Theor Chem Acc (2004) 111:204–209
DOI 10.1007/s00214-003-0525-4

Theoretical
Chemistry Accounts

Regular article

Theoretical investigation into the influence of conformational equilibria on the water-exchange process in magnetic resonance imaging contrast agents

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Received: 30 March 2003 / Accepted: 30 April 2003 / Published online: 5 December 2003

Abstract. The conformational behavior in aqueous solution of four complexes of the Eu(III) ion with bis (*R*–amide) derivatives (*R* = H, methyl, ethyl, butyl) of diethylentriamine pentacetate ligands has been characterized at the ab initio level to rationalize the experimentally observed influence of alkyl substituents on the rate of the exchange process of the water molecule coordinated to the ion with the bulk water. Calculations were performed in vacuo and for aqueous solution, the latter by using the polarizable continuum model. Geometry optimizations provide, for each system, four isomers as stable conformations, all presenting a distorted tricapped trigonal prism coordination geometry around the ion. No significant influence of the alkyl substitution on the coordination geometry, nor on the europium–water distance, was observed. Moreover, increasing the length of the alkyl chain had no significant effect on the relative isomer population in solution. Thus, these results lead us to suppose that other effects, like those deriving from lateral chain folding in solution, should be considered to explain the increased rate of the water-exchange process with alkyl chain lengthening.

Keywords: Magnetic resonance imaging contrast agents – Lanthanide complexes – Ab initio calculations – Polarizable continuum model – Conformational analysis

Contribution to the Jacopo Tomasi Honorary Issue

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Introduction

Owing to the electronic properties of the gadolinium ion, Gd(III) complexes are currently employed in clinical practice as contrast agents in magnetic resonance imaging [1]. Contrast agents improve the contrast in images by enhancing the nuclear magnetic relaxation rates of the water protons in the tissues where they are distributed. The mechanism of relaxation enhancement, i.e. the relaxivity, involves dipolar interactions between the magnetic moment of the metal ion and the nuclear spin of the water protons. Among other effects, the efficiency of the process depends on the exchange rate with the bulk water of the water molecules bound to the ion, and constant effort is being put into clarifying the structural parameters of the complexes that affect the rate of this process [1].

Recently [2], the water-exchange rates for a homologous series of Gd(III) complexes with different bis (*R*–amide) diethylentriamine pentacetate (DTPA) ligands were measured by variable-temperature ^{17}O NMR spectroscopy. The chemical structure of the bis (*R*–amide) DTPA ligand is shown in Fig. 1. Substituent size was found to affect the rate of the exchange process (the larger the substituent, the faster the water-exchange rate) until a plateau is reached for larger groups. Indeed, the effect is quite weak: the water-exchange rate constant measured at 310 K is only doubled, at the most, for the pentyl derivative ($k = 1.74 \times 10^{-6}$ s^{-1}) compared to

