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A Novel Compound in the Lanthanide(III) DOTA Series. X-ray Crystal and Molecular Structure of the Complex $Na[La(DOTA)La(HDOTA)]\cdot 10H_2O$

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Introduction

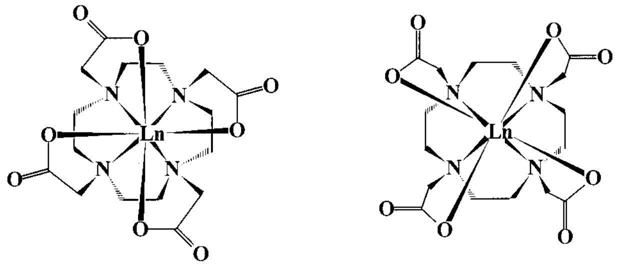
The peculiar stereochemical properties of the macrocyclic ligand DOTA (DOTA = 1,4,7,10-tetraazacyclododecane-*N,N′,N′′,N′′′*-tetraacetic acid) are responsible for the remarkable thermodynamic stability and kinetic inertness of its complexes with lanthanide(III) ions.[1−3] LnDOTA complexes are under intense scrutiny since GdDOTA is one of the most relevant contrast agents for MRI. The previously reported X-ray crystal structures of Ln^{III}DOTA complexes (Ln = Eu,[4] Gd,[5] Lu[6]) show that the ligand provides eight donor sites (four oxygens and four nitrogens) arranged in a *square antiprismatic* geometry with the oxygen plane capped by a coordinating water molecule, irrespective of the fact that, in solution, according to their ^{1}H and ^{13}C NMR, spectra, two structural isomers (with relative population markedly variable along the series) are present.[7]

Insights into the structural differences between the coordination geometries of the two isomers were gained by analysis of the ^{1}H NMR dipolar shifts of the Yb^{3+} derivative. On this basis, it was inferred that the structure of the more abundant isomer **M** of $YbDOTA^-$ is very similar to that found in the solid state whereas the less abundant species (**m**), while maintaining the same conformation of the **M** macrocycle, displays an inverted arrangement of the acetate arms.[7,8] (See Chart 1.)

Interestingly, the solution NMR spectra of several DOTA-like Ln(III) derivatives appear to contain noticeable amounts of the inverted square antiprismatic **m** isomer.[9]

Our interpretation of the ^{13}C NMR spectra of the diamagnetic La^{3+} and Lu^{3+} complexes led us to suggest that there is the occurrence of an opposite distribution of the isomeric species at the two ends of the lanthanide series. Now, having established that the solid state structure of $MDOTA^-$ [4−6,10] (M = Eu^{3+}, Gd^{3+}, Lu^{3+}, Y^{3+}) corresponds to isomer **M**, it is worthwhile to determine the structure of $LaDOTA^-$ which should correspond to isomer **m**.

Chart 1



Experimental Section

Synthesis of the Complex. The procedure used was the same as for the 1:1 complexes of the series. The acid form of the ligand (H_4-DOTA), prepared by following the published procedure,[1] was provided by Bracco Spa (Milan, Italy). The complex was prepared as its sodium salt by mixing stoichiometric amounts of H_4DOTA, lanthanum(III) oxide (Aldrich Chemical Co.), and NaOH. Typically, 0.425 g of La_2O_3 (1.3 mmol), 1.056 g of H_4DOTA (2.6 mmol), and 1.3 mL of 2 N NaOH were added to 24 mL of deionized water. The white suspension was heated at 85 °C under magnetic stirring for several days, until a clear solution was obtained with a pH value around 7. The reaction mixture was then allowed to cool to room temperature, filtered, and centrifuged in order to remove a small amount of undissolved solid. After evaporation to dryness under reduced pressure, 1.4 g of the complex was recovered as a white solid (93%). ^{1}H NMR (D_2O) (ppm): 3.01 (4H, acetate), 2.72 (4H, ring CH_2, axial), 2.37 (4H, acetate), 2.29 (4H, ring CH_2, axial), 1.82 (4H, ring CH_2, equatorial), 1.70 (4H, ring CH_2, equatorial). ^{13}C NMR (D_2O) (ppm): 181.1 (CO), 62.1 (acetate CH_2), 55.3 (ring CH_2), 51.0 (ring CH_2).

