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Sparkle/AM1 Structure Modeling of Lanthanum (III) and Lutetium (III) Complexes

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The sparkle/AM1 model for the quantum chemical prediction of coordination polyhedron crystallographic geometries from isolated lanthanide complex ion calculations, defined recently for Eu(III), Gd(III), and Tb(III) (*Inorg. Chem.* **2005**, *44*, 3299) is now extended to La(III) and Lu(III). Thus, for each of the metal ions we chose a training set of 15 complexes that possess various representative ligands of high crystallographic quality (R factor < 0.05 Å) and oxygen and/or nitrogen as coordinating atoms. In the validation procedure we used a set of 60 more La(III) coordination compound structures, as well as 15 more Lu(III) coordination compound structures, all of high crystallographic quality. For both the 75 La(III) compounds and the 30 Lu(III) compounds, the Sparkle/AM1 unsigned mean error, for all interatomic distances between the metal ions and the ligand atoms of the first sphere of coordination, is 0.08 Å, thus comparable to the accuracy normally achievable by present day ab initio/ECP calculations, while being hundreds of times faster.

Introduction

Many uses of lanthanide ions require their complexation with suitable organic ligands. Therefore, fast and accurate a priori quantum chemical predictions of crystallographic geometries of coordination polyhedra from isolated lanthanide complex ion calculations of trivalent lanthanum and lutetium coordination compounds are of importance to complex design for various purposes. More especially so in the case of combinatorial screenings aiming at achieving optimum molecular architectures for certain applications where dozens of supramolecular structures must have their geometries fully optimized, a task that is not practical using present day ab initio/effective core potential (ECP) calculations.

The relevance of prediction of crystallographic structures for most applications of lanthanide ions has been strengthened recently in light of a comparison between the solid-state structure of a lanthanum complex with the structure of the same compound in solution by NMR measurements of vicinal coupling constants, which shows a rather good coincidence,[1] and which was further confirmed by ab initio/ECP calculations.[1]

A semiempirical quantum chemical model for the prediction of crystallographic structures of trivalent lanthanum and lutetium coordination compounds also gains importance in light of two recent developments in computational quantum chemistry: the MOZYME algorithm, developed by Stewart,[2] which has permitted semiempirical calculations on systems as large as 20 000 atoms, and LocalSCF, developed by Anikin et al., which is a truly linear scaling technique for semiempirical methods, which now allows AM1 calculations on systems as large as 120 000 atoms.[3]

Lutetium complexes are used in a variety of applications. For example, lutetium bisphthalocyanine has been known to be electrochromic for many decades[4] and is also used as an intrinsic molecular semiconductor as the sandwiched buffer layer in organic thin-film transistors because of its high carrier density.[5]

Lu(III) has also been found to enhance the fluorescence intensities of Tb-nucleic acids, which are naturally so weak that the direct use of their fluorescence emission properties to study their biological properties is limited.[6]

Complexes of the beta- and gamma-emitting radionuclide ^{177}Lu are used widely as radiosensitizers (compounds that improve the efficacy of delivered radiation) in radioimmunotherapy. ^{177}Lu is produced by direct neutron capture using isotopically enriched ^{176}Lu targets.[7] For radioimmunotherapy, ^{177}Lu must be linked as a metal complex to a monoclonal antibody or immunoprotein via a suitable bifunctional chelating agent that possesses acceptable thermodynamic and kinetic stabilities to minimize release of the isotope and hence in vivo toxicity.[8] The term “bifunctional chelating agent” refers to a molecule that has at least two functional groups, one of which is a reactive group that can form a bond, such as a covalent bond, to a macromolecule and another that is a metal ion binding group.

Availability of a fast and accurate a priori quantum chemical model for the prediction of structures of Lu(III) coordination compounds may be of importance for the proper design of ^{177}Lu chelating agents to produce ^{177}Lu-chelated antibodies that will be stable in vivo, a property very important for the potential effectiveness of radioimmunotherapy. Stability in vivo depends on the condition that both the chelate linkage and radiolabeling procedures not alter antibody specificity and biodistribution. In addition, synthesis and selection of the chelating agent for ^{177}Lu is critical in order to prevent inappropriate release of the radiometal in vivo. For example, ^{177}Lu-octreotate is used in treatment of patients with gastro-entero-pancreatic tumors.[9] A new class of radiosensitizers that is being explored extensively is called lanthanide texaphyrins, metal-coordinated expanded porphyrins, fully aromatic and highly colored.[9] Lutetium texaphyrin (lu-tex) is also used as a fluorescence imaging agent in the delineation of retinal vascular and choroidal vascular diseases.[10] For example, design of efficient fluorescent lutetium

