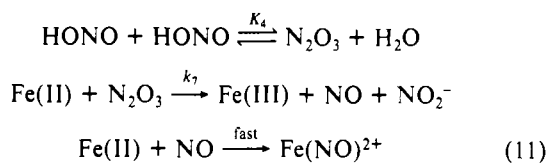


conditions the overall scheme can be summarized by the reactions in (11), for which the corresponding rate law is given in (12). This



$$-d[\text{Fe(II)}]/dt = 2k_7K_4[\text{HONO}]^2[\text{Fe(II)}] \quad (12)$$

suggestion is also in agreement with our findings for the nta and edda complexes, since the first-order reaction path outlined in (2) is more effective due to the significantly lower redox potentials of these complexes. The reaction product is quoted as  $\text{Fe(NO)}_2^{2+}$  in (11), but does not rule out the formation of  $\text{Fe(NO)}_2^{2+}$  as suggested in the literature.<sup>46,47</sup> This could, for instance, occur in a subsequent fast reaction involving  $\text{Fe(NO)}_2^{2+}$  and HONO or NO. However, no evidence for the formation of  $\text{Fe(NO)}_2^{2+}$  under our selected experimental conditions could be found. It follows that the intercept of the plot in Figure 6 represents  $2k_7K_4$ , such that  $k_7 = 1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ , since  $K_4 = 8.4 \times 10^{-2} \text{ M}^{-1}$ .<sup>41,42</sup> The value of  $k_7$  is very reasonable, considering the limit of  $10^4 \text{ M}^{-1} \text{ s}^{-1}$  predicted for the nta and edda complexes in the previous section. An overall comparison of the results reported for the series of complexes investigated in this study reveals a few interesting tendencies. Obviously, the redox potential of the  $\text{Fe}^{\text{II/III}}(\text{L})$  system is not the only important factor. In addition, the overall charge on the complex, the availability of vacant coordination sites and

the possible changeover between outer-sphere and inner-sphere redox mechanisms must be taken into consideration. The overall observed effect is a composite of various contributing factors, which may vary from system to system. Nevertheless, the observed trends seem to fall in with the basic concepts of coordination chemistry in terms of the labilization by chelation on the one hand and steric blocking on the other. The direct reaction between  $\text{Fe}^{\text{II}}(\text{L})$  and NO seems to be very similar for all L and is mainly controlled by the lability of the complex and the availability of coordinate solvent molecules presumably undergoing a rapid substitution reaction with NO. The parallel reaction path involving  $\text{HONO/NO}_2^-$  is more complicated and exhibits larger variations with L, since it involves an electron-transfer process with HONO or  $\text{N}_2\text{O}_3$  during which  $\text{Fe}^{\text{III}}(\text{L})$  and NO are produced. The observed kinetics and their dependence on pH and [HONO] differ significantly for various L. Again, the availability of labile coordination sites and the redox chemistry involved will determine the overall magnitude of this contributing reaction path.

The systematic variation of L has enabled us to investigate the possible influence of this aspect on the overall process involving the simultaneous removal of  $\text{SO}_2$  and  $\text{NO}_x$  from flue gases of coal-fired power plants, as mentioned in the Introduction. The subsequent reactions of the produced  $\text{Fe}^{\text{II}}(\text{L})\text{NO}$  species with  $\text{HSO}_3^-/\text{SO}_3^{2-}$  and the overall catalytic role of the  $\text{Fe}^{\text{II}}(\text{L})$  species will be reported in a forthcoming paper.

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## pH Dependence of Relaxivities and Hydration Numbers of Gadolinium(III) Complexes of Linear Amino Carboxylates

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Spin-lattice relaxivity values ( $R_1$ , 20 MHz, 40 °C) for Gd(III) complexes and the number of inner-sphere-coordinated water molecules ( $q$ , hydration number) in analogous Tb(III) complexes were determined for a series of Gd(III) and Tb(III) amino carboxylate complexes. The observed relaxivity values were found to decrease with increasing pH in the acid region below pH 7. When a Gd(III) complex became fully formed, the relaxivity value became invariant, and this limiting value correlated well with the number of inner-sphere-coordinated water molecules for mononuclear species. Gd(III) complexes of ligands with more donor atoms tended to have lower  $q$  and  $R_1$ . The observed order of  $R_1$  (and  $q$ ) values were found to be as follows:  $\text{Gd}^{3+}(\text{aq})$  (9) >  $\text{Gd}(\text{HEDTA})$  (4) >  $\text{Gd}(\text{EDTA})^-$  (3) >  $\text{Gd}(\text{DTPA})^{2-}$  (1) =  $\text{Gd}(\text{EGTA})^-$  (1) >  $\text{Gd}(\text{TTHA})^{2-}$  (0). The outer-sphere relaxivity for these complexes is estimated to be  $2.2 \pm 0.1 \text{ (mM s)}^{-1}$  and each inner-sphere-coordinated water adds approximately  $1.6 \pm 0.1 \text{ (mM s)}^{-1}$ . Deviations from linearity were observed for TTHA complexes at pH 4-5 and for HEDTA at and above pH 10. The increased relaxivity per complex in these cases is rationalized in terms of an oligomerization, independently observed spectroscopically, which then results in either increased  $\tau_r$  and/or an increase in the magnetic moment that each water proton experiences.