Instrumentation. Proton and carbon NMR spectra were recorded at 298 K on a JEOL EX-400 spectrometer operating at 9.4 T. D_2O was used as solvent and *tert*-butyl alcohol as an internal standard (δ_H = 1.29 ppm; δ_C = 31.3 ppm).

Crystal Structure Determination. Single crystals suitable for X-ray analysis were obtained by diffusion methods from water and acetone (room temperature) after several days.

A prismatic (white) crystal of dimensions 0.32 × 0.42 × 0.16 mm was lodged in a Lindemann glass capillary and centered on a four-circle Philips PW1100 (Febo System) diffractometer with graphite-monochromated (Mo Kα) radiation (λ = 0.710 69 Å). The orientation matrix and cell dimensions were determined by least-squares refinement of the angular positions of 30 reflections. Data were collected at room temperature. Three standard reflections were monitored every 200 reflections. There were no significant fluctuations of intensities other than those expected from Poisson statistics. The intensity data were corrected for Lorentz−Polarization effects and for absorption as described by North et al.[11] No correction was made for extinction.

The structure was solved by the heavy atom method.[12] Refinement was carried out by full-matrix least-squares procedures; the function minimized was $\sum w(F_o^2 - F_c^2)^2$. All nonhydrogen atoms were refined with anisotropic thermal parameters. The H atoms were placed in calculated positions with fixed, isotropic thermal parameters (1.2$\mathbf{U}_{equiv}$ (parent carbon atom)). Structure refinement was carried out with SHELXL-93[13] using the scattering factors included therein; drawings were produced using ORTEP II.[14] Crystal data and experimental details

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(1) Desreux, J. F. *Inorg. Chem.* **1980**, *19*, 1319−1324.

(2) Wang, X.; Jin, T.; Comblin, V.; Lopez-Mut, A.; Merciny, E.; Desreux, J. F. Inorg. Chem. **1992**, *31*, 1095−1099.

(3) Tòth, E.; Brüker, E.; Làzar, I.; Tòth, I. *Inorg. Chem.* **1994**, *33*, 4070−4076.

(4) (a) Spirlet, M. R.; Rebizant, J.; Desreux, J. F.; Loncin, M. F. *Inorg. Chem.* **1984**, *23*, 359−363. (b) Benetollo, F.; Bombieri, G.; Aime, S.; Botta, M. *Abstracts of the XXVth National Congress on Crystallography*, Giardini Naxos, ME, Italy, Sept 25−27, 1995; pp 56−57.

(5) (a) Dubost, J. P.; Legar, J. M.; Langlois, M. H.; Meyer, D.; Schaefer, M. *C. R. Acad. Sci., Paris Ser. II* **1991**, *312*, 349−354. (b) Chang, C. A.; Francesconi, L. C.; Malley, M. F.; Kumar, K.; Gougoutas, J. Z.; Tweedle, M. F.; Lee, D. W.; Wilson, L. J. *Inorg. Chem.* **1993**, *32*, 3501−3508.

(6) Aime, S.; Barge, A.; Botta, M.; Fasano, M.; Ayala, J. D.; Bombieri, G. *Inorg. Chim. Acta* **1996**, *246*, 423−429.

(7) Aime, S.; Botta, M.; Ermondi, G. *Inorg. Chem.* **1992**, *31*, 4291−4299.

(8) Hoeft, S.; Roth, K. *Chem. Ber.* **1993**, *126*, 869−873.

(9) Aime, S.; Botta, M.; Ermondi, G.; Terreno, E.; Anelli, P. L.; Fedeli, F.; Uggeri, F. *Inorg. Chem.* **1996**, *35*, 2726−2736.

(10) Parker, D.; Pulukkody, K.; Smith, F. C.; Batsanov, A.; Howard, J. A. K. *J. Chem. Soc., Dalton Trans.* **1994**, 689−693.

(11) North, A. C. T.; Philips, D. C.; Mathews, F. S. *Acta Crystallogr.* **1968**, *A24*, 351.

(12) Sheldrick, G. M. SHELX-86. *Acta Crystallogr.* **1990**, *A46*, 467.

