the metal relaxation time was comparable to the magnitude of the splitting (partial collapse of the splitting) or that flexibility of the molecules in fluid solution caused uncertainty in the magnitude of the exchange interaction. Resolved spin–spin splitting was observed for the vanadyl complex of EDTA–NO, which is consistent with slow relaxation of the vanadyl unpaired electron.

Conclusions

Resolved spin–spin splitting was observed in the frozen-solution EPR spectra of the Cu(II), vanadyl, Fe(III), Mn(II), and Gd(III) complexes of EDTA–NO. The small differences between the spectra of the Cu(II) complexes of EDTA–CH$_2$–NO and EDTA–NO indicated that the spin–spin interaction in both complexes was primarily dipolar. The large differences in the spectra of the EDTA–NO and EDTA–CH$_2$–NO complexes of vanadyl, Ni(II), Fe(III), Mn(II), and Gd(III) indicated that there was a substantial exchange contribution to the interaction in the EDTA–NO complexes that was greatly attenuated in the EDTA–CH$_2$–NO complexes.

Acknowledgment. This work was supported in part by NIH Grant GM21156. S.S.E. thanks the NSF for a Visiting Professorship for Women, 1984. Professor Belford provided a copy of his fourth-order frequency shift subroutine and helpful comments concerning its use. Dr. Dragutan (Romania) and Professor Hideg (Hungary) provided useful information concerning the synthesis of compound IV. Professor Dervan provided a preprint of the experimental section of ref 6. EI mass spectra were obtained at the Midwest Center for Mass Spectrometry at the University of Nebraska, supported under the National Science Foundation Regional Instrumentation Facilities Program. FAB mass spectra were obtained at the Mass Spectrometry Research Resource at the University of Colorado Health Science Center, which receives partial support from NIH Division of Research Resources, Grant RR01152.

Registry No. I, 102587-64-4; II, 102587-65-5; III, 102587-66-6; IV, 56674-44-3; Et$_3$-EDTA-NO, 102587-67-7; Li$_3$-EDTA-NO, 102587-68-8; Et$_3$-EDTA-CH$_2$-NO, 102587-69-9; Li$_3$-EDTA-CH$_2$-NO, 102587-70-2; Cu(HEDTA-NO)(H$_2$O), 102538-91-0; Cu(HEDTA-CH$_2$-NO)(H$_2$O), 102538-92-1; VO(EDTA-NO)$^-$, 102538-93-2; VO-(EDTA-CH$_2$-NO)$^-$, 102538-94-3; Ni(HEDTA-NO)(H$_2$O), 102538-95-4; Ni(HEDTA-CH$_2$-NO)(H$_2$O), 102538-96-5; Cr(EDTA-NO)(H$_2$O), 102538-97-6; Cr(EDTA-CH$_2$-NO)(H$_2$O), 102538-98-7; Fe(EDTA-NO)(H$_2$O)$_2$, 102538-99-8; Fe(EDTA-CH$_2$-NO)(H$_2$O)$_2$, 102539-00-4; Mn(EDTA-NO)(H$_2$O)$_2$, 102539-01-5; Mn(EDTA-CH$_2$-NO)(H$_2$O)$_2$, 102539-02-6; Cu(H$_2$EDTA)(H$_2$O), 24778-06-1; Cu-(HEDTA)$^-$, 102539-03-7; VO(EDTA)$^{2-}$, 20648-98-0; Cr(HEDTA)(H$_2$O), 76582-41-7; Mn(EDTA)(H$_2$O)$^{2-}$, 38702-75-9; triethyl ethylenediaminetetraacetate, 90359-20-9; 4-amino-2,2,6,6-tetramethylpiperidinyl-1-oxy, 14691-88-4; 4-(hydroxymethyl)-2,2,6,6-tetramethylpiperidinyl-1-oxy, 61546-66-5.

Contribution from Analytical and Radiochemistry,
University of Liège, Sart Tilman (B6), B-4000 Liège, Belgium

Coordination of Lanthanides by Two Polyamino Polycarboxylic Macrocycles: Formation of Highly Stable Lanthanide Complexes

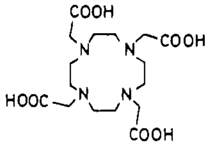
M. F. Loncin, J. F. Desreux,* and E. Merciny

Received December 6, 1985

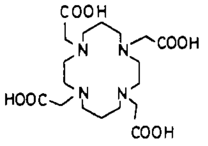
The formation constants of a few lanthanide complexes with DOTA (1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid) and TETA (1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetic acid) have been measured by potentiometric and competition methods. The ligand DOTA forms the most stable lanthanide chelates known so far (log K_{ML} = 28.2–29.2) while the stability of the TETA compounds at 80 °C (log K_{ML} = 14.5–16.5) is comparable to the stability of the EDTA complexes. A competition method with the oxalate anion as a probe had to be used for determining the formation constants of the DOTA lanthanide chelates because of the high stability of these compounds. The relative stability of the DOTA and TETA complexes in accounted for by steric factors with reference to known solution- and solid-state structures.