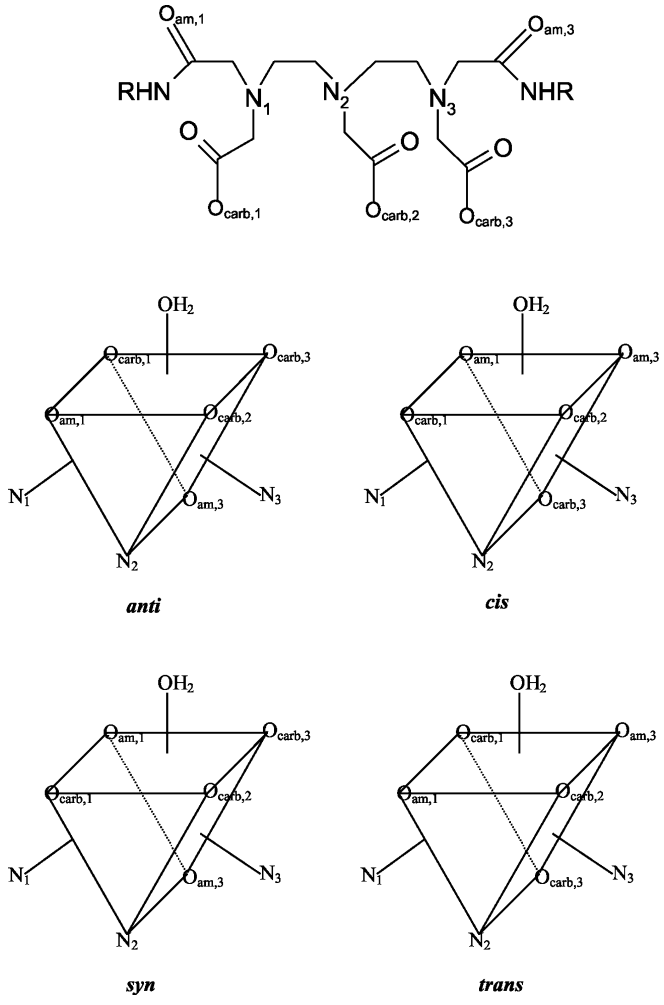

Fig. 1. Molecular structure of bis(*R*–amide) diethylentriamine pentacetate (*DTPA*) ligands and coordination geometry of the ligand around the lanthanide ion in the four isomers of [Eu(DTPA-bis(*R*–amide)(H_2O)] complexes

the unsubstituted [Gd(DTPA-BA)(H_2O)] system ($k = 0.85\times10^{-6}$ s^{-1}). On the other hand, the activation volume of the exchange process has been found to be independent of the nature of the alkyl substituent. This indicates that the different substituents do not modify the steric crowding in the first coordination sphere.

Two possible mechanisms [2] have been proposed for the observed behavior. One involves the folding of the lateral chains in solution, disrupting the hydration shell of the complexes and favoring water exchange by modifying the hydrogen-bond network between the exchanging water molecule and the hydration shell. In this hypothesis, only the first carbon atoms of the chains disturb the structure of the hydration shell that contributes directly to the exchange process. This would explain the plateau reached for the longest alkyl chains.

The alternative explanation of the experimental behavior is based on the influence that the alkyl chains could exert on the conformational equilibrium among the stereoisomers. In fact, it is known that the complexes of lanthanide ions with bis(amide) DTPA derivatives present four diastereoisomers, [3] deriving from the octadentate coordination of the ligand to the ion in a tricapped trigonal prism coordination geometry. The structures of these isomers, labeled anti, cis, syn, and trans, are sketched in Fig. 1. Moreover, it is known that different stereoisomers can present different exchange rates, like in the case of $[Eu(DOTAM)(H_2O)]^{3+}$ (where DOTAM is 1,4,7,10-tetrakis[carbamoyl methyl]-1,4,7,10-tetraaza cyclododecane). [4] These observations let one suppose that the lengthening of the alkyl chains influences the equilibrium between the stereoisomers favoring the stereoisomer with the highest water-exchange rate.

To test this latter hypothesis, we present the results of the theoretical investigation of the conformational behavior of four complexes of the Eu(III) ion with bis(*R*–amide) DTPA ligands (*R* = H, methyl, ethyl, and butyl in Fig. 1), namely the [Eu(DTPA-BA)(H_2O)], the [Eu(DTPA-BMA)(H_2O)], the [Eu(DTPA-BEA)(H_2O)], and the [Eu(DTPA-BBA)(H_2O)] systems. In order to investigate the influence of the electronic effects of the lateral chains on the coordination geometry and on the relative isomer population, the alkyl chains of the amidic substituents of the complexes were considered in the all-trans arrangement. Thus, steric effects arising from the conformational flexibility of the lateral chains are not considered in this study.

Although our interest lies in the behavior of gadolinium complexes, for which the experimental water-exchange rates have been determined, the theoretical study was performed on complexes with the europium ion. In fact, the long electronic relaxation time of the gadolinium ion prevents any observation of NMR spectra. Consequently, the solution structures and properties of gadolinium complexes are generally deduced from the NMR spectra of complexes with other lanthanides that form complexes isostructural with gadolinium. Thus, complexes with europium, which is the closest element to gadolinium in the lanthanide series, are generally investigated by NMR to obtain information on the conformational properties of gadolinium complexes. For this reason, the europium complexes investigated will allow the comparison of theoretical results and NMR data, once such data are available.