(13) Sheldrick, G. M. *SHELXL-93*: *Program for crystal structure refinement*; University Göttingen: Göttingen, Germany, 1993.

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Table 1. Crystallographic Data for $Na[La(DOTA)La(HDOTA)]\cdot 10H_2O$

mol formula	$La_2NaC_{32}H_{138}N_8O_{16}\cdot 10H_2O$
mol wt	1282.74
space group	$P2_1/n$ (No. 14)
a	16.425(3) Å
b	11.942(3) Å
c	25.384(5) Å
β	94.75(4)°
V	4962(2) Å^3
T	23 °C
λ	0.710 69 Å
Z	4
ρ_{calc}	1.717 g cm^{-3}
μ	18.00 cm^{-1}
$R(F_o)^a$	0.040
$R_w(F_o^2)^b$	0.138

[a] $R(F_o) = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $R_w(F_o^2) = (\sum[w(|F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

Table 2. Selected Final Atomic Positional Parameters and Equivalent Isotropic Thermal Parameters (Å^2 × 10^3) with ESD's in Parentheses for $Na[La(DOTA)La(HDOTA)]\cdot 10H_2O$

atom	x	y	z	U_{eq}
La(1)	0.46287(2)	0.24443(3)	0.28352(1)	21.1(1)
La(2)	0.72525(2)	0.08647(3)	0.10584(1)	20.6(1)
N(1)	0.6844(3)	−0.0588(5)	0.0222(2)	30(2)
N(2)	0.8420(3)	0.2144(5)	0.0594(2)	30(2)
N(3)	0.8542(3)	−0.0313(5)	0.0700(2)	25(2)
N(4)	0.6704(3)	0.1869(5)	0.0120(2)	31(2)
N(1B)	0.4238(3)	0.0561(5)	0.3409(2)	28(2)
N(2B)	0.4617(3)	0.0408(5)	0.2284(2)	26(2)
N(3B)	0.3408(3)	0.2233(5)	0.2008(2)	27(2)
N(4B)	0.3028(3)	0.2362(5)	0.3133(2)	26(2)
O(1)	0.6746(3)	−0.1033(4)	0.1261(2)	39(2)
O(2)	0.6618(3)	0.5254(4)	0.3278(2)	33(2)
O(3)	0.7533(3)	0.2797(4)	0.1394(2)	45(2)
O(4)	0.5778(3)	0.1345(5)	0.0917(2)	38(2)
O(1B)	0.5731(3)	0.1518(4)	0.3403(2)	36(2)
O(2B)	0.5643(3)	0.2140(4)	0.2164(2)	33(2)
O(3B)	0.4280(3)	0.3509(5)	0.3624(2)	43(2)
O(4B)	0.4123(3)	0.4177(4)	0.2356(2)	42(2)
O(2A)	0.6666(3)	0.1079(4)	0.1947(2)	34(2)
O(5A)	0.5766(3)	0.3920(4)	0.2964(2)	36(2)

of the structure determination and refinement are reported in Table 1, selected atomic coordinates are listed in Table 2, and selected bond lengths and angles are given in Table 3.