### Introduction

Gadolinium(III) complexes of polyamino polycarboxylate ligands are currently used clinically as magnetic resonance imaging (MRI) contrast agents. A practical MRI contrast agent must remain intact under physiological conditions so as to minimize the concentrations of free metal and ligand, which are poorly tolerated, while strongly affecting the spin-lattice relaxation time ( $T_1$ ) of bulk solvent water.<sup>1</sup> The former is best accomplished through the use of a strongly binding ligand that occupies most of the available coordination sites of the metal, while the latter occurs most effectively with a maximal hydration state of the Gd(III) ion. These conflicting requirements necessitate careful ligand design, as well as study of Gd(III) complex stability, dissociation kinetics, and relaxivity under a variety of conditions.

The stability (as measured by complex formation constants), dissociation kinetics, spin-lattice relaxivity ( $R_1$ , the second-order rate constant that describes catalysis of  $T_1$  relaxation, vide infra), and inner-sphere hydration number ( $q$ , the number of coordinated water molecules) are particularly dependent on the solution pH. At low pH values, the coordinating carboxylate groups become protonated, leading to at least partial dissociation of the complex. Within this pH range, the resulting hydration number will be relatively high. At sufficiently high pH values, coordination of hydroxide ion can occur. This reduces rapid exchange with solvent water and may allow oligomers to form. Both factors may decrease or increase relaxivity.

Relaxivities and inner-sphere hydration states of Gd(III) and Tb(III) complexes of linear amino carboxylic acids were determined as a function of pH to better understand these effects. The ligand systems studied were EDTA (ethylenediaminetetraacetic acid), HEDTA (*N*-(2-hydroxyethyl)ethylenediaminetriacetic acid),

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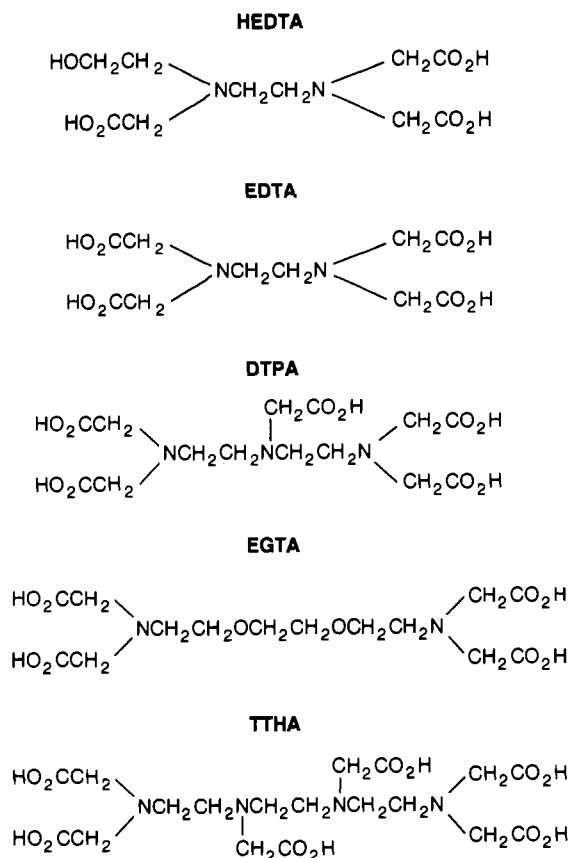


Figure 1. Structural formulas of the ligands used in this study.

DTPA (diethylenetriaminepentaacetic acid), TTHA (triethylenetetraaminehexaacetic acid), and EGTA (ethylenebis(oxyethylenitrilo)tetraacetic acid). The structural formulas of these ligands are shown in Figure 1.

Relaxivities of Gd(III) complexes of a number of these ligands have been previously reported (EDTA<sup>4-</sup>, DTPA<sup>4-</sup>, and EGTA<sup>5</sup> and Gd<sup>3+</sup>(aq)<sup>6</sup>), although considerable variation in reported values exists. Additionally, the inner-sphere hydration numbers of these complexes have not been reported as a function of pH. For simplicity, the charge on each complex is neglected in some parts of the paper.

### Experimental Section

**Materials.** Gadolinium and terbium oxides ( $\geq 99.9\%$ ) were obtained respectively from Alfa Inorganics and Research Chemicals, and oven dried at 110 °C for at least 24 h before use. The complexing ligands used in this work (EDTA, HEDTA, DTPA, EGTA, and TTHA) were used as received from Aldrich.

**Sample Preparation.** A stock Gd<sup>3+</sup> solution was prepared by dissolving an accurately weighed amount of dry Gd<sub>2</sub>O<sub>3</sub> in deionized water (Barnstead Milli-Q) using a minimum amount of 12 M HCl. This Gd<sup>3+</sup>(aq) solution was used as a titrant to standardize solutions of the polyamino polycarboxylate ligands. Ligand titrant solutions consisted of approximately 40 mM solute, prepared at pH 5, by using a 0.5 M acetate buffer. Xylenol orange was used as an indicator for standardization purposes.