The present work adopted the computational approach previously developed for the study of lanthanide–1,4,7,10-tetraaza-1,4,7,10-tetrakis(carboxymethyl) cyclododecane (DOTA) complexes in aqueous solution. [5] This is based on a quantum mechanical treatment of the molecular system at the ab initio level, and on the inclusion of the solvent effect by means of a continuum approach, [6] the polarizable continuum model (PCM).[7] Indeed, previous studies on lanthanide complexes have shown [5] that in order to achieve a reliable description of the behavior of the water molecule coordinated to lanthanide ions it is necessary to include the solvent effects in the computational model. The PCM approach is particularly suited for this scope as it offers

a balanced and theoretically sound treatment of all solute–solvent interactions at very reasonable computational cost, and it has been shown to provide reliable results on lanthanide complexes and lanthanide aquo ions [5, 8].

Computational methods

All the calculations use the quasi-relativistic effective core potential (ECP) of Dolg et al. [9] and the related [5s4p3d] Gaussian-type orbital valence basis sets for the europium ion. This ECP includes $46 + 4f^n$ electrons in the core, leaving the outermost 11 electrons to be treated explicitly. For each compound, full geometry optimizations of the four isomers were performed in vacuo and for aqueous solution. In the starting geometries, the amidic groups were s-cis and the alkyl chains all-trans. Geometry optimizations were performed at the Hartree–Fock level using the 3-21G basis set for the ligand atoms. On the optimized structures, single-point energy calculations were performed at the density functional theory (B3LYP functional) level, using the 6-311G** basis sets for the ligand [10].

Solvent effects were evaluated by the Gaussian98 [11] implementation of the PCM. We selected the C-PCM variant [12] that, employing conductor rather than dielectric boundary conditions [13], allows more robust implementation. In line with the united atom topological model (UATM) [14], the solute cavity is built as an envelope of spheres centered on atoms or atomic groups with appropriate radii. For the Eu(III) ion, the previously parameterized radius [8] was used, neglecting the europium dispersion and repulsion parameters owing to their negligible influence in aqueous solution. All the UATM radii were scaled by a factor of 1.2 [14] in the calculation of electrostatic contributions, while unscaled values were used to calculate other contributions. To avoid convergence problems during geometry optimization, the linear search in the Berny algorithm was removed, and the nonelectrostatic contributions to the energy and energy gradient, viz., cavitation, dispersion, and repulsion contributions, were omitted. Owing to the slow convergence the optimization was, in some cases, stopped when the convergence parameters were less than twice the default values. For this reason frequency analysis was not performed to characterize the stationary points; thus, the final geometries correspond to stable conformations for the chosen minimization algorithm, rather than true minima.

Final free energies, obtained from single-point calculations at optimized geometries in solution, include both the electrostatic and nonelectrostatic contributions of all atoms, the exception being the dispersion and repulsion contributions of europium that are omitted. As the PCM results have free-energy status, [6] the total free energy in solution is labeled in the following as G^{sol}. All the calculations were done using the Gaussian 98 package.

Results and discussion

In the calculated geometries all the systems present a distorted tricapped trigonal prism coordination geometry around the europium ion, both in vacuo and in aqueous solution, in agreement with the available crystallographic structures of the [Gd(DTPA-BMA)(H_2O)] and the [Gd(DTPA-BEA)(H_2O)] complexes [15, 16]. In each system, the four possible isomers are found as stable conformations; the molecular geometries of the four isomers of the [Eu(DTPA-BMA)(H_2O)] complex calculated for aqueous solution are shown in Fig. 2. In all the structures, the amidic groups present the s-cis disposition and the alkyl chains are in the all-trans conformation.

