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Molecular Mechanics Investigation of Gadolinium(III) Complexes

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Parameters for the commercially available modeling package SYBYL have been developed for Gd^{3+} complexes allowing these to be studied with molecular mechanics. With these parameters and a technique termed the "coordination scan", the coordination numbers of Gd(III) based complexes can be predicted, and thus the hydration number *q* determined. Knowledge of *q* has allowed the prediction of molar relaxivities based on correlations to literature values. In addition, the calculated value ΔE_{coord} was found to successfully predict the thermodynamic stability constants for polyamino carboxylate ligands with Gd^{3+}. Gadolinium complexes are commonly utilized as MRI contrast agents, and thus the techniques utilized in this work should aid in the development of new contrast agents.

Introduction

Magnetic resonance imaging (MRI) has become one of the primary imaging modalities in modern medicine. With the wide spread use of MRI has come a demand for efficient paramagnetic contrast agents, used to enhance the contrast between normal and diseased tissue, or to indicate specific organ functions.[1] Future developments in this field will require the development of agents targeted to specific organs or even specific disease states. Research has focused mostly on complexes of the paramagnetic ions gadolinium(III), iron(III), and manganese(II) due to their high magnetic moments and proton relaxivities. Current MRI contrast agents in clinical use are polyamino carboxylate complexes of gadolinium, i.e. MAGNEVIST (GdDTPA, Berlex Laboratories), OMNISCAN (GdDTPA-BMA, Nycomed), ProHance (GdHP-DO3A, Squibb), and DOTAREM (GdDOTA, Guerbet).

Since the number of suitable nuclei for use in MRI contrast agents is limited, new agents with improved properties will depend on the choice of the ligand used to complex the paramagnetic ion. The overall charge, thermodynamic and kinetic stability, lipophilicity, and even the maximization of inner shell solvation can all be affected by ligand design. In regards to developing new agents, it would be desirable to predict these properties for a given complex prior to a lengthy synthetic effort in order to bypass complexes with undesirable properties, such as low *in vivo* stability toward dissociation.[2,3] Computational methods provide a method for understanding structure and its relation to function; thus, the development of force fields and techniques for modeling Gd(III) complexes will provide tools for the design of new contrast agents with enhanced properties.

Paramagnetic metal ions function as contrast agents by increasing the relaxation rates of the observed water protons near the ion, through interactions between the electron spins of the paramagnetic center and the proton nuclei. The relaxivity, enhancement of proton relaxation rate, of a paramagnetic agent can be divided into two parts, the outer-sphere relaxivity (R_2) involving long range interactions with the bulk solvent, and inner-sphere relaxivity (R_1) governed primarily by the exchange of water molecules bound to the paramagnetic ion with the bulk environment. The observed relaxivity is the sum of the inner and outer sphere mechanisms.

$$R_{obs} = R_1 + R_2 \tag{1}$$

The inner-sphere interactions can be modeled using the Solomon−Bloembergen−Morgan (SBM) theory, a simplified version is shown in eqs 2−4.[1,44]

$$R_1 = \left(\frac{M_q}{55.6}\right)\left(\frac{1}{T_{1M} + \tau_M}\right) \tag{2}$$

$$\frac{1}{T_{1M}} = {}^{2}/_{15}\gamma_H{}^2 g^2 \mu_B{}^2 S(S+1) r^{-6}\left(\frac{7\tau_c}{1 + \omega_S{}^2\tau_c{}^2} + \frac{3\tau_c}{1 + \omega_I{}^2\tau_c{}^2}\right) \tag{3}$$

$$\tau_c{}^{-1} = \tau_s{}^{-1} + \tau_M{}^{-1} + \tau_R{}^{-1} \tag{4}$$

The *M* is the concentration of the metal complex, *q* is the hydration number, T_{1M} is the longitudinal relaxation time, and τ_M the mean residence time of the waters on the metal center. The correlation time τ_c depends on the residence time τ_M, the electronic relaxation time τ_s, and the rotational tumbling time of the entire complex, τ_R. The remaining variables in eq 3 are as follows: γ_H, proton magnetogyric ratio; *g*, Landè factor; μ_B, Bohr magneton; *S*, spin quantum number; ω_S, electronic Larmor frequency; ω_I, proton Larmor frequency.

For complexes of similar size and composition the outer sphere relaxivity R_2 values are approximately the same. Thus the observed differences in relaxivities are due primarily to the inner-sphere contribution R_1. Improvements in the relaxivity of MRI contrast agents will therefore depend largely on improvements in the inner-sphere relaxivity.

There are three main approaches to modeling the geometry about a metal ion; the first and most common is the valence

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force field (VFF) method. In the VFF method all L−M−L bond angles are defined by ideal bond angles and force constants. The second approach is the points on a sphere (POS) method. In the POS method the metal−ligand interaction is modeled similar to the the VFF approach (ideal bond angles and force constants); however no force constants are applied to the L−M−L angles, and the geometry about the metal center is thus defined solely by steric repulsions between the donor atoms. The third method is the ionic approach; this method models the metal−ligand interaction entirely with nonbonded van der Waals and electrostatic forces.[9]

In both the VFF and POS approaches, one of the most important parameters required for reproducing experimental structures is the ideal M−L bond lengths; unlike organic molecules the M−L bond stretching force constants are not critical, and often an average value suffices.[10] *Ab initio* calculations as well as spectroscopy can also be utilized in the development of new parameters, particularly in evaluation of M−L bond stretching force constants. With the VFF approach, parameters for all possible angles and torsions have to developed, in addition to new atom type designations which allow for the description of these angles.