Stock Gd(III) complex solutions (henceforth identified as GdL and having a concentration range of 8.0–10.0 mM) were prepared by com-

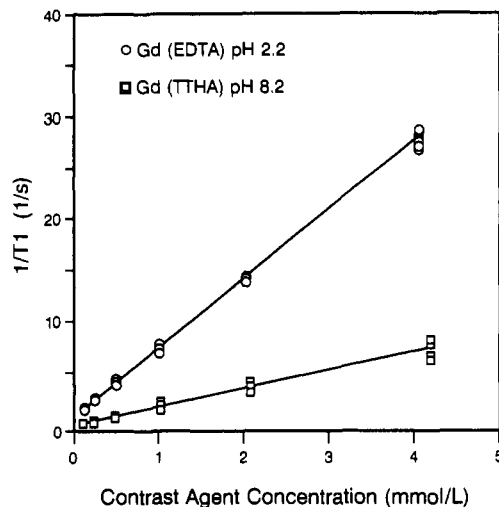


Figure 2. Linear plots of  $(1/T_1)_{\text{obsd}}$  vs  $[GdL]$  for Gd(EDTA)<sup>-</sup> at pH 2.2 and Gd(TTHA)<sup>3-</sup> at pH 8.2.

binning equimolar amounts of the standardized Gd<sup>3+</sup> and ligand solutions without buffer. A slight excess (~2%) of ligand was used to ensure total complexation of all Gd<sup>3+</sup>. These solutions were allowed to equilibrate for at least 1 h at room temperature to ensure completion of the complexation equilibrium.

The final GdL solutions consisting of various pH values and Gd<sup>3+</sup> concentrations were prepared by combining in a 1:1 (v/v) ratio the buffer solution with an appropriately diluted GdL solution. For solutions above pH 6, the samples were first adjusted to pH 5 with NaOH, heated for 2 h at 70 °C to reach equilibrium, and finally adjusted to the desired pH. This procedure was followed to avoid any possibility of forming insoluble hydroxy species.

Five GdL concentrations (0.2–5.0 mM) were prepared by successive dilutions of a stock solution. Individual GdL concentrations were confirmed by using HPLC with fluorescence detection, following the published method.<sup>7</sup> Extension of the relaxivity measurement to 10 mM gave the same results.

The following buffer systems (all 0.1 M, except those at pH 7–7.5) were used: chloroacetic acid/NaOH (pH 2 and 3), acetic acid/NaOH (pH 4 and 5), Tris/HCl (pH 7 [1 M] and 8), ammonia/HCl (pH 9 and 10). The buffers were prepared to yield constant ionic strength (0.1 M). The 0.1 M buffers were sufficient to maintain the solution pH within the desired range, except that a 1 M Tris/HCl buffer was needed for pH 7. The buffered GdL solutions were also allowed to equilibrate for at least 1 h, with the pH of these solutions being determined immediately prior to relaxivity measurements.

**Relaxivity Determination.** Spin–lattice relaxation time ( $T_1$ ) measurements were obtained on an IBM PC/20 Multispec relaxometer operating at a fixed magnetic field of 0.47 T (20 MHz). The instrument is equipped with a 13-mm bore coil maintained at  $40 \pm 1$  °C.  $T_1$  measurements were made using an “inversion-recovery” pulse sequence (180– $\tau$ –90) with phase-sensitive detection.<sup>8</sup> GdL samples (0.5 mL) were placed in 10-mm tubes, which were, in turn, concentric within 13-mm tubes. The instrumental parameters were optimized for each individual sample, and five  $T_1$  values were recorded for each sample.

For a series of concentrations at a given pH, all the  $T_1$  values were used to obtain a relaxivity value through linear least-squares fitting to

$$(1/T_1)_{\text{obsd}} = (1/T_1)_d + R_{1,\text{GdL}}[\text{GdL}] \quad (1)$$

where  $(1/T_1)_{\text{obsd}}$  = observed spin–lattice relaxation rate constant,  $(1/T_1)_d$  = diamagnetic relaxation rate constant ( $\text{s}^{-1}$ ),  $R_{1,\text{GdL}}$  = spin–lattice relaxivity of GdL ( $\text{mM}^{-1} \text{s}^{-1}$ ), and  $[\text{GdL}]$  = Gd chelate (GdL) concentration (mM).

If a mixture of free Gd(III) and GdL is present in the solution (such might exist at low pH), the relaxivity equation can be approximated as

$$(1/T_1)_{\text{obsd}} = (1/T_1)_d + R_{1,\text{Gd}}[\text{Gd}]_{\text{tot}} \quad (2)$$

where

$$[\text{Gd}]_{\text{tot}} = [\text{Gd}]_{\text{free}} + [\text{GdL}] \quad (3)$$

$$R_{1,\text{Gd}}[\text{Gd}]_{\text{tot}} = R_{1,\text{Gd}}[\text{Gd}]_{\text{free}} + R_{1,\text{GdL}}[\text{GdL}] \quad (4)$$

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In that case

$$R_1 = a_{Gd}R_{1,Gd} + a_{GdL}R_{1,GdL} \quad (5)$$

where  $a_{Gd}$  and  $a_{GdL}$  are the fractions of  $Gd^{3+}(aq)$  and  $GdL$ , respectively. Note that eq 5 is only an approximation because the fractions of  $Gd^{3+}(aq)$  and  $GdL$  will vary with the total concentrations of  $Gd^{3+}$  and  $L$ .

An IBM BASIC program for linear least-squares curve fitting and statistical analysis was used to analyze  $T_1$  and concentration data. Figure 2 shows examples of the linear plots obtained for  $(1/T_1)_{obsd}$  vs  $[GdL]$ , in the specific instances of  $Gd(EDTA)$  at pH 2.2 and  $Gd(TTHA)$  at pH 8.2.

**Luminescence Studies and Inner-Sphere Hydration Numbers.** Stock solutions of Tb(III) and the appropriate ligand were prepared by the dissolution of appropriate quantities of material, and the complexes of these were prepared by mixing stoichiometric amounts of the stock solutions. For the luminescence experiments, a final Tb(III) concentration of 10 mM was used. The ionic strength of the solutions was not controlled and was estimated to be less than 0.05.

