shift studies.

Various stable Ln(III) complexes of opposite charges have been prepared by combining the trivalent ions with negatively charged or neutral ligands such as those shown in Figure 1. In general, the lanthanide is bound by the N atoms (of the ethylenediamine backbone) and O atoms (hydroxyl, carboxylate, or phosphonate) of the ligand. Some of these complexes possess physical properties that have rendered them useful as contrast agents for MRI or as paramagnetic shift reagents for in vivo NMR spectroscopy.[3] Recently, Sherry and co-workers reported the formation of a strong ion pair using the well-known in vivo shift reagent for alkali metal and alkaline earth metal ions Tm(DOTP)$^{5-}$ and a positively charged transition metal complex (Co(en)$_3$$^{3+}$).[4] Even more encouraging, osmometric measure-

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ments in this study confirmed a lowering of solution ionic strength with the use of the higher valent counterion.

Here we report the electrostatic interactions between La(THP)$^{3+}$ and the negatively charged Tm(III) complexes of DOTA, DTPA, TTHA, and DOTP. NMR spectroscopy was used to examine the lanthanide-induced shifts (LIS's) of nuclei in the diamagnetic La(THP)$^{3+}$ complex upon adduct formation with oppositely charged paramagnetic Tm(III) complexes (see below). Tm(III) was selected as the paramagnetic lanthanide ion for these studies because it induces both large chemical shifts and relaxation rate enhancements.[1]

Experimental Section

Chemicals. H_5DTPA, H_6TTHA, and 1-adamantanamine were purchased from Acros, La(CF_3SO_3)$_3$ and thulium(III) chloride ($TmCl_3\cdot 6H_2O$) were obtained from Aldrich and (*S*)-(−)-propene oxide was purchased from Fluka.

NMR Spectroscopy. ^{1}H (300 or 400 MHz), ^{13}C (75.5 or 100.6 MHz), ^{31}P (161.9 MHz), and ^{139}La (56.5 MHz) NMR spectra were recorded on either a Varian INOVA-300 or a Varian VXR-400S spectrometer using a 5 mm (^{1}H, ^{13}C, and ^{31}P NMR) or 10 mm (^{139}La NMR) probe. Chemical shifts are reported as δ values, downfield from an internal standard. For measurements in D_2O, *tert*-butyl alcohol was used as the internal standard, with the methyl signal calibrated at 1.2 ppm (^{1}H) or 31.2 ppm (^{13}C). H_3PO_4 (1%) was used as the external chemical shift reference for ^{31}P resonances. The ^{139}La shift was determined with respect to the resonance signal of a 0.1 M solution of $LaCl_3$ in D_2O as the external standard. Spin−lattice relaxation rates were measured using an inversion−recovery pulse sequence. The pH values of the samples were measured at room temperature using a Corning 125 pH meter with a calibrated micro combination probe purchased from Aldrich.

Syntheses of the Ligands. Cyclen (1,4,7,10-tetraazacyclododecane) was prepared by following a multistep method reported in the literature,[5,6] which was slightly modified to increase the yields (overall yield increased from 17% to 61%). The reaction times were increased to 24, 12, and 45 h for the tosylations of diethylenetriamine and diethanolamine and for the condensation reaction, respectively. Reaction products were characterized by ^{1}H NMR spectroscopy and TLC.

(*S,S,S,S*)-(−)-THP was synthesized as described by Morrow and coworkers using free-base cyclen and (*S*)-(−)-propylene oxide.[7] FAB MS *m/z*: 405. ^{1}H NMR (D_2O, 25 °C): δ 1.07 (d, 12 H, CH_3, $J = 6.3$ Hz), 2.28−2.70 (16 H, NCH_2CH_2N), 2.97 (d, 8 H, CH_2CH(OH)(CH$_3$), $J = 9.6$ Hz), 3.96 (m, 4 H, C*H*(OH)(CH$_3$)). ^{13}C NMR (D_2O, 25 °C): δ 21.0 (*C*H$_3$), 51.6 (N*C*H$_2$*C*H$_2$N), 63.7 (*C*H$_2$CH(OH)(CH$_3$)), 65.7 (*C*H(OH)(CH$_3$)).

DOTA and DOTP were synthesized from cyclen·4HCl according to procedures reported by Desreux[8] and by Sherry et al.,[9] respectively.

Preparations of the Metal Complexes. La(THP)(CF_3SO_3)$_3$ was prepared as described previously by refluxing equimolar amounts of La(CF_3SO_3)$_3$ and THP in acetonitrile and trimethyl orthoformate for 1 h.[7] The procedure was modified slightly by carrying out the reaction in air and recrystallizing the crude material from a hot CH_2Cl_2 solution. A white crystalline product was isolated in 90% yield. ^{1}H NMR (D_2O, 25 °C): δ 1.20 (d, 12 H, CH_3, $J = 5.7$ Hz), 2.25−2.45 (12 H, equatorial ring protons and CH_2CH(OH)(CH$_3$)), 3.00 (t, 4 H, CH_2CH(OH)(CH$_3$)), 3.70 (m, 8 H, axial ring protons), 4.75 (m, 4 H, C*H*(OH)(CH$_3$)). ^{13}C NMR (D_2O, 25 °C): δ 21.1 (*C*H$_3$), 50.1, 52.3 (N*C*H$_2$*C*H$_2$N), 60.6 (*C*H$_2$CH(OH)(CH$_3$)), 68.3 (*C*H(OH)(CH$_3$)). ^{139}La NMR (D_2O): δ 272.8.