Results and Discussion

An ORTEP view of the structure of $Na[LaH(DOTA)La(DOTA)]\cdot 10H_2O$, along with the numbering scheme adopted, is reported in Figure 1. As expected, the ligand DOTA behaves as an octadentate ligand toward La^{3+} ions, but the resulting molecular structure shows important differences with respect to those previously reported for the other members of the lanthanide series. The asymmetric unit is formed by two different LaDOTA moieties joined via carboxylate bridges, where the four nitrogen atoms form one square plane and four oxygen atoms, one from each carboxylate group, form a second square plane parallel and twisted relative to the previous one. The resulting geometry of the coordinated atoms is almost midway between prismatic (twist angle between the planes of 0°) and antiprismatic (twist angle 45°) with twist angles of 21 and 23° for La(1) and La(2), respectively. Notably, the orientation of the four-oxygen plane is different from that of the four-nitrogen plane and is opposite to that found in the corresponding structures of Eu^{3+}, Gd^{3+}, Lu^{3+}, and Y^{3+} (twist angle of about 39°) and it can be defined as an "*inverted square antiprism*" arrangement to differentiate it from the usual square antiprismatic geometry found in the previously mentioned derivatives. The two similar coordination spheres of the lanthanum ions are completed in the capping position by an extra oxygen, belonging to a carboxylic group of the adjacent unit. The two square antiprisms are oriented perpendicularly one to another (the angle between the two oxygen squares is about 90°). This basic unit is repeated according to the crystal symmetry with the formation of helices (developing along the b crystallographic axis) (see Figure 2) connected via hydrogen-bond interactions with the crystallization water molecules (40 per unit cell). Although there are numerous water sites, no water is coordinated to the lanthanum ions. Only one sodium position has been detected for the two independent lanthanum ions, suggesting a possible protonation of one carboxylic group. Its identification was not unambiguous as the hydrogen atom positions were not clearly defined and the assignment of the acid hydrogen has been made primarily on the basis of the possibly significant differences in the C−O bonds of the carboxylic groups. We noticed that the C−O bond lengths for the groups whose oxygen is coordinated to the lanthanum fall in a narrow range around 1.27 Å except for one having a C−O bond distance of 1.30 Å consistent with the value accepted for a C−OH carboxylic group (the range of the experimental values is 1.30−1.33 Å).[15] This distance belongs to the C−O(4)B moiety where the oxygen is coordinated to La(1). In addition, a difference Fourier map calculated at $2\theta \leq 30°$ shows a residual of 0.3 e/Å^3 in the proximity of the O(4)B position at a 0.9 Å distance, which may be assigned to a possible hydrogen position (La−O(4)B−H angle is 99°).

Table 3. Selected Bond Distances (Å) and Angles (deg) for $Na[La(DOTA)La(HDOTA)]\cdot 10H_2O$

La(1)−N(2B)	2.806(6)	La(2)−N(1)	2.780(6)
La(1)−N(1B)	2.783(6)	La(2)−N(2)	2.788(6)
La(1)−N(3B)	2.792(5)	La(2)−N(3)	2.758(5)
La(1)−N(4B)	2.797(5)	La(2)−N(4)	2.750(5)
La(1)−O(1B)	2.480(5)	La(2)−O(2A)	2.537(5)
La(1)−O(2B)	2.506(5)	La(2)−O(1)	2.483(5)
La(1)−O(3B)	2.478(5)	La(2)−O(2)^a	2.510(5)
La(1)−O(4B)	2.507(5)	La(2)−O(3)	2.490(5
La(1)−O(5A)	2.568(5)	La(2)−O(4)	2.485(5)

N(3B)−La(1)−N(4B)	64.4(2)	N(3)−La(2)−N(4)	98.2(2)
N(1B)−La(1)−N(4B)	64.4(2)	N(2)−La(2)−N(4)	65.3(2)
N(1B)−La(1)−N(3B)	98.0(2)	N(2)−La(2)−N(3)	64.3(2)
N(2B)−La(1)−N(4B)	97.8(2)	N(1)−La(2)−N(4)	64.5(2)
N(2B)−La(1)−N(3B)	64.6(2)	N(1)−La(2)−N(3)	64.8(2)
N(2B)−La(1)−N(1B)	64.4(2)	N(1)−La(2)−N(2)	98.6(2)
O(4B)−La(1)−O(5A)	72.8(2)	O(2A)−La(2)−O(4)	70.6(2)
O(3B)−La(1)−O(5A)	76.1(2)	O(2)−La(2)−O(3)	71.1(2)
O(3B)−La(1)−O(4B)	83.1(2)	O(2A)−La(2)−O(1)	75.5(2)
O(2B)−La(1)−O(5A)	70.6(2)	O(2)^a−La(2)−O(4)	145.3(2)
O(2B)−La(1)−O(4B)	90.1(2)	O(1)−La(2)−O(3)	146.2(2)
O(2B)−La(1)−O(3B)	146.6(2)		
O(1B)−La(1)−O(5A)	75.2(2)		
O(1B)−La(1)−O(4B)	147.9(2)		
O(1B)−La(1)−O(3B)	88.0(2)		
O(1B)−La(1)−O(2B)	80.6(2)		

Na···O(2B)	2.340(6)	Na···O(3)	2.519(7)
Na···O(5A)	2.781(6)	Na···O(2A)	2.861(7)
Na···Ow(2B)^c	2.29(2)	Na···Ow(2A)^{b,c}	2.48(2)
Na···Ow(3)^c	2.33(2)	Na···Ow(12)^c	2.52(2)

[a] $^3/_2 - x$, $^1/_2 - y$, $^1/_2 - z$. [b] $^3/_2 - x$, $^1/_2 + y$, $^1/_2 - z$. [c] Population 0.5.