The pH of each solution was varied between pH 1.5 and 12, with the required photophysical measurements being made at each pH value. Variation of the solution pH was effected by the addition of microliter amounts of standard NaOH or HCl directly to the cuvette. The solution pH was adjusted to pH 11 first, then gradually down to pH 1, and back to pH 11 to assure reproducibility. The pH was measured with a glass microcombination electrode that could be inserted into the cuvette. The pH meter was calibrated daily with phosphate buffers.

The Tb(III) luminescence lifetimes were obtained by exciting the samples with the pulsed 337-nm output of a nitrogen laser (Model LN-1000, Photochemical Research Associates) and capturing the decay curve on a boxcar averager (model SR-265, Stanford Research Associates). The luminescence decay times and rate constants were obtained by fitting the observed decay curves to a single exponential function over 3 or more half-lives. In no instance was multiexponential decay noted.

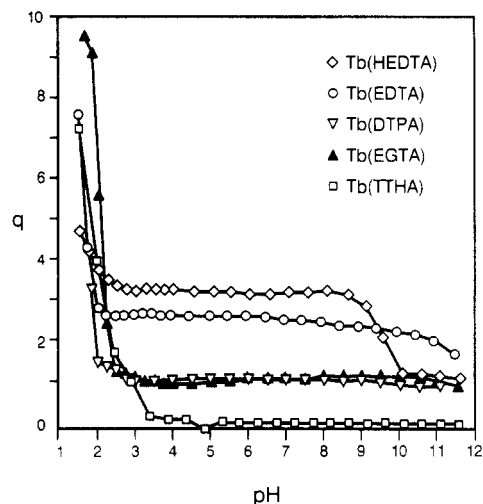
## Results and Discussion

**I. Luminescence Studies.** The molar absorptivity of  $Gd(III)$ -containing species is exceedingly low and its luminescence extremely weak in fluid solution. These properties make it difficult to use spectroscopy to study  $Gd(III)$  compounds directly, and consequently the analogous Tb(III) complexes were prepared for study. Thermodynamic arguments have been advanced that support the assumption that Tb(III) complexes are isostructural with the corresponding  $Gd(III)$  species.<sup>9</sup>

UV excitation of Tb(III) complexes results in reasonably efficient population of the luminescent  $^5D_4$  excited state, and in subsequent emissive transitions to the  $^7F_6$  (490 nm),  $^7F_5$  (545 nm),  $^7F_4$  (585 nm), and  $^7F_3$  (625 nm) states of the ground manifold. The intensities and lifetimes of the various emission bands have been found to be reliable indicators of solution-phase coordination chemistry.<sup>10</sup> The existence of a stable emission intensity of lifetime over a defined pH range usually indicates the presence of a stable complex. It is generally observed that trends associated with the pH dependence of each emission band system are identical, and therefore only results obtained within the  $^5D_4 \rightarrow ^7F_5$  transition were analyzed.

The mechanisms that lead to alteration in the luminescence lifetime of a Tb(III) species are similar to those that affect the emission intensity. High-energy vibrations (around  $3500\text{ cm}^{-1}$ ) are efficient promoters for deactivation of the excited  $^5D_4$  Tb(III) state, and are effective quenchers of the emission lifetime. The  $-OH$  stretching mode of coordinated water molecules is particularly effective in this regard.<sup>11</sup> Most ligands do not contain the required group vibrational frequencies that quench the excited state and therefore are not efficient quenchers of Tb(III) emissive lifetimes. Since the binding of a ligand must result in the expulsion of some of the coordinated water molecules, then it follows that the Tb(III) emission lifetime is a good probe for the study of solution chemistry.

The existence of a deuterium isotope effect in Tb(III) emission lifetimes has been known for some time.<sup>12</sup> While the  $-OH$



**Figure 3.** pH dependence of the hydration state for the Tb(III) complexes with linear amino carboxylic acid ligands. Some of the Tb(HEDTA) data were also published in ref 22.

stretching mode of coordinated water ( $3500\text{ cm}^{-1}$ ) is effective at quenching the Tb(III) excited  $^5D_4$  state, the analogous  $-OD$  stretching mode of coordinated deuterium oxide ( $2800\text{ cm}^{-1}$ ) is far less effective. Horrocks and Sudnick<sup>11</sup> used this phenomenon to develop a spectroscopic method suitable for a determination of the number of water molecules bound at the inner coordination sphere of either Tb(III) or Eu(III). The luminescence lifetime of a given species is measured in both  $H_2O$  and  $D_2O$ , and the rate for luminescence decay is observed in each solvent system. The difference between the rate constants observed in  $H_2O$  and  $D_2O$  is directly proportional to the number of coordinated water molecules, which is calculated by using the proportionality constant provided by Horrocks and Sudnick.<sup>11</sup> The data obtained on all Tb(III) complexes are shown in Figure 3, where the pH dependence of the hydration number is illustrated.

**A. Tb(HEDTA) and Tb(EDTA) Complexes.** Both HEDTA and EDTA begin to bind to Tb(III) above pH 1, and full formation of the Tb(III) complexes causes the number of coordinated water molecules to drop from 8–9 (as would exist in the aqua ion) to around 3. These species persist up to pH 8.5–9, where the number of coordinated waters decreases again, finally leveling off at 1 by pH 10 for the HEDTA complex and 2 by pH 11 for the EDTA complex. This latter species remains stable up to pH 11.5.