Fossheim and Dahl reported a method for correlating log *K* values to molecular energies.[11,12] They utilized an ionic approach with all Gd−L bonds treated as purely electrostatic interactions. Their work was computationally intensive with all atomic charges calculated though *ab initio* methods. In this work, they were able to correlate calculated energies with the log *K* values for GdDOTA, GdDTPA, GdDO3A, GdDTPA-BMA, GdNOTA, and several other complexes. This method required the calculation of the aqueous reaction energy $E_{r,aq}$ which was defined as follows:

$$E_{r,aq} = E_{ML} - E_{L} + E_{h1} + E_{h2} \tag{5}$$

Here E_{ML} is the energy of the complex in the gas phase, E_L is the energy of the free ligand in the gas phase, E_{h1} is the hydration energy of the free ligand, and E_{h2} is the hydration energy of the complex. As expected the primary contribution to $E_{r,aq}$ was the electrostatic interactions between the cation and ligand.

Kumar and Tweedle, investigating the effect of ligand basicity and rigidity on the rates of formation of the Gd complexes of polyaminocarboxylate macrocycles, latter suggested that the ligand strain energy, $E_{d,l}$, defined as $E_{l,c} - E_{l}$, where $E_{l,c}$ is the energy of the ligand in the complex and E_l is the energy of the free ligand, was a determining factor in complex formation.[13] Their postulated mechanism for complex formation involves a protonated intermediate Gd(*HL), which is then deprotonated and reorganizes to give the final complex in the rate-determining step. The calculated strain energies, acting as a measure of ligand rigidity, corresponded to the measured $\Delta G^{\ddagger}$ values of this process. The $\Delta G^{\ddagger}$ values for GdNOTA, GdDO3A, and GdDOTA were determined and compared to the calculated ligand strain energies. An excellent linear correlation ($r^2 = 0.999$) was found suggesting that the reorganization of the intermediate is controlled by the rigidity of the ligand.

In 1991, Hay published a POS approach toward the MM modeling of lanthanide(III) aqua and nitrato complexes.[14] Hay assigned the Gd(III)−oxygen equilibrium bond lengths as 2.25 Å for water and 2.310 Å for nitrato groups. In addition to bond lengths, several angles, including H−O−M and N−O−M, were assigned equilibrium values as were the O−N−O−M and O═N−O−M torsions. Sommerer and co-workers have utilized a similar approach, although they treated the Gd(III)−L bonds as purely electrostatic, to examine the structure and bonding of a Gd(III) Schiff base complex.[15]

Recently, Cundari and co-workers have reported the development of a force field utilizing Hay's approach for Gd(III) complexes.[16] This involved the development of numerous Gd−L equilibrium bond lengths, X−L−Gd angles, and numerous torsion angles. Their force field was then used to model several Gd(III) complexes ranging from GdEDTA to Gd-(Texaphyrin), with excellent agreement (within 3% of bond lengths and angles and within 5% for torsions) to experimental structural data.

In an attempt to develop tools useful in designing new MRI contrast agents, we have undertaken the development of MM force field parameters and techniques useful for the design and evaluation of Gd complexes. Ideally these techniques would allow for the prediction of the number of waters bound to the Gd, which relates to the overall relaxivity, as well as an estimation of the complex's thermodynamic stability. The development of such tools should lead to the rational design of improved MRI contrast agents.

Computational Methods

Force Field Development. All computations were performed with the commercially available modeling package SYBYL,[17] running on a Silicon Graphics Indigo^2. The force field (TAFF) used in this package models molecules by minimizing the total energy *E* with respect to the following equation:[18]

$$E = \sum E_{str} + \sum E_{bend} + \sum E_{oop} + \sum E_{tors} + \sum E_{vdw} \tag{6}$$

Here E_{str} is the energy of a bond stretched from its natural bond length, E_{bend} is the energy of bending bond angles from their natural value, E_{oop} is the energy of bending atoms out of plane, E_{tors} is the torsional energy, and E_{vdw} is the energy due to van der Waals interactions. The overall energy *E* consists of these sums extended over all the bonds, bond angles, torsions, and nonbonded interactions for all atoms not bound to each other or to a common atom.

A POS method was utilized in the modeling of the Gd(III) complexes, the parameters developed for the TAFF force field are found in Table 1. These parameters are the minimal number required for modeling the Gd complexes reported in this work. Parameters not explicitly shown in Table 1 utilize the default parameters of the TAFF force field.[19] These parameters were derived from a total of 12 gadolinium complexes, Gd(EDTA),[20] Gd(DTPA-BEA),[21] GdDOTA,[22] GdDOTA-OH,[23] Gd(DO3MA),[24] GdHP-DO3A,[25] Gd(HAM),[26] Gd(18-

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Table 1. Gd(III) Parameters for SYBYL

Gd Atom Definition

valence	electroneg	atomic weight	temp factor	VDW radius	ϵ
9	2.5	157.25	17.73	3.208	0.1

Bond Length Parameters

L for Gd−L	bond type	equil length (Å)	force const (kcal mol^{-1} Å^{-1})
N sp^2	1	2.616	100
N secondary	1	2.68	100
N tertiary	1	2.695	100
N sp^2 arom	1	2.630	100
O sp^2	1	2.420	100
O sp^3	1	2.397	100

Angle Parameters

angle definition	equil angle (deg)	force const (kcal mol^{-1} deg^{-2})
−Gd−	90	0

Torsion Parameters

atom 1	atom 2	atom 3	atom 4	type	force constant (kcal mol^{-1})	periodicity
O sp^2	C sp^2	O sp^3	Gd	1	1	−2
C sp^3	C sp^2	O sp^3	Gd	1	1	−2

crown-6),[27] Gd(DO3A),[22] GdBOPTA,[28] Gd(DTPA-pn), and Gd(DTPA-en).[29] The most critical parameter found to affect the metal complex structures was the TAFF bond stretch. This parameter determines the equilibrium bond length between the metal and donor atoms, as well as the ease with which this bond can be stretched. The parameters in Table 1 were found to reproduce the crystal structures reasonably well (average positional rms = 0.3624 Å). In all cases, the effects of electrostatics were ignored so that the metal complex structure is determined solely by steric effects.