Introduction

The lanthanide complexes with polyaza polycarboxylic macrocycles such as 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid, DOTA (**1**), or 1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetic acid, TETA (**2**), display a host of unusual properties that are not exhibited by the complexes of similar but noncyclic ligands such as EDTA or DTPA. The DOTA and TETA lanthanide chelates are remarkably rigid, they are highly symmetric, and they adopt the same geometry in solution and in the solid state.[1-4] This lack of lability is most unusual in lanthanide chemistry[5] and has been assigned to the steric requirements of the 12- and 14-membered cycles. The results of recent efforts at determining reliable stability constants of a few lanthanide DOTA and TETA complexes are reported in this paper. Particularly worthy of note is the very high stability of the DOTA compounds that are by far the most stable lanthanide complexes known to date. Their high stability could turn out to be especially important in two very different areas of research where inert complexes are potentially useful, namely for the separation of the lanthanides as a class of metals and for the design of Gd(III) contrast agents for NMR imaging.[6]



1



2

Experimental Section

Materials and Standard Solutions. The syntheses of DOTA and TETA followed previously reported procedures.[1,4] Stock solutions of the ligands were analyzed by potentiometric titration with sodium hydroxide, and stock solutions of metal chlorides or perchlorates were standardized by EDTA titration. Carbonate-free NaOH solutions were used to adjust the pH of the solutions to the desired values.

Solutions of the DOTA and TETA lanthanide complexes were prepared either by direct dissolution of a stoichiometric quantity of a metal oxide into a standardized solution of the ligand at 80 °C or by slowly

---

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

(2) Spirlet, M. R.; Rebizant, J.; Desreux, J. F.; Loncin, M. F. *Inorg. Chem.* **1984**, *23*, 359–363.

(3) Spirlet, M. R.; Rebizant, J.; Loncin, M. F.; Desreux, J. F. *Inorg. Chem.* **1984**, *23*, 4278–4283.

(4) Desreux, J. F.; Loncin, M. F. *Inorg. Chem.* **1986**, *25*, 69–74.

(5) See for instance: Richardson, F. S. *Chem. Rev.* **1982**, *82*, 541–552. Greenwood, N. N.; Earnshaw, A. In *Chemistry of the Elements*; Pergamon: New York, 1984; p 1434.

(6) Weinman, H.-J.; Brasch, R. C.; Press, W.-R.; Wesbey, G. E. *Am. J. Roentgenol.* **1984**, *142*, 619–624.

0020-1669/86/1325-2646$01.50/0 © 1986 American Chemical Society

modifying the pH of stoichiometric mixtures of a lanthanide chloride and a ligand in hot water. Lanthanide DOTA solutions were also prepared by dissolving crystals that were obtained by letting ethanol slowly diffuse into concentrated aqueous solutions of the complexes. Elemental lanthanide, C, N, and H analyses of the crystals were in keeping with published data.[2,3]

Stability Constant Measurements. Potentiometric titrations and calculations of stability constants were performed as described elsewhere.[7,8] The titrations were carried out by generating hydroxyl ions with a constant-current coulometer and monitoring the hydrogen ion activity with a hydrogen electrode and a Ag/AgCl reference electrode. When a glass electrode was used, it was calibrated to measure hydrogen ion concentration by titrating solutions of hydrochloric acid of known concentration and of the appropriate ionic strength.