Na[Tm(DOTA)] and Na$_5$[Tm(DOTP)] were prepared by reacting equimolar amounts of the ligand (DOTA or DOTP) and $TmCl_3\cdot 6H_2O$ in aqueous solutions at elevated temperatures.[8,9] ^{31}P NMR (D_2O, pD 8) for Tm(DOTP)$^{5-}$: δ −343.6. Na$_2$[Tm(DTPA)] and Na$_3$[Tm(TTHA)] were prepared at room temperature by slowly combining aqueous solutions of the ligand and $TmCl_3\cdot 6H_2O$ with gradual adjustment to neutral pH.

Residual salts were removed by ultrafiltration at neutral pH and 20 bar of N_2 using a UTC-60 membrane filter (Toray Industries Inc., Tokyo). Solid samples of Na[Tm(DOTA)], Na$_5$[Tm(DOTP)], and Na$_2$[Tm(DTPA)] were isolated after lyophilization. Na$_3$[Tm(TTHA)] was prepared in situ and used without further purification. All samples were tested for uncomplexed lanthanide ions using xylenol orange as the indicator.[10] The Tm(III) content for a given sample was estimated from the bulk magnetic susceptibility (BMS) shift.[11] To this end, a D_2O (1% *tert*-butyl alcohol) solution of the Tm(III) complex was placed in a 5 mm NMR tube equipped with an inner coaxial reference tube containing TMS (1%) in $CDCl_3$. The BMS was determined from the frequency shift of the *tert*-butyl alcohol signal with respect to that of a diamagnetic sample (1% *tert*-butyl alcohol in D_2O).

^{13}C NMR Shift Studies. Titration experiments were conducted in aqueous solutions at 25 °C and pH 7 without the use of a supporting electrolyte. ρ is defined as the molar ratio of Tm(III) complex and La(THP)$^{3+}$. The interactions of La(THP)$^{3+}$ with Tm(DOTA)$^{-}$ and Tm(DTPA)$^{2-}$ were studied by titrating solutions of La(THP)$^{3+}$ (58 and 38 mM, respectively) in D_2O with solid portions of Tm(DOTA)$^{-}$ and Tm(DTPA)$^{2-}$ ($\rho = 0-3.1$ and $0-2$, respectively). A 40 mM solution (D_2O) of La(THP)$^{3+}$ was titrated with a stock solution of Tm(TTHA)$^{3-}$ (0.27 M in D_2O) for $\rho = 0-1.2$. The experiment with La(THP)$^{3+}$ and Tm(DOTP)$^{5-}$ was conducted at pH 8.0 by titrating a 16 mM (D_2O) solution of Tm(DOTP)$^{5-}$ with solid portions of La(THP)$^{3+}$ ($\rho = 0-2.7$). All volume changes were recorded after each addition.

Calculations. LIS data were fit with a computer program written by our group using Scientist, Version 2.0 (Micromath, Salt Lake City, UT). The speciations used in this program were evaluated by following procedures outlined previously.[12] Molecular diameters for the La(THP)$^{3+}$,Tm(DOTA)$^{-}$ and La(THP)$^{3+}$,Tm(DTPA)$^{2-}$ adducts were estimated by constructing molecular models with HyperChem, Version 3, MM+ force field (Hypercube, Inc., Gainesville, FL). The crystal structures of Eu(DOTA)$^{-}$ [13] and (*S,S,S,R*)-Eu(THP)$^{3+}$ [7] were used as starting geometries. In the latter structure, the (*R*) side chain was inverted into the (*S*) configuration. The molecular volumes were estimated from the dimensions of the smallest box possible enclosing an ion pair.

Results and Discussion

Syntheses of the Ligands and Metal Complexes. The versatile starting compound cyclen was synthesized by using slightly modified literature procedures based on the Richman and Atkins route.[5,6,14] The cyclic polyamino ligands used in this study (Figure 1) were obtained by subjecting cyclen to the appropriate reagents. A single stereoisomer of THP having (*S*) configurations at all α carbons (hereafter denoted simply as THP) was isolated in high yield from the free-base form of cyclen and (*S*)-propylene oxide.[7] The presence of a single stereoisomer was confirmed by ^{1}H and ^{13}C NMR spectroscopy of the ligand. DOTA was generated by a standard procedure from cyclen·4HCl and chloroacetic acid.[8] A Mannich-type reaction of cyclen with formaldehyde and phosphorous acid afforded DOTP.[9]

Both linear polyamino polycarboxylates, DTPA and TTHA, were easily complexed using thulium(III) chloride ($TmCl_3$) in aqueous solutions at room temperature. Complexations of

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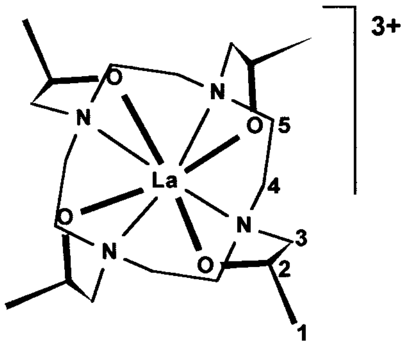

Figure 2. La((*S*,*S*,*S*,*S*)-THP)$^{3+}$ structure with position labeling for ^{13}C NMR assignments.

DOTA and DOTP were carried out similarly with $TmCl_3$; however, high temperatures were necessary because of the exceedingly slow kinetics of complex formation with these cyclic compounds.[8,9] The complexation of THP in aqueous solution was unfavorable due to the formation of insoluble lanthanide hydroxide precipitates. However, under anhydrous conditions, complex formation between THP and lanthanum(III) triflate ($La(CF_3SO_3)_3$) was achieved,[7] and this complex proved to be stable upon dissolution in water.