Coordination Scans. Hancock and co-workers have successfully utilized molecular mechanics to determine the relationship between ligand selectivity and metal ion size.[10,30−32] The technique utilized in these studies is the calculation of the complex strain energy as a function of the M−L bond length. This is accomplished by modeling the complex with a generic metal while varying its ionic radius. The resultant curves give a minimum energy which corresponds to the best-fitting metal ion radius. A highly selective ligand for a particular metal would possess a steep curve with a minima close to the ionic radius, conversely a shallow curve would suggest that the ligand is non-selective in its metal binding.

A related technique is the "coordination scan", wherein similar curves are generated by minimizing complexes with various numbers of water molecules coordinated to the metal ion while changing the M−L bond lengths.[33] The preferred coordination number of the metal is determined by the position of the ionic radius[34] in relation to the location of the intersection points.

The coordination scan technique was used to determine the coordination number of Gd(III) in the various complexes studied. A starting structure was generated from X-ray coordinates whenever possible. The Gd in each complex was then adjusted to the different coordination numbers by covalently binding the appropriate number of waters to the metal. An important point to note is that SYBYL calculates water as having a strain energy of 0.00 kcal/mol; thus the waters added to the complex add no energy other than steric interactions with the ligand.

The Gd(III) ionic radius was effectively varied by systematically altering the Gd−N and Gd−O equilibrium bond lengths in the following manner. The Gd−N bond length was assigned through the following relationship: equil bond length = (Gd ionic radius) + 1.7 Å. Similarly the Gd−O equilibrium bond lengths were assigned using: equil bond length = (Gd ionic radius) + 1.4 Å. The initial Gd ionic radius was set to 0.5 Å; the scaling factors of 1.7 and 1.4 result from the average equilibrium bond length for that Gd−L bond minus the average Gd(III) ionic radius of 1.0 Å. The force constant for the bond stretching was kept at a constant value of 100 kcal mol^{-1} Å^{-1}. The complex was then minimized and the energy of the complex found. The ionic radius was then increased by 0.1 Å, the equilibrium bond length modified to the new value and the complex again minimized. This process is continued until the Gd ionic radius has reached 1.5 Å; this range of 0.5−1.5 Å is sufficiently large that it covers the radii of all the possible coordination states.[34] This procedure is then repeated for the complex with one water, two waters, and so on until all the possible coordination states have been examined.

Plots of the complex energy versus metal ionic radius were then generated for each coordination number. These curves were fit to third order polynomial of the form $y = ax^3 + bx^2 + cx + d$, and the resultant curves were plotted together. The curve equations can then be solved simultaneously in order to determine the intersection points or "crossover points". Examination of the position of these crossover points in relation to the preferred ionic radius for the metal ion in a given coordination state indicates the preferred coordination number. For Gd^{+3} the radius for a six coordinate environment is 0.938 Å, for seven coordinate it is 1.00 Å, for eight-coordinate 1.053 Å, and for nine-coordinate 1.107 Å.[34]

In order for a given coordination state to be favorable, the preferred ionic radius must be on the correct side of the crossover point; the closer an ionic radius is to a crossover point, the more the other coordination state contributes to the equilibrating system. In addition the energy difference between the "ideal radii" of a particular coordination number and the crossover point indicates how readily the coordination of a particular complex will change; a small difference in energies is favorable, while a large difference would disfavor a change in coordination.

Results and Discussion

With the development of suitable Gd(III) parameters for the SYBYL modeling package a MM investigation of Gd(III) complexes was undertaken. Our research has focused on two main areas, the ability to predict the stability of Gd(III) complexes and, second, the ability to predict the effectiveness of a particular compound as a contrast agent. In order to calibrate the results arising from our computational studies, the literature was searched for gadolinium complexes whose thermodynamic stability constants had been determined, as well as having had relaxivity measurements determined under as similar conditions as possible.

In order to minimize the differences between ligand types, classes of ligands were studied separately. The three classes commonly utilized for the coordination of Gd(III) are EDTA type ligands, DTPA type ligands and DOTA type ligands. The latter two classes are the most commonly utilized in the design of MRI agents. Other factors that need to be considered are the number and types of donor groups involved with binding to the metal.