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complexes that are also photosensitizers may represent a unique opportunity to couple diagnosis with therapy. Another application of a fast a priori quantum chemical model for the prediction of structures of Lu coordination compounds could be the design of complexes for pretargeting, in which a nonradioactive monoclonal antibody−receptor conjugate or fusion protein is first administered and allowed to reach maximum uptake in tumors, and then radionuclide therapy is given in the form of a ^{177}Lu complex that binds rapidly to the monoclonal antibody−receptor structure with high affinity and specificity.[7] Because radiolabeled complexes typically exhibit extremely fast targeting and whole body clearance properties, pretargeting often results in immediate tumor uptake of radioactivity and very high tumor-to-normal tissue ratios with a significantly superior therapeutic efficacy and normal tissue toxicity, compared to conventionally radiolabeled monoclonal antibodies.[7]

Lanthanum complexes also have many applications, such as catalysts.[11] The aggregation of lanthanum complexes on the surface of nucleic acids resulted in enhanced intensity of resonance light scattering with a linear relationship between the enhanced intensity and the concentration of nucleic acids, with a detection limit at the ng level.[12] As another example, when lanthanum (III) ions form complexes with tetracycline molecules, they enhance their antibiotic activity, making them more toxic against gram-positive organisms.[13] However, there is clear disagreement in the literature about the metal−ligand binding sites in complexes of this ligand,[13] a situation that provides a clear example of how useful it would be to be able to accurately model lanthanum complexation via semiempirical methods. Indeed, tetracycline itself can assume 64 different tautomeric forms that could conceivably be involved in the complexation process, each with a handful of complexation sites.[14] Modeling all of these possibilities by ab initio/ECP calculations could perhaps prove too demanding.

The chemical bonds of lanthanide ions appear to be essentially electrostatic and may be attributed to the fact that the 4f orbitals are lower in energy, not spatially expanded, and often considered as core orbitals with negligible angular effects. This leads to a handful of unusually high coordination numbers, to small energy variations among their various coordination geometries and, consequently, to weak stereochemical preferences. Thus, so far, because of a lack of quantitative structure prediction methodologies, prior knowledge of persistent structural motifs has been normally used and shown to be of help in the design of lanthanide coordination networks.[15]

The sparkle model for the semiempirical prediction of geometries of europium complexes was originally conceived in 1994.[16] The sparkle model replaces the trivalent lanthanide ion by a Coulombic charge of $+3e$ superimposed to a repulsive exponential potential of the form $\exp(-\alpha r)$, which accounts for the size of the ion. In 2004 the Eu(III) sparkle model was improved[17] with the introduction of Gaussian functions in the core−core repulsion term in order to make it consistent with AM1 as well as with the inclusion of the europium atomic mass. More recently, a new paradigm, Sparkle/AM1, has been introduced based on a much more sophisticated parametrization scheme to predict geometries of lanthanide complexes with nitrogen or oxygen directly coordinated to the lanthanide ion, at a level of accuracy useful for luminescent complex design and comparable to geometries obtained from present day ab initio/ECP calculations. Sparkle/AM1 parameters are already available for Eu(III), Gd(III), and Tb(III).[18] In the present paper we extend Sparkle/AM1 to La(III) and Lu(III) complexes.

TABLE 1: Parameters for the Sparkle/AM1 Model for the La(III) and Lu(III) Ions

	Sparkle/AM1 − La(III)	Sparkle/AM1 − Lu(III)
GSS	55.7344864002	56.1751741742
ALP	2.1879021346	4.0203424467
a_1	1.3207809006	1.0381638761
b_1	7.1394307023	8.4911797242
c_1	1.8503281529	1.7034420896
a_2	0.3425777564	0.3342233253
b_2	8.7780631664	7.2729946604
c_2	3.1678964355	2.9153096100