In addition, while the averages of the La−O distances are very close in the two coordination polyhedra ($La(1)-O_{av}$ = 2.493(5) and $La(2)-O_{av}$ = 2.492(5) Å), there are differences in the La−N bond distances, the averaged values being La(1)−N = 2.794(6) and La(2)−N = 2.769(6) Å. This is in agreement with the observation made for the compound La-

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(14) Johnson, C. K. *ORTEP II*; Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

(15) Orpen, A. G.; Brammer, L.; Allen, F. H.; Kennard, O.; Watson, D. G.; Taylor, R. *J. Chem. Soc., Dalton Trans.* **1989**, S1−S83.

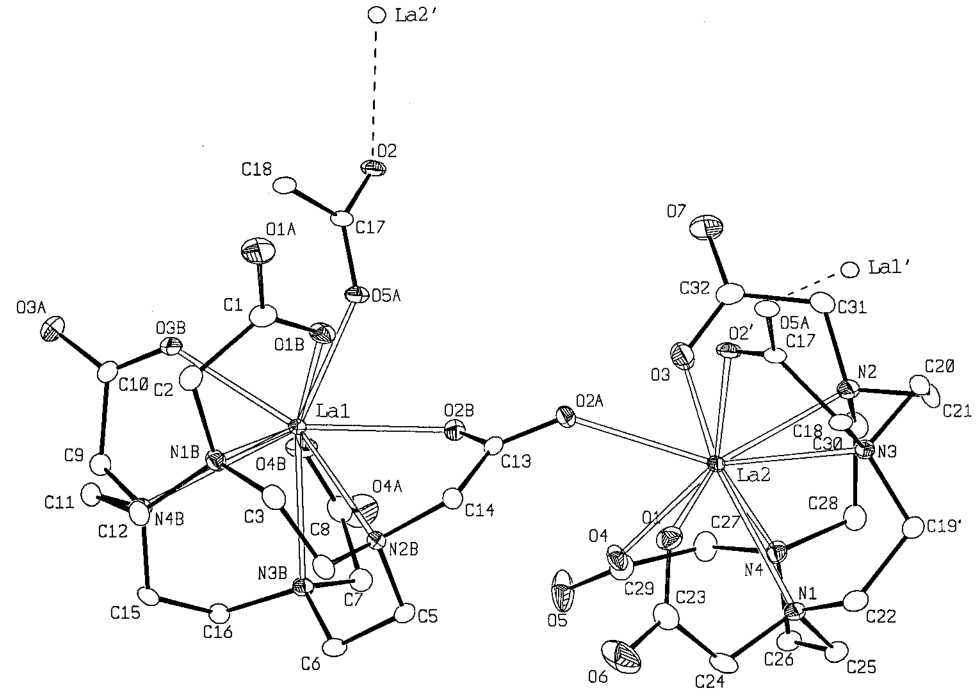

Figure 1. Solid state conformation of the [La(HDOTA)La(DOTA)] complex anion. (Ellipsoids are at 40% probability, and hydrogen atom positions are omitted for the sake of clarity).