The parameters for the modeling of Gd(III) complexes with the TAFF force field as implemented in SYBYL may be found in Table 1; other necessary parameters come from the default values of the TAFF force field.[19] A minimalist approach was utilized in this study with a surprisingly small number of parameters required for reasonable agreement to experimentally

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Table 2. Coordination Scan Compared to Experimental Determination of q^a

complex	predicted q	exptl q	ref
GdEDTA	3	3	20
GdDTPA	1	1	46
GdDTPA-BMA	1	1	44
GdDTPA-BEA	1	1	21
GdDTPA-BPA	1	1 (NMR)	47
GdBOPTA	1	1	28
GdDOTA	1	1	22
GdDO3A	2	1.8 (lum)	22
GdDO3MA	2	2	24
GdDOTA-OH	1	1	23
GdHP-DO3A	1	1	25
GdHAM2	3	3	57

[a] All values of q are from the solid state unless otherwise noted.

determined structures. Two important parameters found in this work are the torsions involving carboxylates bound to Gd and the equilibrium bond lengths. Without the inclusion of these torsional parameters the carboxylates have a tendency to bind the metal in a bidentate manner. The equilibrium bond lengths used in this work are in general significantly longer than those reported by Hay[14]and Cundari,[16] which is most likely due to the differences between the TAFF and MM2 force fields.

One of the goals of this study was the development of modeling techniques which would allow for the prediction of the hydration number q. The more waters that can be directly bound to the paramagnetic ion, the greater the overall relaxivity and the more efficient the contrast agent. The most obvious way to increase q is to remove ligating groups from the ligand; however, by lowering the denticity of the ligand, complex stability is negatively affected.

The "coordination scan" allows the determination of the coordination number and thus q; it also helps to determine the molecular weight of the solvated complex which is important for the rotational motion. This technique appears to be quite successful in predicting the number of waters bound to the Gd, as seen in Table 2. The results for GdEDTA, GdDTPA, GdDTPA-BMA, GdDTPA-BEA, GdDTPA-BPA, GdBOPTA, GdDOTA, GdDO3A, GdDO3MA, and GdHP-DO3A all match the experimental q values found in the literature.

In the "coordination scan", curves of complex strain energy as a function of ionic radii are generated by minimizing complexes with various numbers of water molecules coordinated to the metal ion.[33] The preferred coordination number of the metal is determined by the position of the ionic radius in relation to the location of the intersection points. If a given coordination has a radius to the right of the intersection point, than that coordination number is favored. If the radius is to the left of the intersection, than that coordination number is disfavored and a smaller coordination number is favored. A representative example, the coordination scan of GdDTPA is found in Figure 1. The ionic radius for nine coordinate Gd(III) is 1.107 Å, which lies to the right of the 8/9 coordinate intersection; thus a nine-coordinate Gd(III) complex is favored over an eight-coordinate species which means the complex will bind one water molecule to give a hydration number, q, of one.

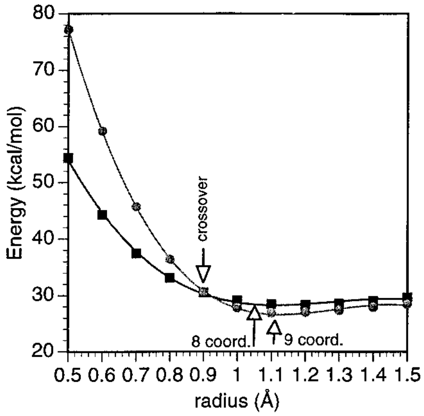

Figure 1. Coordination scan of GdDTPA: Eight-coordinate $q = 0$ scan. ■, preferred nine-coordinate $q = 1$ scan, ●.

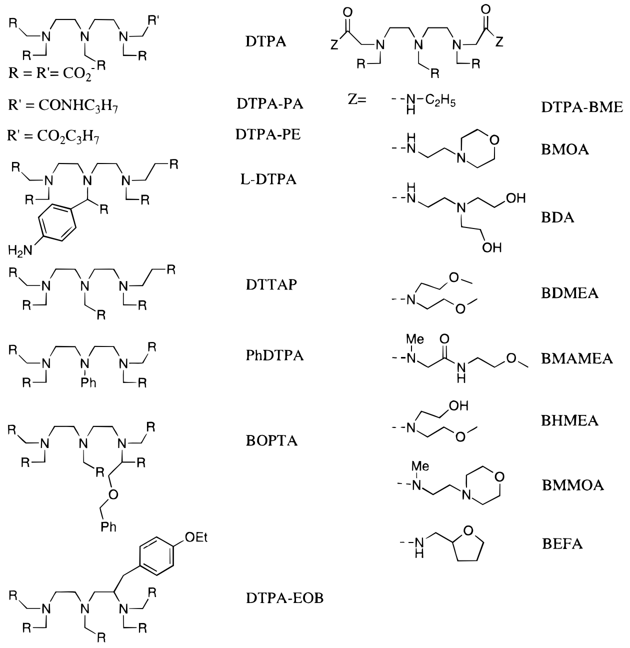

Figure 2. Structure of ligands found to give $q = 1$ Gd(III) complexes.

An intriguing observation has been made through the use of the "coordination scan". The energy difference $\Delta E_{\mathrm{coord}}$, between the complex with the appropriate inner-sphere solvation and the desolvated complex, appears to correlate with the thermodynamic stability constant log K. This energy difference represents the energetic cost in changing the coordination number of Gd in a given complex from the preferred state (appropriate inner-sphere solvation) to that due entirely to the denticity of the ligand alone. A remarkable feature of this correlation is that it arises solely from steric interactions, electronic and electrostatic effects are not considered in this MM treatment.

Instead of dividing the Gd(III) complexes by type of ligand, such as EDTA or DTPA, it is more informative to classify them by the number of waters bound to the metal. Three main categories arise from this scheme, those with a hydration number of 1, 2, and 3. The following section will discuss these categories in terms of stability and, in the case of $q = 1$, the relaxivities. Unfortunately, no relaxivity comparisons can be made for $q = 2$ and 3 as too few complexes have had their relaxivities measured. For all the complexes discussed, the structures were first built and minimized, starting from X-ray coordinates whenever possible. These were then adjusted to various coordination states and subjected to coordination scans in order to determine q and $\Delta E_{\mathrm{coord}}$.