Estimation of Binding Constants for La(THP)$^{3+}$,Tm(ligand)$^{n-}$ Adducts. The ion-pair interactions between diamagnetic La(THP)$^{3+}$ and the negatively charged paramagnetic Tm(III) complexes (see Figure 1) were evaluated by using the lanthanide-induced ^{13}C NMR shifts. Attempts to include the ^{1}H NMR shifts in this study were precluded because of excessive line broadening and convergence of La(THP)$^{3+}$ signals upon addition of the Tm(III) compounds. The numbering of the ^{13}C nuclei in La(THP)$^{3+}$ is shown in Figure 2. As stated previously, ρ is the molar ratio of the appropriate Tm(III) complex and La(THP)$^{3+}$ ($\rho = [\text{Tm(ligand)}^{n-}]_{\text{tot}}/[\text{La(THP)}^{3+}]_{\text{tot}}$).

Upon addition of Tm(DOTA)$^{-}$, Tm(DTPA)$^{2-}$, or Tm(TTHA)$^{3-}$, all ^{13}C resonances of La(THP)$^{3+}$ showed concentration-dependent induced shifts, indicating fast exchange on the ^{13}C NMR time scale between La(THP)$^{3+}$ ions in the free state and in an adduct (see Figure 3). The experimental induced shifts were evaluated using a model that assumed the formation of 1:1 or 2:1 adducts, depending on the La(THP)$^{3+}$,Tm(ligand)$^{n-}$ system under consideration (see below). Equilibrium constants are given by

$$\beta_{\text{AB}} = [\text{AB}]/[\text{A}][\text{B}] \qquad (1)$$

$$\beta_{\text{A}_2\text{B}} = [\text{A}_2\text{B}]/[\text{A}]^2[\text{B}] \qquad (2)$$

where A and B represent La(THP)$^{3+}$ and Tm(ligand)$^{n-}$ in their free forms, respectively. AB and A_2B depict the bound adduct forms of these compounds. Using eqs 1 and 2 and the mass balances and beginning with an initial assumption for β_{AB} and $\beta_{\text{A}_2\text{B}}$, we calculated the concentrations of the various species by an iteration procedure described previously.[12] From these values, the fractions of A in the free form (f_{A}) and of A bound as AB (f_{AB}) or A_2B ($f_{\text{A}_2\text{B}}$) were obtained, allowing the induced shifts at various ρ values to be calculated by applying eq 3.

$$\delta_{\text{calc}} = f_{\text{AB}}\Delta_{\text{AB}} + f_{\text{A}_2\text{B}}\Delta_{\text{A}_2\text{B}} \qquad (3)$$

The agreement between the calculated and observed shifts was optimized using an iteration with β_{AB}, $\beta_{\text{A}_2\text{B}}$, and the bound shifts ($\Delta$) as variables. The data for adducts formed with Tm(DOTA)$^{-}$ and Tm(DTPA)$^{2-}$ could be fit with a 1:1 model, whereas, for the Tm(TTHA)$^{3-}$ system, the formation of 2:1 adducts had to be included. The resulting β and Δ values are compiled in Table 1.

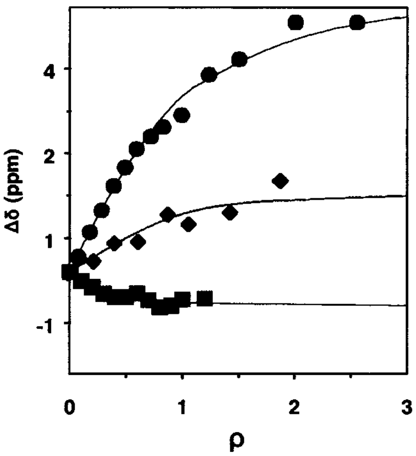

Figure 3. Titration curves showing the chemical shifts for C2 of La(THP)$^{3+}$ induced by Tm(III) complexes of DOTA (●), DTPA (◆), and TTHA (■). Solid curves represent fits of experimental data. Titration curves for the other ^{13}C nuclei of La(THP)$^{3+}$ are given in the Supporting Information (Figure S1).

Table 1. Binding Constants (β) and Bound Shifts (Δ) for the Adduct Formation of La(THP)$^{3+}$ with Tm(DOTA)$^{-}$, Tm(DTPA)$^{2-}$, and Tm(TTHA)$^{3-}$

	Tm(DOTA)$^{-}$	Tm(DTPA)$^{2-}$	Tm(TTHA)$^{3-}$
binding constants	64 ± 2^{a}	296 ± 104^{a}	$(2.6 \pm 0.6) \times 10^{4\,b}$
bound shifts (ppm)	Δ(AB)	Δ(AB)	$\Delta(A_2B)$
C1	4.1 ± 0.1	−0.4 ± 0.1	−0.8 ± 0.1
C2	5.8 ± 0.2	1.5 ± 0.2	−0.7 ± 0.1
C3	5.0 ± 0.1	1.0 ± 0.2	−0.6 ± 0.1
C4	5.1 ± 0.1	1.0 ±0.2	−0.8 ± 0.1
C5	4.6 ± 0.1	0.9 ± 0.2	−1.2 ± 0.1

[a] β_1 (M^{-1}). [b] β_2 (M^{-2}).

It should be noted that the accuracy of the Δ values obtained is good, whereas the β values are less accurately determined. This is a generally observed phenomenon in fitting titration curves for 1:1 complexes.[15] From the data obtained and from the shapes of the titration curves, it is clear that the strengths of the interactions increase with the negative charges of the Tm(III) complexes.