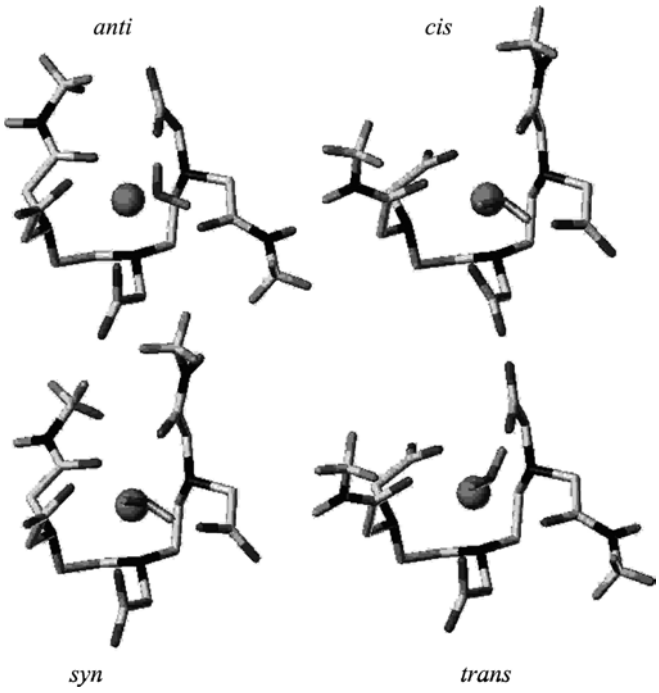

Fig. 2. Molecular geometries of the four isomers of the [Eu(DTPA-BMA)(H_2O)] complex calculated in aqueous solution

The calculated values of the coordination bond distances for the four isomers of each europium complex, together with the available experimental values of gadolinium complexes, are shown in Table 1. The calculated molecular geometries compare well with the corresponding crystallographic structures, and the geometries optimized for aqueous solution provide a general better agreement with the experimental ones. The root-mean-square values between the experimental and ab initio structures, calculated on the Cartesian coordinates of all the atoms except hydrogens, are 0.79 and 0.68 Å (in vacuo) and 0.49 and 0.33 Å (in aqueous solution) for the trans isomer of the DTPA-BMA and the DTPA-BEA complexes, respectively. In agreement with the crystallographic evidence, there appeared to be no significant variation in the calculated coordination bond distances on increasing the substituent size, just as there were only small differences in these distances among the isomers.

The distances between the europium ion and the coordinated water molecule, Eu–O_w, for all the structures optimized for aqueous solution, are reported in Table 1 and Fig. 3. These results show that the europium–water distance is fairly unaffected by the substituent size on the amidic group. However, it can be observed (Fig. 3) that increasing the chain length decreases the differences in the Eu–O_w distance between the stereoisomers.

Moreover, the Eu–O_w distance presents almost similar values in all the isomers; only the anti isomer has a significantly higher value (on average, 0.03 Å) than the others. In the case of the $[Ln(DOTA)(H_2O)]^-$ systems, which present two antiprismatic isomers in aqueous

Table 1. Values of coordination bond distances (Å) of experimental and calculated (in vacuo and in aqueous solution) structures of the four isomers of the compounds investigated. The average values are reported with standard deviations in *parentheses*. Experimental values refer to gadolinium complexes