Gd(III) Complexes with $q = 1$. The majority of these complexes are derived from DTPA and DOTA type parent ligands; structures of these ligands are found in Figures 2 and 3. A total of 23 Gd(III) complexes examined with the coordination scan were found to bind one water molecule, the results of these studies are found in Table 3. The majority of these complexes are eight coordinate in terms of the ligand denticity; the binding of one water then brings the Gd(III) to a coordination number of nine.

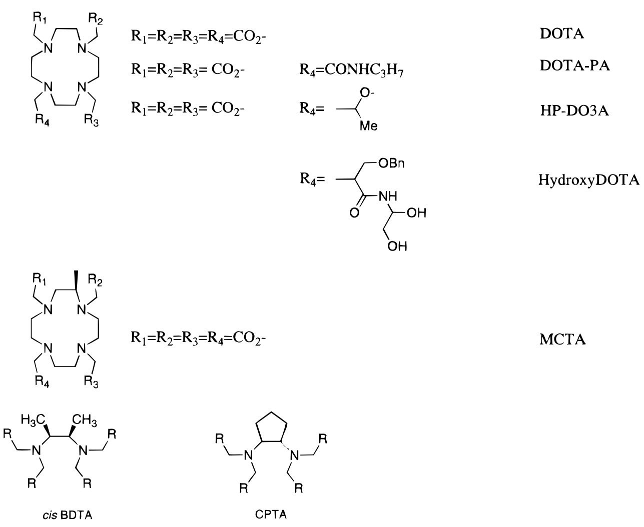

Figure 3. Structure of additional ligands found to give $q = 1$ Gd(III) complexes.

Table 3. Gd(III) Complexes with $q = 1$

ligand	exptl R_1 ($mM^{-1}\ s^{-1}$)	log K	MW ($g\ mol^{-1}$)	ΔE_{coor} ($kcal\ mol^{-1}$)	refs
DOTA	3.4	24	575.653	2.4510	48, 49
MCTA	3.5	27	589.68	1.6155	49
HP-DO3A	3.65	23.8	575.697	3.8023	25, 43
DOTA-OH	4.49	25.9	769.907	1.3333	23
DTPA	3.7	22.39	563.574	3.1546	48, 1
L-DTPA		21.99	668.714	5.4967	37
BOPTA	4.39		682.717	0.3185	41
DTPA-EOB	5.3		697.752	5.3284	50
DTTAP		19.74	577.601	5.7760	48
CPDTA		18.22	503.544	8.9999	48
BDTA cis		17.03	491.533	8.9004	48
−1 CO_2H					
PhDTPA		15.42	582.644	8.1120	48
DOTA-PA		20.1	617.757	2.8602	51
DTPA-PA		19.68	605.680	4.1654	52
DTPA-PE		18.91	606.665	1.1070	52
−2 CO_2H					
DTPA-BEFA	4.4	16.3	731.858	0.5821	53
DTPA-BDA	4.7	16.7	825.972	2.1053	53
DTPA-BMAMEA	4.3	17.1	821.94	2.7100	53
DTPA-BMMOA	4.1	20.3	817.996	5.2632	53
DTPA-BME	4.7	16.8	679.782	4.0805	53
DTPA-BMOA	4.7	16.1	789.942	2.1447	53
DTPA-BHMEA	4.2	17.5	767.888	17.3109	53
DTPA-BDMEA	4.4	19.2	795.942	4.8598	53

As has been previously noted, Kumar and Tweedle found an excellent correlation between the ligand strain energy, $E_{d,l}$, and $\Delta G^{\ddagger}$ for the reorganization of the intermediate Gd(*HL) in the case of polyaminomacrocycles.[13] If we consider the energetic cost of reorganizing the complex from the inner-sphere solvated, maximum coordination, to the inner-sphere desolvated complex, minimum coordination, as a measure of ligand rigidity, one would expect to find a correlation between ΔE_{coord} and the thermodynamic stability constant.

When the thermodynamic stability constant log K is plotted against ΔE_{coord}, a linear correlation was discovered ($r^2 = 0.91$). This plot (Figure 4) clearly shows that the relationship between the stability and ΔE_{coord} is unaffected by the type of ligand, linear or macrocyclic. As ΔE_{coord} increases, the thermodynamic stability decreases, suggesting that a key step of complex formation involves a reorganization of the ligand during a change in the coordination number for the Gd in an essentially complete complex. When there is an increase in the rigidity of a complex, thereby lowering ΔE_{coord}, the thermodynamic stability shows a concomitant increase.

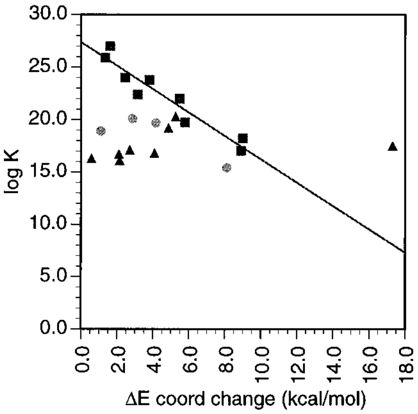

Figure 4. Plot of thermodynamic stability constants, log K, as a function of ΔE_{coord} for Gd(III) complexes binding one water molecule: ■, ligands with only carboxylate groups; ▲, ligands with one carboxylate replaced; ●, ligands with two carboxylates replaced.