Tm(III)-Induced ^{13}C NMR Relaxation Rate Enhancements of La(THP)$^{3+}$ in Its Adducts with Tm(DOTA)$^{-}$ and Tm(DTPA)$^{2-}$. Longitudinal ^{13}C relaxation rates for La(THP)$^{3+}$ upon addition of Tm(DOTA)$^{-}$ and Tm(DTPA)$^{2-}$ were measured at $\rho = 0.7$ and $\rho = 1.0$, respectively. The adduct formed with Tm(TTHA)$^{3-}$ was not included in this study because of the complexity of the system. If we assume fast exchange between the free and bound ion pairs on the NMR time scale, the observed relaxation rate ($1/T_{1,\text{obs}}$) is given by the weighted average of the relaxation rates of bound and free La(THP)$^{3+}$ ions ($1/T_{1,\text{AB}}$ and $1/T_{1,\text{A}}$, respectively):

$$\frac{1}{T_{1,\text{obs}}} = \frac{1 - f_{\text{AB}}}{T_{1,\text{A}}} + \frac{f_{\text{AB}}}{T_{1,\text{AB}}} \qquad (4)$$

If the diamagnetic contribution to the Tm(III)-induced relaxation rate of AB is identical to the relaxation rate of free A ($1/T_{1,\text{A}}$),

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Table 2. Tm(III)-Induced Longitudinal ^{13}C Relaxation Rates (at 100.6 MHz) of La(THP)$^{3+}$ in the Free Form and in Its Adducts with Tm(DOTA)$^{-}$ and Tm(DTPA)$^{2-}$ in D$_2$O, Along with the Calculated ^{13}C−Tm(III) Distances (r)[a]

	La(THP)$^{3+}$	La(THP)$^{3+}$,Tm(DOTA)$^{-}$			La(THP)$^{3+}$,Tm(DTPA)$^{2-}$		
nucleus	$1/T_{1,A}$ (s^{-1})	$1/T_{1,obs}$ (s^{-1})[b]	$1/T_{1,AB}$ (s^{-1})	r (Å)	$1/T_{1,obs}$ (s^{-1})[c]	$1/T_{1,AB}$ (s^{-1})	r (Å)
C1	1.63	5.21	7.55	4.1	4.74	3.96	6.0
C2	2.31	4.86	5.40	5.8	4.82	3.20	6.2
C3	4.25	5.72	3.10	6.2	7.54	4.19	6.0
C4	4.29	7.0	5.63	5.1	8.31	5.12	5.8
C5	4.45	5.54	2.29	6.5	7.18	3.48	6.1

[a] Calculated using eqs 5 and 7. [b] $\rho = 0.7$. [c] $\rho = 1.0$.

eq 5 can be deduced, where $1/T_{1p,AB}$ represents the paramagnetic

$$\frac{1}{T_{1,obs}} = \frac{1 - f_{AB}}{T_{1,A}} + \frac{f_{AB}}{T_{1,AB}}\left(\frac{1}{T_{1,A}} + \frac{1}{T_{1p,AB}}\right) = \frac{1}{T_{1,A}} + \frac{1}{T_{1p,AB}} \quad (5)$$

contribution to the relaxation rates of the ^{13}C nuclei of the La(THP)$^{3+}$,Tm(DOTA)$^{-}$ adduct, while f_{AB} is the fraction of A bound as AB. The experimental relaxation rates and the values of $1/T_{1p,AB}$ are given in Table 2.

The lanthanide-induced relaxation rate enhancements contain information regarding internuclear distances. Two contributions to the total longitudinal relaxation rate ($1/T_{1,AB}$) must be considered:

$$\frac{1}{T_{1p,AB}} = \frac{1}{T_{1,d}} + \frac{1}{T_{1,\chi}} \quad (6)$$

Here, $1/T_{1,d}$ represents the dipolar contribution which results from through-space interactions originating from random fluctuations of the electronic field of the Ln(III) ion. $1/T_{1,\chi}$ is the Curie contribution which arises from the interaction of the nuclear spin with the thermal average of the electronic spins.[16,17] It is often assumed that the Curie contribution is negligible for relatively small paramagnetic Ln(III) complexes; however, it cannot be neglected for such large adducts.[18]

If zero-field-splitting (ZFS) effects are neglected,[19] then $1/T_{1,d}$ may be expressed by the reduced Solomon−Bloembergen equation,[20,21] which gives, after combination with the expression for the Curie contribution[16,17]

$$\frac{1}{T_{1,d}} = \left(\frac{\mu_0}{4\pi}\right)^2 \left[\frac{4}{3}\gamma_I^{\,2}\mu_{eff}^{\,2}\beta^2 T_{1e} + \frac{6}{5}\left(\frac{\gamma_I^{\,2}H_o^{\,2}\mu_{eff}^{\,4}\beta^4}{(3kT)^2}\right)\left(\frac{\tau_R}{1 + \omega_I^{\,2}\tau_R^{\,2}}\right)\right]\frac{1}{r^6} \quad (7)$$

where $\mu_0/4\pi$ is the magnetic permeability for a vacuum, μ_{eff} is the effective magnetic moment of Tm(III), γ_I is the magnetogyric ratio of the nucleus under study, β is the Bohr magneton, τ_R is the rotational tumbling time of the adduct, and r is the distance between the nucleus under study and Tm(III). When T_{1e} and τ_R are known, the r values may be evaluated directly form the relaxation rates using eqs 5 and 7. Due to the r^{-6} relationship, the accuracy of the estimated T_{1e} and τ_R values need not be high to obtain accurate r values; an error of 30% in T_{1e} corresponds to a 5% error in r.