	In vacuo				In aqueous solution				Experiment
	Anti	Cis	Syn	Trans	Anti	Cis	Syn	Trans	Trans
[Eu(DTPA-BA)(H_2O)]									
Eu–N	2.823 (0.161)	2.767 (0.143)	2.775 (0.083)	2.796 (0.139)	2.795 (0.112)	2.785 (0.106)	2.787 (0.095)	2.820 (0.125)	
Eu–O_{carb}	2.325 (0.078)	2.325 (0.016)	2.318 (0.033)	2.320 (0.056)	2.313 (0.012)	2.317 (0.015)	2.312 (0.011)	2.308 (0.017)	
Eu–O_{am}	2.418 (0.011)	2.454 (0.001)	2.535 (0.075)	2.473 (0.011)	2.447 (0.023)	2.468 (0.011)	2.463 (0.006)	2.479 (0.006)	
Eu–O_w	2.506	2.521	2.460	2.506	2.521	2.481	2.477	2.492	
[Eu(DTPA-BMA)(H_2O)]									Ref. [15]
Eu–N	2.784 (0.103)	2.759 (0.138)	2.772 (0.083)	2.782 (0.135)	2.800 (0.120)	2.768 (0.090)	2.797 (0.108)	2.814 (0.119)	2.669 (0.076)
Eu–O_{carb}	2.332 (0.060)	2.328 (0.019)	2.321 (0.033)	2.321 (0.054)	2.311 (0.023)	2.326 (0.010)	2.312 (0.012)	2.310 (0.014)	2.361(0.015)
Eu–O_{am}	2.448 (0.024)	2.442 (0.001)	2.523 (0.069)	2.463 (0.016)	2.462 (0.057)	2.468 (0.002)	2.474 (0.004)	2.469 (0.007)	2.387 (0.015)
Eu-O_w	2.505	2.546	2.469	2.540	2.511	2.492	2.469	2.483	2.479
[Eu(DTPA-BEA)(H_2O)]									Ref. [16]
Eu–N	2.786 (0.100)	2.755 (0.129)	2.778 (0.086)	2.788 (0.137)	2.796 (0.114)	2.775 (0.096)	2.787 (0.099)	2.812 (0.118)	2.697 (0.060)
Eu–O_{carb}	2.330 (0.060)	2.329 (0.015)	2.320 (0.036)	2.322 (0.055)	2.310 (0.021)	2.324 (0.010)	2.313 (0.010)	2.311 (0.018)	2.365 (0.018)
Eu–O_{am}	2.444 (0.008)	2.444 (0.005)	2.515 (0.059)	2.465 (0.018)	2.464 (0.055)	2.465 (0.006)	2.473 (0.017)	2.467 (0.000)	2.394 (0.061)
Eu–O_w	2.504	2.543	2.474	2.532	2.508	2.484	2.475	2.486	2.425
[Eu(DTPA-BBA)(H_2O)]									
Eu–N	2.785(0.103)	2.758(0.131)	2.779(0.086)	2.788(0.137)	2.812(0.129)	2.781(0.103)	2.783(0.093)	2.812 (0.117)	
Eu–O_{carb}	2.330(0.063)	2.328(0.014)	2.321(0.036)	2.321(0.054)	2.315(0.027)	2.323(0.011)	2.314(0.012)	2.312 (0.018)	
Eu–O_{am}	2.443(0.003)	2.443(0.006)	2.512(0.059)	2.465(0.020)	2.454(0.059)	2.460(0.006)	2.472(0.023)	2.466 (0.000)	
Eu–O_w	2.517	2.544	2.477	2.533	2.508	2.483	2.477	2.482	

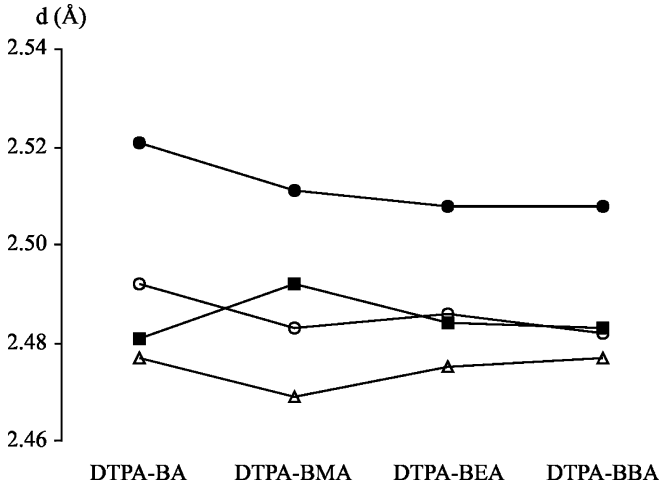

Fig. 3. Values, calculated for aqueous solution, of the distance between the europium ion and the coordinated water molecule (Eu–O_w, Å) in the anti (*closed circles*), cis (*squares*), syn (*triangles*), and trans (*open circles*) isomers of the compounds investigated

solution (labeled as A and IA, respectively), previous investigations [5] showed that the IA isomer always has a Ln–O_w distance longer than the A isomer (the difference in distance between the two isomers is 0.08 and 0.11 Å for the Gd and the Ho complexes, respectively). Moreover, in agreement with the experimental evidence, it was found that at the end of the lanthanide series, when the decrease in the ionic radius significantly reduces the space in the coordination cage, the IA isomer loses the water molecule. In the case of $[Eu(DOTAM)(H_2O)]^{3+}$ the exchange rates of the two isomers were determined experimentally,[4] and the IA isomer was found to be the highest. These results suggest that the equilibrium value of the Ln–O_w bond distance can be adopted as a rough criterion to predict the rate of the exchange process, at least within the limits of a dissociative mechanism: the longer the distance, the faster the exchange process. Thus, in the case of the bis(*R*–amide) DTPA systems investigated, comparable values of the exchange rate along the homologous series of the compounds investigated could be expected owing to the negligible influence of the alkyl substitution on the Eu–O_w values. Moreover, fairly comparable values of the water-exchange rate could also be expected for the four isomers (perhaps with the exception of the anti isomer), as all the isomers present almost similar Eu–O_w distances.