A comparison of the macrocyclic ligands DOTA and MCTA clearly shows the relation between ΔE_{coord} and log K. The addition of a single methyl group on the backbone of MCTA increases the rigidity of the ligand, lowering ΔE_{coord} and resulting in increased stability. This effect can also be seen with two EDTA type ligands, which were found to bind only one water. The ligand CPTA is extremely rigid with a cyclopentyl ring incorporated within the ethylene bridge, while *cis* BDTA has two methyl groups on the backbone imparting rigidity.

A recent report suggested that an important factor affecting the proton relaxivity of lanthanide(III) complexes is the ability of the metal to pass through an intermediate with a coordination number of 8 during the process of water exchange.[35] If this were the case, then one would expect to see a correlation between ΔE_{coord} and the experimental relaxivities; no such correlation was found in this work. It would appear that any effect ΔE_{coord} has on the relaxivity is quite small and is easily overpowered by the rotational tumbling effects which are dependent on the molecular mass.

As can be seen in Table 3, modification or loss of a carboxylate group has a significant effect on the complex stability. Replacement of a carboxylate with an amide, DTPA-PA and DOTA-PE, lowers the stability constant by 10^2-10^3.[36] Similarly replacement of a carboxylate by an ester DTPA-PE lowers the stability constant by 10^3-10^4.[36] The replacement of a carboxylate by a nonligating group, such as phenyl in PhDTPA, lowers the stability by an even larger amount, 10^7. Replacement of two carboxylates by amides lowers the stability constants by 10^2-10^6.

Those ligands with amide oxygens coordinated to Gd(III) show a lower than expected stability. A reasonable explanation for this observation would be the difference in bond strengths between Gd(III) and an amide oxygen, compared to a carboxylate oxygen. In all of the bis(amide) complexes two strong carboxylate−Gd(III) interactions have been replaced by the weaker amide−Gd(III) interaction with a commensurate drop in stability of approximately 10^5. All of the bis(amides) examined have an unsubstituted DTPA backbone, the changes

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are all in the amide groups which are removed from the metal center, and thus one would expect these substitutions to play little role in changing the steric environment about the metal.

Relaxivity. As can be seen from eqs 2 and 3, several possibilities exist for improving the relaxivity. One method is to increase the correlation time, τ_c. From eq 4, τ_c depends on the residence time, the electronic relaxation rate, and the rotational motion of the complex. Of these, the two factors most easily modified are the residence time and the rotational motion. The rotational motion is easily changed by modifying the molecular weight of the complex, most commonly by designing the compound to be conjugated to macromolecules.

The residence time τ_m, is equivalent to $1/k_{ex}$ (k_{ex} is the exchange rate constant) and is on the order of 10^{-6}–10^{-9} s.[39] Until recently, the rate of water exchange of Gd(III) based contrast agents was assumed to be approximately the same as that found for the Gd^{3+} aqua ion $(8.3 \pm 1.0) \times 10^8$ s^{-1}.[40] In a series of variable temperature and pressure NMR studies, Merbach and co-workers found that the water exchange rates, k_{ex}, for Gd complexes of DTPA and DOTA were actually 2 orders of magnitude lower (GdDTPA k_{ex} $(4.1 \pm 0.3) \times 10^6$ s^{-1}; GdDOTA k_{ex} $(4.8 \pm 0.4) \times 10^6$ s^{-1}).[38] Obviously, the presence of the aminocarboxylate groups affect the rate of exchange compared to that of the aqua complex. In a more recent study Merbach found that waters exchange via a dissociative mechanism with GdDTPA-BMA and speculates that the exchange rate could be controlled by the ligand steric requirements at the water binding site.[38]

Aime and co-workers have found a correlation between the molecular weight and the inner sphere relaxivity R_1.[23,41] For compounds of similar size and mass, and therefore diffusion rate, at relatively high magnetic field strengths the outer sphere R_2 contributions will be approximately the same. Tweedle and co-workers have shown this experimentally for a series of linear and macrocyclic amino carboxylate complexes; at 0.47 T and 40 °C, they found an average R_2 value of 2.0 ± 0.3 $(\mathrm{mM{\cdot}s})^{-1}$.[42,43] For Gd(III) complexes with identical values of q, any differences in relaxivities will be due to differences in the inner sphere contribution R_1. The primary factor affecting R_1 in most cases is the value of τ_R. One exception is observed with the bis(amide) complexes; in these cases τ_M is seen to effect the relaxivity. As can be seen in Figure 5, a good correlation between the experimental relaxivity R_1 and the molecular weight of the solvated complexes exists.

In most poly(amino) carboxylates the major factor determining τ_c is the fastest of τ_s, τ_M, and τ_R, with τ_R usually being the fastest. Aime et al. investigated the magnetic field dependence of the water relaxation rate of GdDTPA-BMA and found that τ_M was approximately 4-fold longer than τ_M of GdDTPA; this increase was enough to make the contribution of τ_M significant.[44] They then postulated two possible explanations for this lengthening of τ_M; one is the presence of an extended three-dimensional network of hydrogen-bonded waters between the amides and the carboxylate groups. Alternatively the presence of the amide groups effects the partial atomic charge on the Gd resulting in the increase of τ_M. This work is unable to determine if either of these hypotheses are correct, although both are amenable to future computational study.