The La(THP)$^{3+}$ ^{13}C−Tm(III) distances of the adduct were evaluated using eqs 5 and 7. $1/T_{1,A}$ values were determined by measuring the ^{13}C longitudinal relaxation rates of the diamagnetic La(THP)$^{3+}$ complex ($\rho = 0$). In the calculations, the T_{1e} value used was 0.369 ps (Tm^{3+} aquo ion), since values of T_{1e}, except for that of Gd(III), are generally independent of the bound ligand structure.[22,23] The value of τ_R was estimated with the use of the Debye−Stokes−Einstein equation[24]

$$\tau_R = 4\pi a^3 \eta / 3kT \quad (8)$$

where a is the molecular radius of the adduct and η is the viscosity of the solution. Estimates of a were obtained with the use of molecular models, and from these numbers, we calculated τ_R values of 155 ps ($a = 5.55$ Å) and 172 ps ($a = 5.75$ Å) for the La(THP)$^{3+}$,Tm(DOTA)$^{-}$ and La(THP)$^{3+}$,Tm(DTPA)$^{2-}$ adducts, respectively. The calculated Curie relaxation contributes approximately 38% and 40% to the total longitudinal relaxation rates for the La(THP)$^{3+}$,Tm(DOTA)$^{-}$ and La(THP)$^{3+}$,Tm(DTPA)$^{2-}$ adducts, respectively, and thus may not be neglected.

From the observed relaxation rates and by applying eqs 5 and 7, we were able to determine the average distances between each C nucleus in the THP complex and the Tm(III) ion of Tm(DOTA)$^{-}$ (see Table 2).

DOTA coordinates Ln(III) ions in capped square antiprismatic arrangements, each with the four nitrogens and four carboxylate oxygens forming the basal and upper planes, respectively.[13] Therefore, the negative charge density is concentrated in the positive shift cone. Since the cyclen backbone of the complex is hydrophobic, it is unlikely that charged species would associate with this region.

The C nuclei of the La(THP)$^{3+}$ complex are located at distances between 4.1 (C1) and 6.5 (C5) Å from the Tm(III) ion. This implies that the La(THP)$^{3+}$ countercation is located in the second coordination sphere of the Tm(III) ion. Assuming a 5% error both in the bound relaxation rates and in τ_R, we may expect about a 2% error in the values calculated for r. On this basis, it is apparent that all C nuclei of the La(THP)$^{3-}$ complex occupy essentially the same net location with respect to the Tm(III) ion, which indicates the occurrence of rapid inter-ion-pair exchange and/or rapid ion-pair rotation. Similar results were reported by Sherry et al. for the Co(en)$_3^{3+}$,Ln(DOTP)$^{5-}$ adducts.[4] The ^{1}H and ^{59}Co nuclei of Co(en)$_3^{3+}$ were found to occupy the same averaged location at a distance of 5.0 Å from the Ln(III) cation. These calculations were based on the

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assumption of a dipolar contribution only; therefore, the actual distances are presumably 16% longer due to the r^{-6} dependence. The distance between C1 and C4 of the La(THP)$^{3+}$ complex (5 Å) would result in a larger difference of the corresponding relaxation rates if a preference was shown for a particular orientation of La(THP)$^{3+}$ with respect to Tm(DOTA)$^-$ in the ion pair. It should be noted that, during averaging over various orientations, the nuclei most closely approaching Tm(III) are overweighted due to the r^{-6} dependence. As a consequence, the calculations above reflect distances for the closest approach of the relevant nuclei to the Tm(III) ion during the dynamic process of reorientation.

In the same manner, the La(THP)$^{3+}$,Tm(DTPA)$^{2-}$ system was investigated. It is apparent from the average C−Tm(III) distances obtained (5.8−6.2 Å; see Table 2) that, here too, the La(THP)$^{3+}$ cation is situated within the second coordination sphere of the Tm(III) ion. Compared to the case of the Tm(DOTA)$^-$ system, the closeness of the average distances is further exemplified by the fact that two carbon atoms occupy the same averaged locations (C1 and C3; 6.0 Å). Again, the similar average C−Tm(III) distances may be related to the dynamic countercation motion suggested above. Here, an additional mechanism may be the exchange of La(THP)$^{3+}$ among locations near the five carboxylates of the Tm(DTPA)$^{2-}$ complex.

Tm(III)-Induced ^{13}C NMR Shifts of La(THP)$^{3+}$ in Its Adducts with Tm(DOTA)$^-$, Tm(DTPA)$^{2-}$, and Tm(TTHA)$^{3-}$. No covalent interactions are involved in the ion-pair formation between the oppositely charged Ln(III) complexes. Consequently, only diamagnetic and pseudocontact contributions have to be considered. Since diamagnetic shifts are generally insignificant except for that of the Ln(III)-bound nucleus, we chose to ignore this contribution. For axial systems, the induced pseudocontact shifts may be described by

$$\Delta = DG = D\frac{3\cos^2\theta - 1}{r^3} \tag{9}$$

where G is the geometric factor of the nucleus under observation and θ defines the angle between the r vector and the principal symmetry axis of the system (i.e., the 4-fold symmetry axis of Tm(DOTA)$^-$).[25,26] The magnetic proportionality constant, D, is characteristic of the Ln(III) ion and the ligand. D values have been reported for various Ln(III) complexes with ligands such as DOTA and DOTP.[27,28]

It is clear from eq 9 that large Δ values indicate that the nuclei of the molecule must approach the Ln(III) ion rather closely and must have a preferential orientation with respect to Ln(III). Without a preferred orientation, the nuclei would experience all possible orientations equally and the $3\cos^2\theta - 1$ term in eq 9 would average to zero, resulting in an averaged dipolar shift of zero.