TABLE 2: Number of Lanthanum(III) and Lutetium(III) Complexes in the Validation Set, Classified into Each Ligand Group

ligand group number	ligand type	number of structures La(III)	number of structures Lu(III)
1	β-diketones	1	0
2	nitrates	32	10
3	monodentates	6	6
4	bidentates	2	2
5	tridentates	3	0
6	polydentates	19	7
7	dilanthanides	12	5

Results and Discussions

The parametrization procedure used for La(III) and Lu(III) was essentially the same as the one described in our previous work on Eu(III), Gd(III), and Tb(III)[18] and will not be repeated here. Accordingly, we used only high quality crystallographic structures (R factor < 5%) taken from the "Cambridge Structural Database 2003" (CSD).[19−21] Fifteen different representative structures of La(III) and Lu(III) complexes, with nitrogen or oxygen as coordinating atoms, were chosen as the training set, with β-diketone, nitrate, monodentate, bidentate, tridentate, and polydentate ligands as well as dilanthanide complexes.

The heats of formation of the lanthanide ions were obtained by adding their first three ionization potentials to their respective atomic heats of atomization,[22] yielding 928.9 kcal·mol^{-1} for lanthanum and 1031.2 kcal·mol^{-1} for lutetium, which were assigned to EHEAT(103). Finally, the atomic masses of La(III) and Lu(III) were set at 138.9055 and 174.9670 amu, respectively.[22]

To find the parameters, we carried out a nonlinear minimization of an eight-dimension response function, using a combination of Newton−Raphson and Simplex methods, aimed at finding one of its local minima, which ideally should be the global minimum and make chemical sense. The Sparkle/AM1 parameters obtained for La(III) and Lu(III) are shown in Table 1.

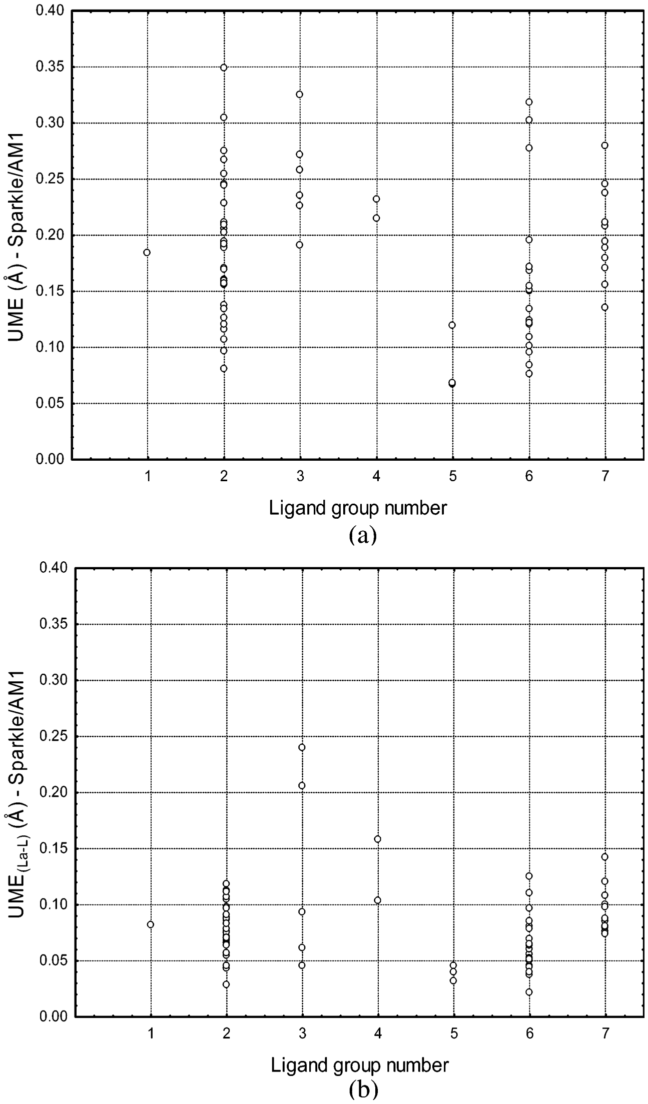
In the validation procedure, we used a set of 60 more structures for La(III) and 15 more structures for Lu(III), also of high crystallographic quality, for a total of 75 and 30 coordination compounds considered for La(III) and Lu(III), respectively (Table 2).