The trends in coordinated solvent molecules are consistent with the known coordination chemistry of lanthanide HEDTA and EDTA complexes. By the use of energy transfer from Tb(HEDTA) or Tb(EDTA) donor species to Eu(HEDTA) or Eu(EDTA) acceptor species, it has been shown that the complexes are capable of existing either as monomer or oligomer units.<sup>13</sup> Between pH 3 and 8.5, lanthanide HEDTA and EDTA complexes exist as monomers, but above pH 9, they self-associate into oligomer units. The energy-transfer data also indicate that the degree of self-association is far less for EDTA complexes than for HEDTA complexes. This latter property explains the smaller change in hydration state noted for Tb(EDTA) relative to Tb(HEDTA). Potentiometric titration evidence<sup>14</sup> suggested that the oligomers could most likely be  $\mu$ -hydroxy-bridged dimers.

**B. Tb(EGTA) and Tb(DTPA) Complexes.** As is evident in Figure 3, the binding of both EGTA and DTPA to Tb(III) becomes significant around pH 2, with the complex being fully formed by pH 3. At that point, only one water of hydration is bound at the inner coordination sphere of either Tb(EGTA) or Tb(DTPA). No change in hydration state was noted up to pH 11.

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**Table I.** Limiting and pH 7  $T_1$  Relaxivity Values of Gd(III) Complexes<sup>a</sup>

complex	pH	$T_1$ relaxivity ( $R_1$ ), (mM s) <sup>-1</sup>
Gd(EDTA)	7.1 ± 0.1	7.15 ± 0.07
	limiting <sup>b</sup>	6.07 ± 0.14
Gd(HEDTA)	7.4 ± 0.3	8.13 ± 0.05
	limiting <sup>b</sup>	7.61 ± 0.15
Gd(DTPA)	7.4 ± 0.2	4.70 ± 0.03
	limiting <sup>b</sup>	3.91 ± 0.03
Gd(TTHA)	7.5 ± 0.1	2.97 ± 0.02
	limiting <sup>c</sup>	2.12 ± 0.05
Gd(EGTA)	7.1 ± 0.1	4.41 ± 0.02
	limiting <sup>b</sup>	3.90 ± 0.08

<sup>a</sup> Average relaxivity values and 95% confidence limits are reported, 40 °C and 20 MHz. <sup>b</sup> Average of relaxivity values over the pH range 4–9. <sup>c</sup> Average of relaxivity values over the pH range 8–10.

The energy-transfer studies carried out on lanthanide EGTA and DTPA complexes indicate that no formation of polynuclear species takes place at any pH value.<sup>13</sup> This phenomenon is undoubtedly due to the large backbone and high denticity of the EGTA and DTPA ligands. These ligands evidently are more effective at encapsulating the Tb(III) ion and preventing association with another Tb(III) complex species. The observation that  $q$  does not change from 1 between pH 3 and 11 is taken as further confirmation of the monomeric nature of the Tb(EGTA) or Tb(DTPA) complexes.

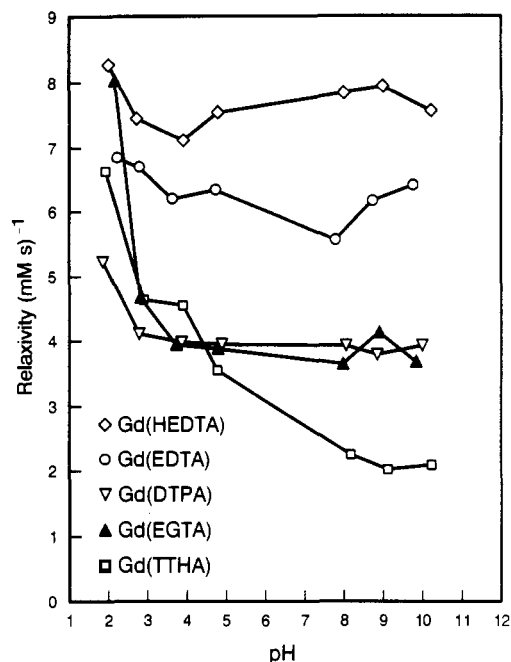
**C. Tb(TTHA) Complexes.** The TTHA ligand contains the largest number of potential donor atoms and should therefore represent the most sterically demanding ligand of the polyamino polycarboxylate series. As is evident in Figure 3, TTHA binding to Tb(III) begins around pH 1.5 and becomes complete by pH 3.5. At that point,  $q = 0$  for the Tb(TTHA) complex. This anhydrous inner coordination sphere persists up to pH 12. Examination of the literature reveals that only the tris lanthanide complexes of pyridine-2,6-dicarboxylic acid<sup>11</sup> were reported to contain no inner-sphere-coordinated water in solution.

In a separate study, intermolecular energy transfers from Tb(TTHA) donor to Eu(TTHA) acceptor species were carried out to determine whether the complexes were capable of forming oligomers under any pH condition.<sup>15</sup> It was determined that in the pH region of pH 3 to 7.5, the partially protonated lanthanide complexes of TTHA exist as oligomeric species. A well-defined polynuclear species was found to exist between pH 4 and 6, characterized by a Stern–Volmer association constant<sup>16</sup> of 125. Between pH 6 and 8, the oligomer species were found to dissociate, and above pH 8, only monomeric lanthanide TTHA complexes were found to exist.

The water-counting data clearly indicate that no inner-sphere waters of hydration are bound by the lanthanide ion in either the monomer or oligomer species. All data are consistent with the interpretation that the TTHA ligand contains more steric bulk and donor atoms than the DTPA ligand.