As far as concerns the relative stability of the isomers, Table 2 reports the relative total energies in vacuo and the relative total free energies in solution, calculated with respect to the cis isomer, namely $\Delta E^0 = E^0_{isomer} - E^0_{cis}$ and $\Delta G^{sol} = G^{sol}_{isomer} - G^{sol}_{cis}$. The in vacuo results show that the stability is not significantly affected by alkyl substitution, and the cis isomer is always the favored species. Also in aqueous solution the cis isomer is preferred (Table 2), and the lengthening of the chain seems to have little influence on the stability scale of the isomers. Thus, on the basis of these results, the observed increase in the exchange process rate along the series cannot be explained in terms of the influence of the alkyl chains on the isomeric composition in solution. The only significant variation in the stability

Table 2. In vacuo relative total energies ($\Delta E^0 = E^0_{isomer} - E^0_{cis}$, kcal mol^{-1}) and conductor-like polarizable continuum model (*C-PCM*) relative total free energies in aqueous solution ($\Delta G^{sol} = G^{sol}_{isomer} - G^{sol}_{cis}$,kcal mol^{-1}), calculated at the B3LYP/6-311G**level for geometries optimized, in vacuo and aqueous solution, at the HF/3-21Glevel

	ΔE^0, in vacuo				ΔG^{sol}, in solution			
	Anti	Cis	Syn	Trans	Anti	Cis	Syn	Trans
[Eu(DTPA-BA)(H_2O)]	11.14	0	9.45	5.34	1.09	0	2.21	−0.95
[Eu(DTPA-BMA)(H_2O)]	8.05	0	8.22	4.87	2.77	0	2.32	1.92
[Eu(DTPA-BEA)(H_2O)]	7.20	0	8.16	4.91	2.62	0	1.60	1.60
[Eu(DTPA-BBA)(H_2O)]	6.63	0	8.23	4.63	3.97	0	2.67	1.77

Table 3. B3LYP/6-311G** relative total energies calculated for geometries optimized in vacuo ($\Delta E^0 = E^0_{isomer} - E^0_{cis}$, kcal mol^{-1}) and C-PCM relative total free energies ($\Delta G^{sol} = G^{sol}_{isomer} - G^{sol}_{cis}$,kcal mol^{-1}) calculated for geometries optimized for aqueous solution. For the latter, the contributions to the total free energies are reported [$\Delta G^{sol} = \Delta E^{sol}$ + (electrostaticcontribution) + (nonelectrostatic contribution)]: relative total energies ($\Delta E^{sol} = E^{sol}_{isomer} - E^{sol}_{cis}$, kcal mol^{-1}) and relative total electrostatic and nonelectrostatic terms (kcal mol^{-1}). The molecular dipole moment calculated in vacuo (μ^0, D) and in aqueous solution (μ^{sol}, D) for geometries optimized for aqueous solution are reported

	[Eu(DTPA-BA)(H_2O)]				[Eu(DTPA-BMA)(H_2O)]			
	Anti	Cis	Syn	Trans	Anti	Cis	Syn	Trans
ΔE^0	11.1	0	9.45	5.34	8.05	0	8.22	4.87
ΔE^{sol}	11.1	0	11.5	3.87	15.3	0	11.4	4.52
Electrostatic	−11.0	0	−10.1	−5.81	−13.5	0	−10.2	−2.85
Nonelectrostatic	1.06	0	0.79	1.00	1.01	0	1.09	0.25
ΔG^{sol}	1.11	0	2.24	−0.94	2.79	0	2.29	1.93
μ^0	16.6	13.9	22.3	7.0	17.8	13.7	22.5	7.4
μ^{sol}	23.6	17.6	30.6	9.4	25.0	17.2	30.8	9.8

scale of the isomers in solution is seen in the case of the unsubstituted amide, the [Eu(DTPA-BA)(H_2O)] complex. Here, the trans isomer is the stablest species; compared with the alkyl-substituted complexes the trans and the cis isomers exchange their relative positions, just as do the anti and syn isomers.