Competition reactions between lanthanide DOTA complexes and the oxalate anions were carried out at 20 °C. The ionic strength of all solutions was adjusted to 1.0 with sodium chloride. It should be noted that sodium perchlorate could not be used as the neutral salt because the lutetium DOTA chelate forms an insoluble mixed complex with the perchlorate ion in acidic media. Aliquots of stock solutions of a lanthanide DOTA complex and of sodium oxalate at the same pH were mixed and agitated in close vessels for 48 h. The reaction mixtures were initially 5–8 mM in lanthanide DOTA and 20–40 mM in sodium oxalate, the pH being adjusted between 2.0 and 3.5. In these conditions, from 15 to 35% of the lanthanide complex was converted into the insoluble sodium dioxalate. Each precipitate was isolated by centrifugation, washed with a small amount of water, and dissolved in a 6 N solution of sulfuric acid. The oxalate concentration was obtained by titration with a standardized solution of $KMnO_4$. Five measurements were performed for each lanthanide ion. The formation constants K_{ML} of the DOTA complexes were obtained by straightforward calculations taking into account the solubility products and the stability constants reported by Grenthe et al.[9] and the stepwise protonation constants of DOTA determined by Desreux et al.[8] The equations used for the computation of log K_{ML} and the experimental results are given in the supplementary material. The validity of the competition method was assessed by measuring the stability of EuDTPA; we obtained a stability constant (log K_{ML} = 22.3 ± 0.1) that is in close agreement with published values.[10] Moreover, preliminary potentiometric measurements indicated that the monoprotonated form of the lanthanide DOTA complexes can be neglected between pH 2.0 and 3.5. Furthermore, it was verified that the competition equilibrium with DOTA was reached in less than 2 days and that the insoluble oxalate complexes had the expected composition.[9] Finally, the exchange reaction between solid terbium oxalate and a solution of DOTA was also investigated under the experimental conditions mentioned above. The forward and backward equilibrium constants were in good agreement, but the partial dissolution of the oxalate salt required 3–4 weeks.

Results

In our early work[11] on the macrocyclic lanthanide polyaza polyacetates, it was mentioned that the DOTA complexes are exceedingly stable but no accurate values of the stability constants K_{ML} could be obtained with the automatic equipment currently used in our laboratory.[7] Indeed, the pH titration curves are very close to the neutralization curve of a strong acid and the complexation reaction of the heavy lanthanides is very slow below pH 7. Many experimental difficulties were also encountered in various attempts at the evaluation of the stability constants K_{ML} by indirect approaches. Working with metal or amalgam electrodes to determine the concentration of Hg(II), Pb(II), or Pd(II) ions placed in competition[12,13] with a lanthanide for the DOTA ligand did not prove useful because of the insufficient stability of the chelates of these ions or because of the formation of mixed complexes with chloride or perchlorate anions.[14] Moreover, Ni(II) did not appear as a more convenient probe[15] for competition experiments. A new and intense absorption band occurs at 540 nm when Ni(II) is complexed by DOTA, and the competition reaction is easily monitored by spectrometry. However, the formation of a partially insoluble lanthanide–nickel mixed complex in 0.5 M $NaClO_4$ at pH 5 prevents the reliable determination of the stability constants of the lanthanide chelates. In view of recent studies[16] of the DOTA complexes, it is suggested that this complex is polymeric.

Table I. Stability Constants K_{ML} of Lanthanide DOTA Complexes (20 °C, 1 M NaCl)[a]

Ln^{3+}	DOTA	EDTA[b]	DTPA[b]
Eu^{3+}	28.2 ± 0.2	17.32	22.39
Tb^{3+}	28.6 ± 0.1	17.92	22.71
Lu^{3+}	29.2 ± 0.2	19.80	22.40

[a] K_{ML} = [ML]/[L][M] where M is a lanthanide ion and L is a ligand. [b] Taken from ref 10.

Table II. Stability Constants K_{ML} of Lanthanide TETA Complexes and K_{HML} of Their Monoprotonated Forms (80 °C, 1 M NaCl)[a]

Ln^{3+}	log K_{ML}	log K_{HML}	Ln^{3+}	log K_{ML}	log K_{HML}
Nd^{3+}	14.51 ± 0.06	4.56 ± 0.17	Dy^{3+}	16.04 ± 0.02	3.10 ± 0.09
Sm^{3+}	14.97 ± 0.03	3.90 ± 0.13	Er^{3+}	16.49 ± 0.02	3.50 ± 0.10
Eu^{3+}	15.46 ± 0.02	3.77 ± 0.09	Yb^{3+}	16.55 ± 0.02	2.44 ± 0.20
Gd^{3+}	15.75 ± 0.04	3.75 ± 0.13			

[a] K_{ML} = [ML]/[M][L] and K_{HML} = [HML]/[H^+][ML] where M is the lanthanide ion and L the ligand.