**II. Relaxivity Studies.** The spin–lattice relaxivities ( $R_1$  values) for the entire series of Gd(III) complexes at various pH values (ionic strength 0.1 M) are plotted in Figure 4. The pH 7 (ionic strength 1.0 M) and “limiting” relaxivity values are listed in Table I (vide infra). The relative standard deviations associated with these values are estimated to be ±5% of the measured  $R_1$  values.

The relaxivity of a paramagnetic metal complex consists of two components: the inner-sphere and outer-sphere relaxivities.<sup>1,17</sup> Since all ligands studied have similar functional groups and the final Gd(III) chelate structures and sizes are similar, it is assumed that, to a first approximation, the outer-sphere relaxivities are



**Figure 4.** pH dependence of the relaxivity for the five Gd(III) complexes with linear ligands, all in 0.1 M buffers (pH 7 data excluded) at 20 MHz and 40 °C.

similar. Thus, the observed relaxivity variation is primarily attributed to variation in the inner-sphere contribution.

The inner-sphere-relaxivity differences at a fixed radio frequency and temperature depend on various parameters as shown in eq 6, where  $q$  is the inner-sphere hydration number,  $\mu_{\text{eff}}$  is the effective

$$R_1 \propto q(\mu_{\text{eff}})^2 \tau_c / r^6 \quad (6)$$

magnetic moment of the metal ion (the spin-only value for metal ions in symmetric ground states),  $\tau_c$  is the correlation time during which the proton nucleus experiences a constant magnetic field from the paramagnetic species, and  $r$  is the internuclear distance between the metal ion and the protons of the coordinated water molecules. The spin-only  $\mu_{\text{eff}}$  value is 7.94  $\mu_B$  for Gd(III) complexes.<sup>18</sup> The Gd–O bond lengths for Gd(III)–OH<sub>2</sub> systems are normally 2.50 ± 0.04 Å.<sup>19,20</sup> Since all the complexes studied consist of Gd(III) bound to similar ligands,  $r$  and  $\mu_{\text{eff}}$  will be considered constant for the current study. However,  $q$  and  $\tau_c$  can vary significantly, leading to a range of  $R_1$  values.

The correlation time,  $\tau_c$ , may have contributions from molecular rotation ( $\tau_r$ ), electron spin relaxation ( $\tau_s$ ), and water exchange ( $\tau_M$ ):<sup>1,17</sup>

$$\tau_c^{-1} = \tau_r^{-1} + \tau_s^{-1} + \tau_M^{-1} \quad (7)$$

For most small Gd(III) complexes, water exchange and electron-spin relaxation (at 20 MHz) are relatively slow when compared to rotation; only  $\tau_r$  contributes significantly to  $\tau_c$ . A study on water solutions of Gd(III) further delineated that  $\tau_r$  is the property that mainly determines  $\tau_c$ .<sup>21</sup> This situation may change, however, if oligomerization decreases the rotation rate or induces antiferromagnetism or ferromagnetism, which would be expected to increase the electron-spin relaxation rate.<sup>22</sup>

**A. Buffer Effects on Relaxivity.** The ideal buffer system for the present study would be one used in low concentration, while

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still maintaining the desired pH values, and one that would not associate with the Gd(III) complex under any conditions. Chloroacetate, acetate, Tris, and ammonia buffer systems were used in an attempt to meet as many of these criteria as possible. These span the desired pH ranges and were chosen for their inability to coordinate Gd(III).

A 0.1 M Tris buffer was too weak to buffer the GdL solutions at pH 7, so a 1 M buffer was used. The effect of this buffer on the relaxivity data is evident in Table I. The uniformly higher relaxivity values for the more concentrated buffers are most likely due to their viscosity. A more viscous solution would decrease the rotation of the GdL complex and increase the  $\tau_r$  value. On the other hand, 0.05 and 0.1 M ionic strengths were equivalent with respect to our method of measurement.

**B. pH Effects on Relaxivity.** Except for Gd(TTHA), the relaxivity data exhibit little pH dependence above pH 4. At very low pH values, the carboxylate oxygen and the nitrogen atoms are successively protonated and are no longer coordinated. As the ligand functional groups dissociate, an increase in the number of water molecules coordinated to the metal ion ( $q$ ) increases. These species exhibit higher relaxivity values due to their higher hydration state.

A reasonable treatment on the low pH relaxivity data assumes that the overall relaxivity is given by the weighted sum of contributions of all Gd(III) species in the solution as described in eqs 2–5. Protonated chelates, such as Gd(HL) and Gd(H<sub>2</sub>L), may be present for some ligands and should ideally be taken into account for accurate computations. We are unable to do this because the uncertainties involved in the ligands' low  $pK_a$  values and the chelate–ligand speciation. The following treatment is approximate.

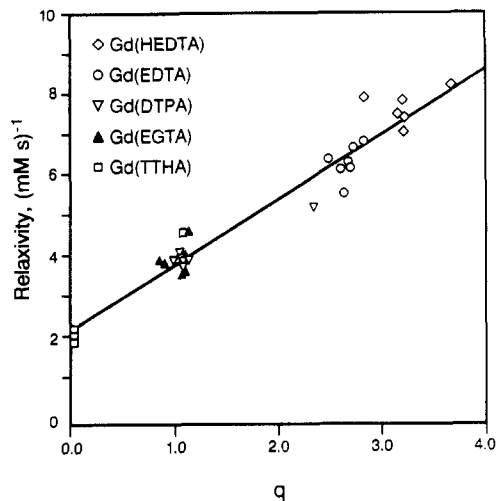
Assuming that only two Gd(III) species are present in solution at low pH, the fractions  $a_{Gd}$  and  $a_{GdL}$  can be calculated using the conditional formation constant value at each pH value. The relaxivity of a particular GdL solution can therefore be estimated by using eqs 2–5,  $R_{1,Gd}$ , and the "limiting" value of  $R_{1,GdL}$  (Table I). This last parameter is calculated by averaging all the observed relaxivity values in the pH range 4–9, except for Gd(TTHA)<sup>3-</sup>, for which relaxivity values in the pH range 8–10 are averaged.