As an accuracy measure, we used the average unsigned mean error for each complex i, UME_i, defined as

$$UME_i = \frac{1}{n_i}\sum_{j=1}^{n} |R_{i,j}^{\mathrm{CSD}} - R_{i,j}^{\mathrm{calc}}| \qquad (1)$$

where n_i is the number of ligand atoms directly coordinating the lanthanide ion. The total UME is obtained by running the summation of UME$_i$ values over all 75 and 30 coordination compounds considered for La(III) and Lu(III).

Two cases have been examined: (i) UME values involving the interatomic distances, R_j, between the lanthanum or lutetium



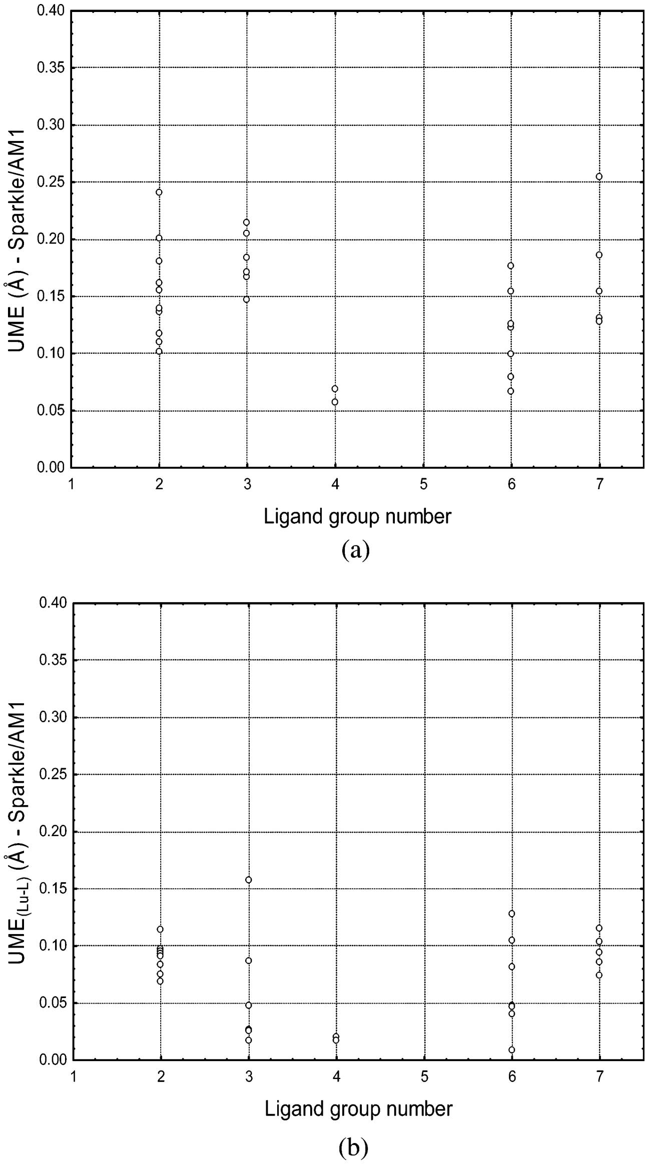
(a)

(b)

Figure 1. Unsigned mean errors for each of the 75 lanthanum (III) complexes, assembled according to the ligand group numbers defined in Table 2. Figure 1a presents the UME values, and Figure 1b presents the $\mathrm{UME}_{(\mathrm{La-L})}$ values. The same scale has been used in both to facilitate comparison.

central ion and the atoms of the coordination polyhedron, as well as the interatomic distances, R_j, between all atoms of the coordination polyhedron, and (ii) $\mathrm{UME}_{(\mathrm{Ln-L})}$ values involving only the interatomic distances, R_j, between the lanthanum or lutetium central ion and the atoms of the coordination polyhedron.

Parts a and b of Figure 1 show these accuracy measures for all 75 lanthanum complexes studied, grouped according to the classification of Table 1. All lanthanum complexes possess UME values below 0.35 Å, and their average UME is 0.18 Å.



(a)

(b)

Figure 2. Unsigned mean errors for each of the 30 lutetium (III) complexes, assembled according to the ligand group numbers defined in Table 2. Figure 2a presents the UME values, and Figure 2b presents the $\mathrm{UME}_{(\mathrm{Lu-L})}$ values. The same scale has been used in both to facilitate comparison.