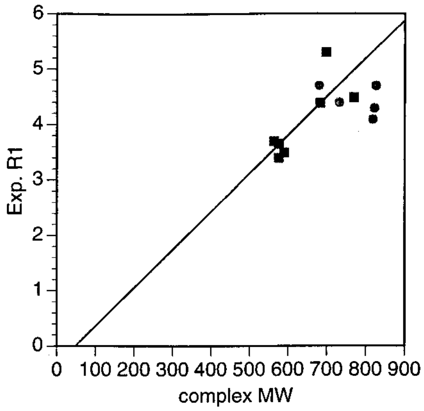

Figure 5. Plot of inner-sphere relaxivity as a function of solvated complex molecular weight: ■, ligands with only carboxylate groups; ●, ligands with two amide groups.

Table 4. Gd(III) Complexes with $q = 2$

ligand	log K	ΔE_{coord} (kcal mol^{-1})	refs
DO3A	21	4.8025	54, 43
MeDTPA	8.79	13.3350	48
MeDETA	14.7	6.4464	55
Me2DETA	10.4	4.1443	55
NOTMA	12.8	11.2574	56

Gd(III) Complexes with $q = 2$. A total of five Gd(III) complexes were found to have a hydration number of 2, as shown in Table 4. The structures of these ligands are found in Figure 6. Of these only MeDTPA is nonmacrocyclic; in this ligand an additional coordination site on the Gd is available due to the quaternization of the central amine group on the ligand. As was found for those Gd(III) complexes with $q = 1$, a linear correlation between log K and ΔE_{coord} exists ($r^2 = 0.85$); this relationship is shown in Figure 7. The one complex that has a lower than expected stability is Me2DETA, where the addition of two methyl groups to the triazacyclodecane ring somehow destabilizes the complex, although this appears to not be due to addition of steric strain to the complex. As seen in Table 4, ΔE_{coord} of Me2DETA is actually lower than for MeDETA, suggesting steric hindrance is not the reason for the lower stability; a likely explanation is a change in nitrogen basicity due to electronic effects of the alkyl substituents.

The slope of the correlation, as well as the x and y intercepts were very close to those found with the $q = 1$ complexes. This suggests a similar mechanism for complex formation is in effect for both classes.

Gd(III) Complexes with $q = 3$. A total of 13 Gd(III) complexes examined with the coordination scan were found to have a hydration number of 3. As can be seen in Figure 8, all of these complexes have a denticity of six, leaving three coordination sites open for binding waters to give the Gd(III) a coordination number of 9. The results of these studies are found in Table 5. Unfortunately, only the relationship between ΔE_{coord} and log K could be examined, as the only complexes whose relaxivities have been measured are GdEDTA, GdHAM, and GdHAM2. These three measurements are insufficient for forming a correlation. As was shown by the DTPA bis(amides), relaxivities are quite sensitive to changes in ligating atoms;the expected difference between an amino carboxylate and hexaza macrocycles, such as HAM and HAM2, would surely be larger than that of an amino amide to an amino carboxylate.

As in the complexes with q values of 1 and 2, a linear correlation between ΔE_{coord} and log K was found as shown in

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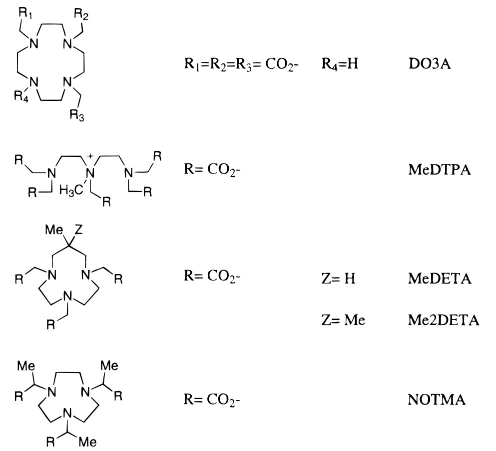

Figure 6. Structure of ligands found to give $q = 2$ Gd(III) complexes.

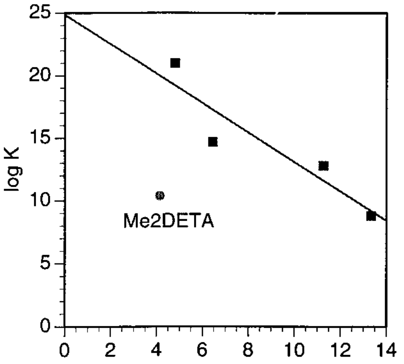

Figure 7. Plot of thermodynamic stability constants, log *K*, as a function of $\Delta E_{\mathrm{coord}}$ for Gd(III) complexes binding two water molecule. The ligand Me2DETA was found to not correlate with the other ligands in this class.

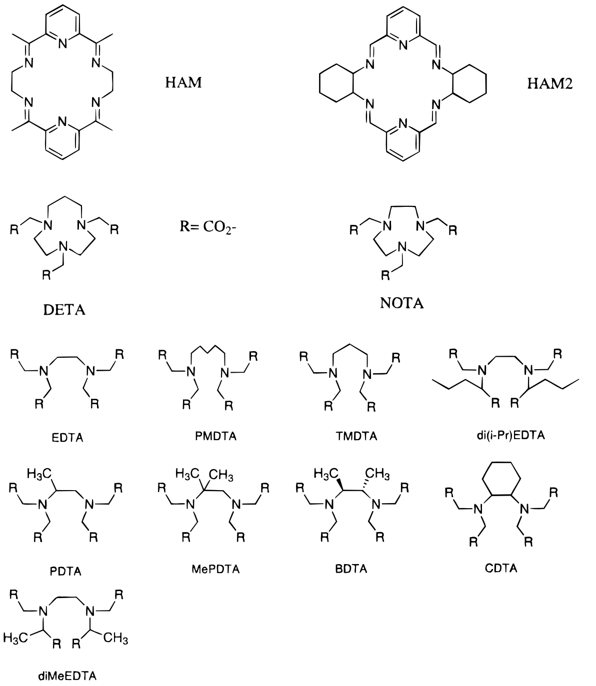

Figure 8. Structure of ligands found to give $q = 3$ Gd(III) complexes.