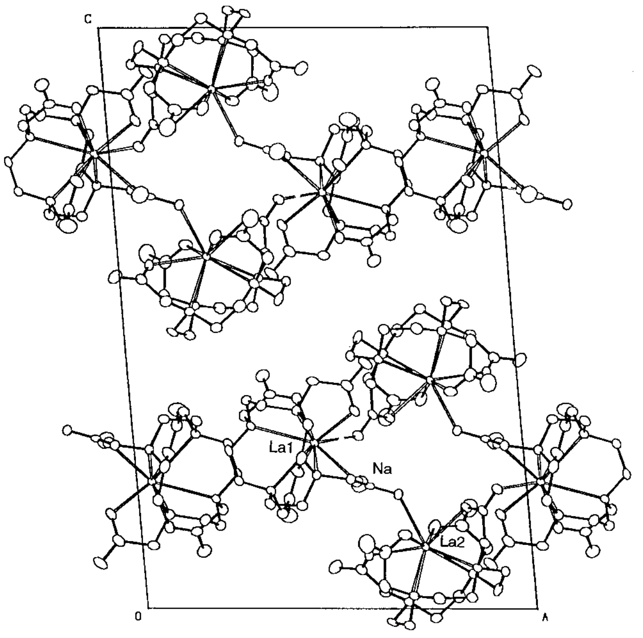

Figure 2. Unit cell content showing the formation of helices (Water positions are omitted for the sake of clarity).

$(H_2O)AH \cdot 3H_2O$ (H_4A = EDTA),[16] where the removal of the acid hydrogen produces the $[La(H_2O)_3A]^-$ [17] complex with a significant tightening of all chelating linkages. Here the La(2) anionic entity has a La−N average distance shorter than that in the La(1) entity and the La(2)−O(2)A distance of the capping position (2.537(5) Å), is shorter than the corresponding La(1)−O(5)A distance (2.568(5) Å), adding further support to the formulation Na[La(1)(HDOTA)La(2)(DOTA)].

Additional evidence for the 1:2 stoichiometry of Na:La was obtained by electron microscopy.

In summary, the most important result of this work is the demonstration that the *inverted square antiprismatic geometry* suggested for the **m** isomer from solution NMR data is actually found for the first time, in the solid state, in the title compound having a polymeric structure. It is worth noting that the **m** isomer is present in the X-ray crystal structures of LaDOTPAM (DOTPAM = 1,4,7,10-tetrakis(2-carbamoylethyl)-1,4,7,10-tetraazacyclododecane),[18] EuTHP (THP = 1,4,7,10-tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane),[19] GdDO$_3$MA (DO$_3$MA = (1*R*,4*R*,7*R*)-α,α′,α″-trimetyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid),[20] and YbDOTPBz$_4$ (DOTPBz$_4$ = 1,4,7,10-tetraazacyclododecanetetrakis(methylenebenzylphosphinic acid))[21] even though they were simply described as having distorted square antiprismatic geometries. The observation that the **m** and **M** structures can be unambiguously assigned to the isomers present in the solution of LnDOTA complexes puts this classification on a firm basis. The **m** and **M** structural types can be easily recognized in the ^1H NMR spectra of paramagnetic complexes as they are characterized by a chemical shift range narrower for the **m** isomer than for the **M** isomer. From a comparison of the proton spectra of a number of Ln^{3+} ions with DOTA-like ligands bearing substituents either on the acetate arms or on the macrocyclic ring, it is becoming apparent that the regular antiprismatic structure (**M**) is much less common than originally expected. The structural data for the complex reported here will facilitate theoretical investigations on the energy difference between the two isomeric structures.

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Supporting Information Available: Tables of crystallographic experimental details, non-hydrogen atomic coordinates and equivalent isotropic thermal parameters, bond lengths and angles, anisotropic thermal parameters, and hydrogen atomic coordinates (9 pages). Ordering information is given on any current masthead page.

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(16) Lind, M. D.; Lee, B.; Hoard, J. L. *J. Am. Chem. Soc.* **1965**, *87*, 1611−1612.

(17) Hoard, J. L.; Lee, B.; Lind, M. D. *J. Am. Chem. Soc.* **1965**, *87*, 1612−1613.

(18) Morrow, J. R.; Amin, S.; Lake, C. H.; Churchill, M. R. *Inorg. Chem.* **1993**, *32*, 4566−4572.

(19) Chin, K. O. A.; Morrow, J. R.; Lake, C. H.; Churchill, M. R. *Inorg. Chem.* **1994**, *33*, 656−664.

(20) Kang, S. I.; Ranganathan, R. S.; Emswiler, J. E.; Kumar, K.; Gougoutas, J. Z.; Malley, M. F.; Tweedle, M. F. *Inorg Chem.* **1993**, *32*, 2912−2918.

(21) Aime, S.; Batsanov, A. S.; Botta, M.; Howard, J. A. K.; Parker, D.; Senanayake, K.; Williams, G. *Inorg. Chem.* **1994**, *33*, 4696−4706.