Reliable measurements of the stability constants of the lanthanide DOTA complexes were finally carried out at 25 °C by a competition method using an auxiliary ligand rather than an auxiliary metal ion. The very high stability of the DOTA complexes strictly limits the choice of an appropriate ligand, and the oxalate ion was selected because it forms sparingly lanthanide bis complexes. The competition experiments were conducted for three metal ions only, namely Eu(III), Tb(III), and Lu(III). Indeed, Grenthe et al.[9] have restricted their solubility studies to the case of four lanthanides, three of which form only one solid phase in the presence of an excess of sodium oxalate. Accurate values of the solubility products and of the stability constants of the oxalate complexes have been reported by these authors, and to our knowledge, no other reliable values have been published.[17] As shown in Table I, the lanthanide DOTA complexes are some 10 orders of magnitude more stable than the corresponding EDTA complexes and are approximately 6 orders of magnitude more stable than the DTPA complexes. The latter were considered so far as the most stable lanthanide complexes known. We want to stress here that solubility measurements always lack the precision of potentiometric determinations but that the high stability of the lanthanide DOTA chelates appears to preclude the possibility of studying their formation by any other method. The good agreement between the stability constant of GdDOTA that was determined previously[11] and the data presented in Table I is probably fortuitous.

Determining the stability constants of the TETA complexes proved to be easier because these compounds are less stable and because the kinetics of complexation is sufficiently fast at 80 °C to allow accurate pH titrations. The data collected for a few lanthanides are listed in Table II. The La(III) complex did not lend itself to study because it forms a sparingly soluble protonated species.

Discussion

As shown in Tables I and II, both DOTA and TETA are less selective than EDTA. The stability of their complexes increases with decreasing crystal radius of the metal ions. These ligands thus behave as classical noncyclic complexing agents and there

---

(7) Merciny, E.; Gatez, J. M.; Swennen, L.; Duyckaerts, G. *Anal. Chim. Acta* **1975**, *78*, 159–169. zur Nedden, P.; Merciny, E.; Duyckaerts, G. *Anal. Chim. Acta* **1973**, *64*, 197–207.

(8) Desreux, J. F.; Merciny, E.; Loncin, M. F. *Inorg. Chem.* **1981**, *20*, 987–991.

(9) Grenthe, I.; Gardhammar, G.; Rundcrantz, E. *Acta Chem. Scand.* **1969**, *23*, 93–108.

(10) Martell, A. E.; Smith, R. M. In *Critical Stability Constants*; Plenum: New York, 1974; Vol. 1 and references cited therein.

(11) Desreux, J. F. *Bull. Cl. Sci. Acad. Belg.* **1978**, *64*, 814–839.

(12) Schmid, R. W.; Reilley, C. N. *J. Am. Chem. Soc.* **1956**, *78*, 5513–5518.

(13) Gritmon, T. F.; Goedken, M. P.; Choppin, G. R. *J. Inorg. Nucl. Chem.* **1977**, *39*, 2021–2023.

(14) Kragten, J.; Decnop-Weever, L. G. *Talanta* **1983**, *30*, 449–453.

(15) Delgado, R.; Frausto da Silva, J. J. R. *Talanta* **1982**, *29*, 815–822.

(16) Riesen, A.; Zehnder, M.; Kaden, T. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1336–1338.

(17) Birnbaum, E. R. In *Gmelin Handbook of Inorganic Chemistry*, 8th ed.; Springer Verlag: Berlin, 1984; Vol. D5, p 136.

is no "macrocyclic effect" comparable to the one reported for the crown ethers.[18] The internal cavities of DOTA and TETA are indeed too small to accommodate a lanthanide ion,[2,3] and the tetraaza rings simply act as frames to constrain the nitrogen atoms and the carboxylic groups into a nearly spherical arrangement.

The remarkable stability of the DOTA chelates is assigned at least partially to the favorable conformation that these compounds adopt both in the solid state and in solution. Previous studies[1,2] have shown that in crystallized NaEuDOTA, the eight donor atoms of the ligand are located at the eight vertices of a square antiprism. The repulsion energy[19] of this geometry is smaller than for any other eight-coordinate polyhedron. Furthermore, the tetraaza cycle of DOTA spans one square face of the complex and adopts its most stable and most rigid conformation, the quadrangular (3.3.3.3) structure[20] in which all CH_2 moieties are fully staggered and all nitrogen atom are pointing toward the same side of the ring. The free ligand itself probably adopts the same conformation.[20]