For example, at pH 2.2, the conditional formation constant of Gd(EDTA) is  $5 \times 10^4 M^{-1}$ . Thus, a 10 mM Gd(EDTA) solution at pH 2.2 consists of 0.45 mM Gd(EDTA) and 9.55 mM Gd<sup>3+</sup>(aq) or 4.5% and 95.5%, respectively. The relaxivity for the Gd(EDTA) solution at pH 2.2 can be estimated to be  $11.2(0.045) + 6.07(0.955)$ , for a total of  $6.30 (mM s)^{-1}$ . This is close to the experimentally determined value of  $6.84 (mM s)^{-1}$ . The difference can be attributed to the presence of other protonated species such as Gd(HL) and Gd(H<sub>2</sub>L), and experimental error.

The relaxivity values for Gd(TTHA) at pH 3.9 and pH 4.8 are 4.6 and  $3.6 (mM s)^{-1}$ , respectively. These values are significantly higher than the "limiting" value  $2.1 (mM s)^{-1}$ , which suggests that either the Gd(TTHA) complex may be partially protonated at such pH, allowing the coordination of inner-sphere water molecule(s) or that polymeric species form. Either expanded  $q$  or oligomerization will result in greater relaxivity.

Partial protonation of Gd(TTHA)<sup>3-</sup> at low pH is indeed consistent with the result of a previous potentiometric study<sup>23</sup> in which the respective protonation constants for Gd(TTHA)<sup>3-</sup> to form [HGd(TTHA)]<sup>2-</sup> and [H<sub>2</sub>Gd(TTHA)]<sup>-</sup> were found to be  $10^{4.7} M^{-1}$  and  $10^{2.9} M^{-1}$ . The protonation site for the monoprotinated chelate is very likely at a terminal nitrogen atom. However, because the water-counting data clearly indicate that no inner-sphere waters of hydration are bound by the lanthanide ion between pH 4 and 8 (vide supra), the monomeric structure with one inner-sphere coordination water molecule, i.e. [HGd(TTHA)(H<sub>2</sub>O)]<sup>2-</sup>, proposed by Yingst and Martell,<sup>24</sup> is unlikely.

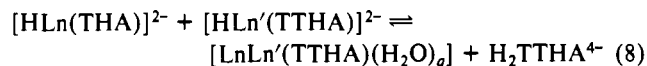
Thus, a better explanation for the anomalously high relaxivities of the Gd(TTHA) species at pH 4 and 5 is that Gd(TTHA) forms



**Figure 5.** Linear plot of  $R_1$  vs  $q$  for five Gd(III) complexes. The  $R_1$  and the corresponding  $q$  values at a designated pH were obtained from data presented in Figures 3 and 4. Low pH data and data from polymeric species were neglected.

oligomers with anhydrous inner-sphere coordination. This is consistent with the notion that higher molecular weight would result in higher outer-sphere relaxivity as was evident from studies of nitroxides and other relaxation agents.<sup>25–28</sup>

One reviewer of this paper suggested that the oligomerization could be a disproportionation of the following type:



The published structure of the dinuclear transition-metal complex  $[Cr_2(TTHA)(H_2O)_2]$  was cited to support the argument.<sup>29</sup> However, this is unlikely since the resulting dinuclear  $[LnLn'(TTHA)(H_2O)_q]$  species would be required to exhibit  $q > 2$ , in contradiction with the experimental data. The prediction of  $q > 2$  arises due to the fact that aqueous solutions of lanthanide amino carboxylate complexes are normally 8- or 9-coordinated, and one TTHA ligand with only 10 donor atoms could not satisfy the complete coordination requirement of two Gd(III) ions. In addition, the  $\log K_{ML}$  value<sup>23</sup> for Gd(TTHA) is 23 and the  $\log K_{M_2L}$  value for Gd<sub>2</sub>(TTHA) is  $\sim 28$  (using the Sm(TTHA) datum).<sup>30</sup> A speciation calculation using these data and  $pK_a$  values of TTHA shows that the concentration of  $[LnLn'(TTHA)(H_2O)_q]$  is  $< 0.1\%$  when  $[Gd^{3+}] = [TTHA] = 10$  mM. This concentration is too low to have any significant effect.

**C. Coordination Number Effects on Relaxivity.** The number of coordinated water molecules bound to the Gd<sup>3+</sup>(aq) ion appears to be between 8 and 9 in aqueous solution, and yields a relaxivity value of  $11.3 \pm 0.1 (mM s)^{-1}$  at pH 5.3 (without ionic strength and pH adjustment). A value of  $9.1 (mM s)^{-1}$  has been reported,<sup>6</sup> and the reason for the discrepancy is not clear.