Table 5. Gd(III) Complexes with $q = 3$

ligand	log *K*	$\Delta E_{\mathrm{coord}}$ (kcal mol^{-1})	refs
HAM		7.7825	26
HAM2		8.3767	57
GdNOTA	13.70	7.0607	55
GdDETA	15.10	3.1648	55
GdEDTA	17.35	4.5686	48
GdCDTA	19.47	6.0272	48
Gd(diiPrEDTA)	16.60	5.7039	48
GddiMeEDTA	17.00	4.7931	48
GdBDTA trans	18.64	4.6447	48
GdTMDTA	13.83	−0.0984	48
GdPMDTA	10.37	7.2269	48
GdMePDTA	17.09	2.7604	48
GdPDTA	18.20	3.2227	48

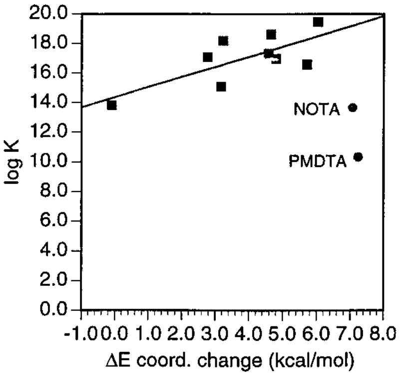

Figure 9. Plot of thermodynamic stability constants, log *K*, as a function of $\Delta E_{\mathrm{coord}}$ for Gd(III) complexes binding three water molecule. The ligands NOTA and PMDTA were found to not correlate with the other ligands in this class.

Figure 9. This correlation is much lower than that found for the other two classes of complexes, $r^2 = 0.54$, in addition the slope of the correlation line is opposite that found for $q = 1$ and 2 compounds. This would suggest a change in mechanism from that of the DOTA and DTPA type ligands . The low correlation found for this class is not surprising due to the large structural variety of the ligands comprising the class.

Examination of the structures of these ligands leads to some insight into the effect of substitution upon the thermodynamic stability. Incorporation of alkyl groups on the carboxylic acid arms appears to disfavor a coordination number of 9 most likely due to steric hindrance. The ligand NOTA favors the binding of three waters, while the similar ligand NOTMA containing methyl groups on each carboxylate arm favors the binding of only two waters.

Another example, while less dramatic, may be found in the stability differences between EDTA and the ligand diMeEDTA with two methyl groups placed on two arms; this substitution lowers the stability by 0.35 log units. The stability difference between EDTA and di(i-Pr)EDTA, as expected by the incorporation of sterically larger isopropyl groups on the arms, is 0.75 log units. The differences in the steric requirements for NOTA and EDTA type ligands would appear to be significant. Alkyl substitution on NOTA causes a drop in coordination number, whereas substitution on the less sterically constrained EDTA results in a slight lowering of log *K* without affecting the coordination number.

Substitution on the ethylene backbone also affects the coordination number of the Gd(III) complexes as well as the stability. The complex GdCDTA has a cyclohexane ring incorporated in the ethylene bridge and prefers to be nine coordinate, while GdCPDTA with a cyclopentane ring prefers to be seven coordinate. Another striking difference can be seen in *cis*- and *trans*-GdBDTA; the *trans* ligand prefers to be nine coordinate while the *cis* prefers to be seven coordinate.

In terms of stabilities, alkyl substitution of the ethylene backbone tends to increase the log *K* values. When the log *K* of GdEDTA is compared to GdCDTA, *trans*-GdBDTA, and GdPDTA, increases in stability are observed. However alkyl substitution can also lower the log *K* value, a comparison of GdEDTA and GdMePDTA finds that the addition of two methyls on one of the backbone carbons lowers the stability rather than increasing it. Increasing the size of the backbone is also disfavored; the ligand TMDTA with a propyl backbone instead of an ethyl group as in EDTA has a much lower stability $\Delta \log K = 3.52$; this issue of chelate ring size has been extensively reviewed.[45] The ligand PMDTA with a five-membered backbone is extremely destabilized compared to EDTA, $\Delta \log K = 6.98$, as shown in Figure 9.

Summary and Conclusion

In an attempt to develop tools useful in designing new MRI contrast agents, we have successfully developed MM force field parameters for Gd(III) complexes. The use of these parameters and the coordination scan in the analysis of various Gd(III) complexes found in the literature has provided a great deal of insight into the factors affecting thermodynamic stability and relaxivity. The coordination scan allows for the prediction of the number of waters bound to the Gd, which relates to the overall relaxivity, as well as an estimation of the complex's thermodynamic stability. Through correlation to these experimental stability and relaxivity measurements, MM allows for the prediction of these properties for novel Gd(III) complexes. In addition, the correlation between $\Delta E_{\mathrm{coord}}$ and log *K* suggests a common mechanism of complex formation for both DTPA and DOTA type ligands involving a rearrangement of an intermediate structurally similar to the final complex. The development of these techniques and correlations should lead to the rational design of improved MRI contrast agents.

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Supporting Information Available: A table showing the rms fits of all non-hydrogen atoms to the published X-ray structures for each tested complex (1 page). Ordering information is given on any current masthead page.

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