Distances between the lanthanide ion and the ligands are more accurately described, with 72 complexes possessing $\mathrm{UME}_{(\mathrm{La-L})}$ values below 0.15 Å. Considering $\mathrm{UME}_{(\mathrm{La-L})}$ values of only the distances between the lanthanum ion and the directly coordinated atoms, their average is 0.08 Å.

Parts a and b of Figure 2 show these accuracy measures for all 30 lutetium complexes studied, grouped according to the classification of Table 1. Twenty nine lutetium complexes

TABLE 3: Sparkle/AM1 Unsigned Mean Errors for All Distances Involving the Central Lanthanide Ion, Ln, and the Ligand Atoms of the Coordination Polyhedron, L, for 96 Eu(III)[18] Complexes, 70 Gd(III)[18] Complexes, 42 Tb(III)[18] Complexes, and all 75 La(III) and 30 Lu(III) Complexes Considered

	unsigned mean errors for specific types of distances (Å)					
model	Ln−Ln	Ln−O	Ln−N	L−L′	Ln−L and Ln−Ln	Ln−L, Ln−Ln, and L−L′
Sparkle/AM1 − Eu[18]	0.1624	0.0848	0.0880	0.2170	0.0900	0.1900
Sparkle/AM1 − Gd[18]	0.1830	0.0600	0.0735	0.2082	0.0658	0.1781
Sparkle/AM1 − Tb[18]	0.2251	0.0754	0.0440	0.2123	0.0746	0.1823
Sparkle/AM1 − La	0.2126	0.0865	0.0478	0.2079	0.0780	0.1832
Sparkle/AM1 − Lu	0.2219	0.0844	0.0466	0.1701	0.0751	0.1498

possess UME values below 0.25 Å, and their average UME is 0.15 Å. Once again, distances between the lanthanide ion and the ligands are described more accurately, with 29 complexes possessing $\mathrm{UME}_{(\mathrm{Lu-L})}$ values below 0.15 Å. Considering $\mathrm{UME}_{(\mathrm{Lu-L})}$ values of only the distances between the lutetium ion and the directly coordinated atoms, their average is also 0.08 Å.

Table 3 shows a comparison of the unsigned mean errors for various types of distances between La(III) and Lu(III) and the three atoms parametrized previously: Eu(III), Gd(III), and Tb-(III).[18] Clearly, from Table 3, there are no major discrepancies between the numbers, with lanthanide−ligand atom distances, again, appearing as the most accurately predicted ones.

As reported previously,[18] ab initio RHF/6-31G*/ECP calculations on seven Eu(III) complexes led to an unsigned mean error, for the distances between the Eu(III) ion and the directly coordinating ligand atoms, of 0.06 Å, whereas the same value for the Eu(III) Sparkle/AM1 for the same set of complexes was 0.05 Å. According to Table 3, the same quantity for the Sparkle/AM1 model for all 96 Eu(III) complexes is 0.09 Å, whereas for both La(III) and Lu(III) it is 0.08 Å. Moreover, even nowadays RHF/6-31G*/ECP calculations of lanthanide complexes take too long, are generally prohibitive, and are therefore extremely rare in the literature.[18]

Conclusions

As such, we can safely extend the conclusion we arrived at for Eu(III)[18] that Sparkle/AM1 for both La(III) and Lu(III) possesses geometry prediction accuracies competitive with present day ab initio/ECP calculations on lanthanide complexes, while being hundreds of times faster. Indeed, Sparkle/AM1 may prove useful for ligand design where many different combinations of ligands and substituents must be evaluated in a combinatorial way.

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Supporting Information Available: Instructions and examples on how to implement the La(III) and Lu(III) Sparkle/AM1 model in Mopac93r2. Parts of the codes of subroutines Block.f, Calpar.f, and Rotate.f that need to be changed as well as their modified versions for both La(III) and Lu(III). Examples of Mopac93r2 crystallographic geometry input (.dat) and optimized geometry summary output (.arc) files from Sparkle/AM1 calculations for the La(III) complex EGOBAD, for the dilanthanum complex HETALA11, for the Lu(III) complex XEPLUZ, and for the dilutetium complex XEWYIH. Additional figures showing schematic two-dimensional representations of the 15 complexes that constituted both parametrization training sets. Additional tables with Sparkle/AM1 unsigned mean errors for each of the 75 La(III) and 30 Lu(III) complex CSD[19−21] high-quality crystallographic structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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