Examination of the data reveals that EDTA and HEDTA complexes yield relatively high relaxivities within the pH range 4–10, i.e. 6.3 and  $7.9 (mM s)^{-1}$ , respectively. This appears to be due to the large number of coordinated water molecules:  $q = 3$  for Gd(EDTA)<sup>-</sup>, and  $q = 3–4$  for Gd(HEDTA). Gd(DTPA)<sup>2-</sup> and Gd(EGTA)<sup>-</sup> each exhibit  $q = 1$  and have similar relaxivity values, ranging from  $3.6$  to  $4.1 (mM s)^{-1}$  in the pH region 4–10.

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The small variations observed between the two complexes are probably due to experimental uncertainties and variations in  $\tau_r$  and outer-sphere contributions.

For Gd(HEDTA),  $R_1$  at pH 10 is unchanged from those of pH 8 and 9, while the  $q$  value has decreased to 1. The possibilities are as follows: (1) the concentration difference between Tb (10 mM) and Gd (0.2–5 mM) studies favors oligomerization in the Tb case; (2)  $\tau_r$  increased on oligomerization, raising  $R_1$  as  $q$  decreased; (3) an oligomer formed that allowed several Gd(III) ions to relax some or all of the protons simultaneously, resulting in an effective increase in the magnetic moment experienced by the protons. A separate study concluded that points 2 and 3 were the most likely possibilities.<sup>22</sup>

The relaxivity of Gd(TTHA) decreases with increasing pH and reaches a minimum value of  $2.1 \text{ (mM s)}^{-1}$  at pH 8.0. This evidence and the results from fluorescence water counting and energy

transfer indicate that Gd(III) is fully coordinated by the TTHA ligand after pH 8.0 to form monomeric species. A plot of  $R_1$  vs  $q$  values for all complexes in monomeric forms gives a straight line with an intercept of  $2.2 \pm 0.1 \text{ (mM s)}^{-1}$ , a slope of  $1.6 \pm 0.1 \text{ (mM s)}^{-1}$  per water, and a correlation coefficient of 0.97 (Figure 5). The intercept value is very similar to the limiting relaxivity value of  $\text{Gd(TTHA)}^{3+}$ , which represents the outer-sphere relaxivity for Gd(III) complexes of amino carboxylate ligands (without the TTHA data, the intercept of the linear regression analysis was  $2.2 \pm 0.2$ ). The value of the slope is the estimated contribution of each inner-sphere water to  $R_1$  for this series of simple mononuclear Gd(III) amino carboxylate complexes.

It is noted that the luminescence temperature (27 °C) and relaxivity temperature (40 °C) were different. However, variation of temperature only changes the  $q$  number and relaxivity to a small extent. The overall linear relationship between  $q$  and  $R_1$  still exists.

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## Equilibrium Studies of Lanthanide Nitrate Complexation in Aqueous Methanol

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The complexation between Er(III) and Nd(III) with nitrate and perchlorate was studied by UV-vis spectroscopy. In water, no complexes are detected between the lanthanide cations and perchlorate. The addition of methanol causes complexation only between Er(III) and perchlorate. Under the same conditions, the stoichiometries of the nitrate complexes in water are different for Nd(III) and Er(III) compared to Eu(III). These differences continue as a function of solvent composition even at low water mole fractions where Eu(III) and Er(III) form complexes up to the tris complex, whereas Nd(III) only forms complexes up to the bis complex. Equilibrium constants and complexation thermodynamics are presented and used in discussing differences within the lanthanide series.

### Introduction

Because of the increased utility of lanthanide ions as spectroscopic probes in biological systems, more detailed knowledge of the coordination behavior of these ions with simple counterions is needed. It is commonly believed that the chemistry of the lanthanide ions in solution is predominantly electrostatic in nature, with the chemical and physical properties determined by size differences within the series. In addition, there has been a long-standing debate about whether or not a coordination number change occurs within the lanthanide series.<sup>1</sup> Recent probes of the structures and reactivities of the inner solvation shells of the lanthanide cations have involved techniques such as FT-IR and FT-NMR spectroscopy.<sup>2–4</sup>

Ultrasonic relaxation investigations of the lanthanide nitrates in water not only can measure the extent of the interaction within the lanthanide series but also can separate the absorption into contributions from both inner- and outer-sphere complexes.<sup>5</sup> Repeating these measurements in aqueous methanol solutions has provided even more insights into not only the interactions between the lanthanide ion and the ligand but also the effect of solvent upon the complexation process.<sup>6</sup> Evidence that the ultrasonic data can predict some of the chemistry of the lanthanides in aqueous methanol comes from an examination of the data for the complexation between Er(III) and  $\text{Cl}^-$ .<sup>7</sup> Using the variation of the relaxation frequency for inner-sphere complexation, we predicted that below a water mole fraction,  $X$ , of 0.07 the  $\text{ErCl}_2^+$  species is formed. Hamze et al. investigated the corresponding Nd(III) complex in 5% water by volume and found only the mono complex with  $\text{Cl}^-$ .<sup>8</sup> However, at 0% water, both  $\text{NdCl}_2^+$  and  $\text{NdCl}_2^+$  were found. Although differences in the ultrasonic data

were observed between Nd(III), Eu(III), and Er(III) with nitrate, in the absence of complete equilibrium studies it is impossible to give a detailed explanation for the ultrasonic differences. Hence, we initiated the equilibrium studies on lanthanide nitrate systems.

Complexation between lanthanide ions and nitrate in water has been detected by techniques such as difference spectroscopy,<sup>9,10</sup> UV-vis absorption spectroscopy,<sup>11,12</sup> solvent extraction,<sup>13–15</sup> lu-

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