To better understand the influence of solvation on the relative stability of the isomers an analysis was made of the different contributions to the total free energies in solution. For the DTPA-BA and the DTPA-BMA complexes, Table 3 reports the relative total free energies in solution, calculated with respect to the cis isomer (ΔG^{sol}), together with the values of the different contributions to the total free energies, i.e., the relative total energies (ΔE^{solv}) and the relative total electrostatic and nonelectrostatic contributions. The relative total energies calculated on geometries optimized in vacuo (ΔE^0) and for aqueous solution (ΔE^{solv}) show similar trends in both complexes (Table 3): cis < trans < anti≅syn. The most evident solvation effect is the stabilization of the isomers with the highest dipole moments (Table 3), i.e., the anti and the syn isomers with respect to the cis and trans isomers, as highlighted from the values of the electrostatic contribution to the total free energy. In the case of DOTA complexes it was observed [17] that an increase in the ionic strength of the solution, by the addition of salts, favors the IA isomer, i.e., the isomer with the highest dipole moment [5]. In the case of bis(*R*–amide) DTPA systems it can be expected that the increase in the ionic strength of the solution should favor the anti and the syn isomers.

It is interesting to note that in spite of the variation in the relative stability scale on passing from the DTPA-BA to the DTPA-BMA complex, the exchange rate determined for [Gd(DTPA-BMA)(H_2O)] is only 20% greater than the exchange rate of [Gd(DTPA-BA)(H_2O)] [2]. This suggests that the isomeric population has little influence on the rate of the exchange process, probably because the Eu–O_w bond distances in each of the four isomers are similar.

In conclusion, these results highlight that the electronic effects due to alkyl chain lengthening have no significant influence on the structural features of the coordination cage, or on the equilibrium distance between the europium ion and the coordinated water molecule; nor do such effects influence the relative population of the isomers in solution. Consequently, the study does not support the hypothesis that the lengthening of the alkyl chains influences the equilibrium between stereoisomers, favoring the stereoisomer with the highest water-exchange rate.

Summary

The conformational analysis performed for aqueous solution at the ab initio level on a series of Eu(III)

complexes of different bis(alkylamide) DTPA ligands provides the following main results:

1. For each compound four isomers are found as stable conformations.
2. The lengthening of the alkyl chains in an all-trans arrangement has only minor effects on the coordination geometry around the ion and on the distance between the ion and the coordinated water molecule.
3. The distance between the ion and the coordinated water molecule assumes almost similar values in all the isomers, with the exception of the anti isomer, which presents $Eu–O_w$ values longer than the other isomers.
4. The chain length only marginally affects the relative population of the isomers in solution.

Thus, the experimentally observed increase in the water-exchange rate increasing the chain length of the substituents cannot be explained on the basis of the hypothesis that the lengthening of the alkyl chains influences the equilibrium between the stereoisomers favoring the stereoisomer with the highest water-exchange rate. Rather, the observed phenomenon could be ascribed to the conformational flexibility of the lateral chains in solution: their folding disturbs the hydration shell of the complexes, favoring the water-exchange process. To test this hypothesis, the chain conformational flexibility will be included in further investigations on these systems by performing molecular dynamics simulations with a molecular representation of the water solvent.

Acknowledgements. The authors acknowledge the continued scientific effort of Prof. Jacopo Tomasi in developing new methods and computational tools suitable for dealing with complex molecular systems. Moreover, those in our research group are grateful to Professor Tomasi for his long friendship and the scientific interest he has shown us, promoting both our cultural and scientific growth through his capability of passing on his great culture, marked enthusiasm, and notable curiosity to young and less young researchers. Grazie Jacopo! Computational support from the CINECA computational center together with financial support from the Italian National Research Council (CNR Target Project on Biotechnology, grant no. 01.00265.PF49) are gratefully acknowledged.

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