A θ angle less than 54.7° ($0° < \theta < 54.7°$) gives a positive geometric factor (G), while a θ angle greater than 54.7° ($54.7° < \theta < 125.3°$) yields a negative geometric factor. Any nuclei located on the surface of a cone with $\theta = 54.7°$ will have $G = 0$. Other factors that may influence the sign of the LIS values include Bleaney's constant (C_D)[25] for a given Ln(III) and the crystal field coefficients, all of which are incorporated into D (eq 9).

Table 3. Comparison of Experimental LIS Values for La(THP)$^{3+}$ Nuclei in the La(THP)$^{3+}$, Tm(DOTA)$^-$ Adduct with Calculated Values for Structural Models[a]

		calcd	
nucleus	exptl	θ(La) = 0°	θ(La) = 17° [b]
C1	4.1	1.63	3.96
C2	5.8	2.31	3.20
C3	5.0	4.25	4.19
C4	5.1	4.29	5.12
C5	4.6	4.45	3.48

[a] Calculated with eq 9; $D = 12\,243$. Shifts of symmetry-related nuclei were averaged. [b] Angle between symmetry axes of Tm(DOTA)$^-$ and La(THP)$^{3+}$ was taken as −45°.

The ^{13}C isotropic shifts of La(THP)$^{3+}$ in the presence of Tm(DOTA)$^-$ are all positive (see Table 1). No splitting of the signals occurred, which suggests that the C_4 symmetry in the adduct is, at least effectively, preserved. This could be explained by coincidence of the axes of symmetry of the Tm(DOTA)$^-$ and La(THP)$^{3+}$ components of the molecule, which would lead to identical LIS values for the symmetry-related nuclei. Alternatively, rapid exchange among the relevant nuclei via rotation about the C_4 axis of the La(THP)$^{3+}$ moiety could explain the absence of splitting for any other orientation of the two Ln^{3+} complexes with respect to each other. Obviously, random rotations would lead to identical zero LIS values.

The magnetic proportionality constant (D) for the major isomer of Yb(DOTA)$^-$ has been reported as 5082 ± 209 ppm Å^3.[27] Scaling this value by the ratio of dipolar shifts for the isostructural Yb(III) and Tm(III) complexes[1c,25] (53:22, respectively) provides an estimate for D of 12 243 ppm Å^3 for Tm(DOTA)$^-$. The observed shifts for La(THP)$^{3+}$, therefore, indicate that C nuclei of the THP complex are located predominantly within the cone defined by the θ angle ($0° < \theta < 54.7°$) from the 4-fold symmetry axis of Tm(DOTA)$^-$. This is in agreement with the positive LIS values for the ^{13}C nuclei of DOTA, which are located in the same cone. However, the LIS values are very small. In Table 3 they are compared with LIS values calculated for a model in which the C_4 symmetry axes of Tm(DOTA)$^-$ and La(THP)$^{3+}$ coincide ($\theta_{La} = 0°$, where θ_{La} is the angle between the Tm−La vector and the symmetry axis of Tm(DOTA)$^-$), with a Tm−La distance of 7 Å and with the pendant arms of both Ln^{3+} complexes pointing toward each other. The average Tm^{3+}−C distances obtained from the relaxation rates (see Table 2) indicate that rotation in the adduct does not occur exclusively about the 4-fold symmetry axis of La(THP)$^{3+}$. However, rapid interconversion of possible adducts with the coinciding C_4 axes of Tm(DOTA)$^-$ and La(THP)$^{3+}$ (head−head, head−tail, tail−tail, tail−head) cannot explain the small observed LIS values either. It is more likely that the La(THP)$^{3+}$ complex is located near the carboxylate groups of Tm(DOTA)$^-$, which would lead to a location of the La(THP)$^{3+}$ ion closer to the "0-shift" region. For example, the shifts calculated for a somewhat arbitrarily chosen structural model where $\theta_{La} = 17°$ and where the C_4 axis of La(THP)$^{3+}$ forms an angle of −45° with the symmetry axis of Tm(DOTA)$^-$ are of the same magnitude and have the same signs as the observed shifts (see Table 3). In summary, the distances show that ion pairs are formed and the shifts suggest that La(THP)$^{3+}$ is located near the carboxylate groups of Tm(DOTA)$^-$, whereas there is some anisotropic rotation of La(THP)$^{3+}$ with respect to Tm(DOTA)$^-$.

Addition of Tm(DTPA)$^{2-}$ caused the La(THP)$^{3+}$ resonances of C2−C5 to be shifted toward higher frequencies while that of C1 was shifted to a lower frequency (see Table 1). The shift

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values observed for this system are even smaller than those observed for the Tm(DOTA)$^-$ system . This may be due to nonspecific binding, which would result in the observation of an average shift, or to the location of the ^{13}C atoms of La(THP)$^{3+}$ on or near the “0-shift” region. The latter explanation cannot be excluded but is rather unlikely. In a previous study on Ln(III) complexes with DTPA,[29] the induced shift of the ^{6}Li counterion in Li$_2$[Tm(DTPA)] was found to be only -0.91 ppm owing to averaging, which led to a net shift of approximately zero. Apparently, the counterions in Ln(DTPA)$^{2-}$ complexes (Li$^+$) occupy a number of locations, most likely exchanging coordination with the five unbound O atoms of the carboxylate groups. In the present case, the situation is similar yet complicated owing to the presence of a more complex countercation. Crystal structure descriptions of several Ln(DPTA)$^{2-}$ complexes indicate a considerably more expanded general structure[30] relative to that of the DOTA complexes, with four of the carboxylate oxygens directed outward slightly above the Ln(III) ion and the fifth carboxylate oxygen positioned below it. Owing to the greater dispersion of the negatively charged regions, it is not surprising that the dipolar shifts and angles for some nuclei of substrates involved in adducts with Ln(DPTA)$^{2-}$ correspond to binding in the negative shift cone ($\theta > 54.7°$).

For the La(THP)$^{3+}$,Tm(TTHA)$^{3-}$ adduct, all ^{13}C resonances of the La(THP)$^{3+}$ complex were shifted to lower frequencies upon addition of Tm(TTHA)$^{3-}$. As with the La(THP)$^{3+}$,Tm(DTPA)$^{2-}$ adduct, the induced ^{13}C shifts are rather small and can most likely be explained by the same nonspecific binding phenomenon (see above).

Similar NMR phenomena were observed for the interactions between the structurally well-defined and rigid 1-adamantylammonium (ADA) ion and the Tm(III) complexes of DTPA and DOTP (see Supporting Information).

La(THP)$^{3+}$,Tm(DOTP)$^{5-}$ Ion Pairs: Chiral Resolution of Tm(DOTP)$^{5-}$ Stereoisomers. Tm(DOTP)$^{5-}$ was used to further explore the effects of increasing counterion charges on the interaction strengths of ion pairs formed with La(THP)$^{3+}$. A common feature of cyclen-based macrocyclic Ln(III) complexes is the existence of various isomers that may display dynamic behavior on the NMR time scale. Simultaneous conformational change of the cyclen ethylene groups and concerted arm rotation lead to enantiomerization. Structures of Ln(DOTP)$^{5-}$ complexes have been examined by solution-state ^{1}H and ^{13}C NMR spectroscopy[31] and recently by X-ray crystallography.[32] The octadentate DOTP ligand coordinates to Ln(III) ions in a square antiprismatic arrangement. Similar to other cyclen-based macrocycles, DOTP exhibits two enantiomeric forms, each of which is defined by a clockwise or a counterclockwise arrangement (Δ or Λ) of the methylenephosphonate arms. As a result, Ln(DOTP)$^{5-}$ complexes exist as racemic mixtures in solution. Rapid interconversion of the two enantiomers gives rise to indistinguishable NMR signals at room temperature.

The chiralities of the hydroxypropyl groups in (*S,S,S,S*)-THP complexes give rise to two possible diastereomers rather than an enantiomeric pair. However, ^{1}H and ^{13}C NMR studies as well as molecular orbital calculations of lanthanide and alkali metal complexes of (*S,S,S,S*)-($-$)-THP indicate that these species each exist predominantly as a single diastereomer (Δ) in methanolic and aqueous solutions.[7,33]

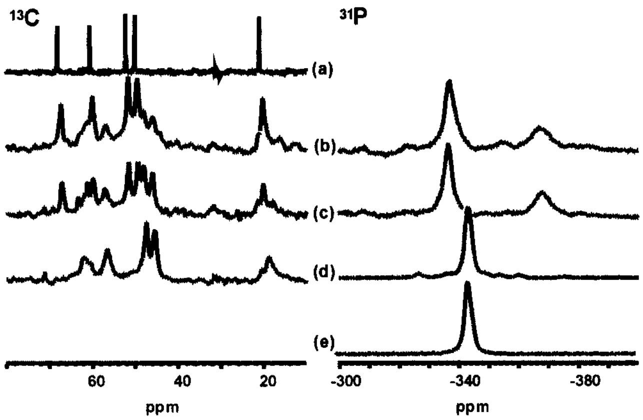

Figure 4. ^{13}C NMR and ^{31}P spectra of the La(THP)$^{3+}$,Tm(DOTP)$^{5-}$ titration showing resonances observed for La(THP)$^{3+}$ upon increasing Tm(DOTP)$^{5-}$ concentration: (a) $\rho = 0.0$, (b) $\rho = 0.4$, (c) $\rho = 0.5$, (d) $\rho = 1.5$, (e) $\rho = \infty$ (Tm(DOTP)$^{5-}$).

Upon addition of Tm(DOTP)$^{5-}$, the ^{13}C resonances of the THP complex were slightly shifted to lower frequencies with concomitant broadening and the appearance of a new set of signals (also at lower frequencies than the corresponding resonances of free Tm(DOTP)$^{5-}$). This is opposite to what has been observed for the ^{1}H and ^{59}Co shifts of Co(en)$^{3+}$ induced by Yb(DOTP)$^{5-}$ and Tm(DOTP)$^{5-}$, respectively.[4] However, the signals are shifted in the same direction as those of the ^{1}H nuclei of the Tm(DOTP)$^{5-}$ complex. Since a shift to higher frequency is also observed for the ^{23}Na counterion in complexes with Tm(DOTP)$^{5-}$, Sherry et al. conclude that Co(en)$^{3+}$ and ^{23}Na bind similarly in the upper shift cone of Tm(DOTP)$^{5-}$.[4] A related binding domain is observed for the ADA,Tm(DOTP)$^{5-}$ adduct, where all Tm(III)-induced ^{1}H shifts are to higher frequencies (see Supporting Information). The variance in sign of the LIS for the La(THP)$^{3+}$,Tm(DOTP)$^{5-}$ adduct suggests an alternate binding position for the La(THP)$^{3+}$ countercation. Presumably, La(THP)$^{3+}$ is oriented toward one of the negatively charged phosphonates in the outer region of the upper cone; however, the large width of the THP complex most likely brings the ^{13}C nuclei outside the positive cone.

Increasing the Tm(DOTP)$^{5-}$:La(THP)$^{3+}$ ratio from $\rho = 0$ to $\rho = 0.4$ resulted in a gradual increase of all ^{13}C shifts by approximately the same magnitude. Additional signals were observed in the range $0.4 < \rho < 1.5$, the intensity of which increased with increasing ρ at the expense of the intensities of the original set of signals. Finally, at $\rho \approx 1.5$, only single broadened signals of the new set were detected. The ^{13}C NMR spectrum of La(THP)$^{3+}$ for $\rho = 0-1.5$ is shown in Figure 4. The ^{13}C signals reached maximum LIS values in the range $0.5 < \rho < 1.5$, including -2.9 ppm (C1), -6.6 ppm (C2) -4.2 ppm (C3), -4.7 ppm (C4), and -4.8 ppm (C5). The shifts are relatively small, which suggests that La(THP)$^{3+}$ is located near the 0-shift region ($\theta = 54.7°$).

The ^{31}P spectra of Tm(DOTP)$^{5-}$ in the above samples (see Figure 4) each revealed the presence of two signals with intensities and shifts dependent on ρ. Variable-pH and -concentration experiments indicate that the dynamics are very sensitive to these parameters. A variable temperature ^{13}C NMR

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study (25−80 °C) at $\rho = 0.6$ was carried out on the mixture where the La(THP)$^{3+}$,Tm(DOTP)$^{5-}$ ratio was approximately 2:1. The sets of signals of the THP complex began to converge at 35 °C, with coalescence occurring at 50 °C.

Apparently, two adducts are formed from La(THP)$^{3+}$ and Tm(DOTP)$^{5-}$. At room temperature, the exchange between these adducts is slow on the ^{13}C and ^{31}P NMR time scales, whereas the exchanges between each of these species and free La(THP)$^{3+}$ and Tm(DOTP)$^{5-}$ are rapid. These phenomena can be explained by chiral resolution of the two Tm(DOTP)$^{5-}$ isomers (see above) as a result of ion-pair formation with the chiral La(THP)$^{3+}$ complex. There are precedents for this type of chiral selectivity and its ensuing spectral discrimination. The degeneracies of Ln(DOTP)$^{5-}$ resonances were shown to be lifted by ion-pair formations with the complexes *N*-methyl-D(−)-glucamine (MEG)[2] and (+)-Co(en)$_3{}^{3+}$.[4] In each case, the two components of the split signals did not exhibit equal intensities, reflecting a degree of stereoselectivity which was attributed to structural effects. Along these lines, the single Δ isomer of La(THP)$^{3+}$ may bind with different geometries to the enantiomers of Tm(DOTP)$^{5-}$, thus producing two diastereomeric adducts. This may explain the split signals in the ^{13}C NMR spectra of the La(THP)$^{3+}$ complex; however, at first sight, it fails to account for the intensity variations of the two sets of resonances observed between $\rho = 0.5$ and $\rho = 1.5$ (see Figure 4). This system differs from the two described above because new signals appear to grow with increasing ρ of Tm(DOTP)$^{5-}$ until ultimately the initial signals collapse completely. Rather than the coexistence of the two diastereomeric adducts in varying amounts, this system displays signs of the presence of more than one type of adduct with varying stoichiometries of Tm(DOTP)$^{5-}$ and La(THP)$^{3+}$. This behavior may be consummated by the initial formation of 1:2 diastereomeric adducts (Δ,Δ,Δ and Δ,Δ,Λ) at $\rho = 0-0.5$. Upon an increase in ρ, the equilibrium shifts to the diastereomeric 1:1 adducts (Δ,Δ and Δ,Λ). The appearance of single resonances at higher Tm(DOTP)$^{5-}$:La(THP)$^{3+}$ ratios may indicate exclusive binding with a single enantiomer of Tm(DOTP)$^{5-}$. The stereoselectivity could be accounted for by providing a specific orientation that is more suited to H-bond formation between the phosphates and the hydroxyl groups of La(THP)$^{3+}$ and/or by the steric requirements of the bulky countercation.

All diastereomeric adducts are in rapid exchange with free La(THP)$^{3+}$ and Tm(DOTP)$^{5-}$ under the conditions applied. ^{13}C NMR spectra recorded at various total concentrations showed that the line widths of the resonances are dependent on the concentration. Upon a decrease in the concentration, an increase in line width was observed, suggesting an increase in the rate of exchange between the enantiomers. The observation of line broadening with decreasing concentrations is suggestive of an associative exchange mechanism.[34,35]

Conclusion

We have demonstrated the viability of inducing strong ion-pair interactions between oppositely charged Ln(III) complexes. It is clear that the charged complexes form tight ion pairs, with each component located in the pseudo first coordination shell of the other.

The knowledge gained from these studies has implications for the development of multinuclear systems as new-generation contrast agents. These supramolecular compounds may prove useful in increasing the effective dose of Gd^{3+} which, in turn, would serve to increase the efficacy of the contrast agent. It is also expected that ion pairs will dissociate more efficiently for expulsion as compared to high molecular weight covalent compounds. Beyond improvement of image contrast, agents based on electrostatic interactions may serve to improve patient comfort by alleviating painful injections caused by using compounds of high ionic strengths. The most exciting aspect of these results is the possibility of increasing the efficiency of CA's even further by increasing molecular weight if this approach is extended to the cross-linking of larger systems such as biopolymers via oppositely charged Gd(III) chelates.

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Supporting Information Available: ^{13}C NMR titration curves showing La(THP)$^{3+}$ shifts induced by Tm(III) complexes of DOTA, DTPA, and TTHA and a discussion of an ^{1}H NMR study of the interactions between the 1-admantylammonium (ADA) ion and Tm(III) complexes of DTPA and DOTP along with ^{1}H NMR titration curves showing the ADA shifts induced by the Tm(III) complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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