The stability constants of the DOTA and TETA complexes were not obtained at the same temperature, but it is obvious from a comparison of the data listed in Tables I and II that the former are considerably more stable than the latter. Several factors could account for this difference. The propylenediamine groups of the TETA cycle form six-membered rings with the metal ions. These rings are known to be sterically more crowded than the five-membered rings, a phenomenon that results in a decrease in stability as indicated by a comparison between the K_{ML} values of EuEDTA (log K_{ML} = 17.32) and of europium(III) 1,3-propanediamine-*N,N′,N″,N‴*-tetraacetate (log K_{ML} = 13.62).[17] Furthermore, in the solid state as in solution,[3,4] the TETA lanthanide chelates adopt a dodecahedral geometry. This geometry is known to exhibit a higher repulsion energy coefficient than the square antiprism, the difference being of chemical significance according to Kepert.[13]

We are now actively pursuing research that takes advantage of the high stability and the kinetic inertness of the lanthanide DOTA derivatives.

Acknowledgment. J.F.D. is grateful for support by the Fonds National de la Recherche Scientifique of Belgium. J.F.D. is Chercheur Qualifié at this institution.

Supplementary Material Available: Experimental conditions for the DOTA–oxalate competition experiments and equations plus a table of data used for calculation of K_{ML} (3 pages). Ordering information is given on any current masthead page.

---

[18] Massaux, J.; Desreux, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 2967–2972.

[19] Kepert, D. L. In *Inorganic Chemistry Concepts*; Springer Verlag: Heidelberg, 1982; Vol. 6, pp 5, 152.

[20] Dale, J. *Isr. J. Chem.* **1980**, *20*, 3–11 and references cited theirin.

Contribution from the Department of Chemistry,
The University of Alberta, Edmonton, Alberta, Canada T6G 2G2

Transformation of a Terminal to a Bridging Carbonyl Ligand Accompanied by Ir–Ir Bond Cleavage: An Example of Transmission of Electronic Effects from One Metal Center to Another

Martin Cowie,* Giuseppe Vasapollo,† Bruce R. Sutherland, and Jimmie P. Ennett

Received December 20, 1985

The alkyne-bridged complex $[Ir_2Cl_2(CO)(\mu\text{-DMA})(DPM)_2]$ (DMA = dimethyl acetylenedicarboxylate, DPM = bis(diphenylphosphino)methane) reacts with 1 equiv of CO, PMe_3, $P(OMe)_3$, or NCMe to give one of two types of species. Reaction with CO yields the complex $[Ir_2Cl_2(CO)_2(\mu\text{-DMA})(DPM)_2]$, in which both carbonyl groups are terminally bound, one to each metal. However, reaction with L = PMe_3, $P(OMe)_3$, or NCMe yields the adducts $[Ir_2Cl_2L(\mu\text{-CO})(\mu\text{-DMA})(DPM)_2]$, in which the carbonyl group bridges the metals with no accompanying Ir–Ir bond. A rationalization of the different structures observed with the different ligands is presented. The structure of the acetonitrile adduct was determined by X-ray techniques. This species crystallizes in space group $P2_1/c$ with a = 13.060 (5) Å, b = 15.742 (2) Å, c = 30.756 (5) Å, β = 92.75 (2)°, V = 6315.9 Å^3, and Z = 4. On the basis of 5807 unique observations and 418 parameters varied, the structure converged at R = 0.051 and R_w = 0.073. The long metal–metal separation of 3.4580 (7) Å results in a geometry at the bridging carbonyl ligand that is reminiscent of sp^2 hybridization (Ir–C(O)–Ir angle of 119.4 (6)°).

Introduction

Complexes containing two or more metal centers can, in principle, give rise to reactivity patterns that differ from those displayed by single-metal-containing complexes.[1] Two fundamental characteristics that are unique to multicenter complexes, and that may therefore be important in determining reactivity differences from the mononuclear species, involve the formation of bridged-ligand bonding modes and the formation and breaking of metal–metal bonds. With the unbiquitous carbonyl ligand it seems that these two aspects are intimately connected in much of its chemistry, so that in most complexes containing bridging carbonyl groups, accompanying metal–metal bonds are also present.[2] It is only recently that examples in which bridging carbonyls *not* accompanied by metal–metal bonds have been characterized.[3-7] Although it seems clear that the presence of additional bridging groups stabilizing these species is important, it is not altogether clear what other factors may be important.

We had previously observed that the complexes $[Rh_2X_2(\mu\text{-CO})(\mu\text{-RC}_2R)(DPM)_2]$ (**1**: X = Cl, I; R = CF_3, CO_2Me; DPM = $Ph_2PCH_2PPh_2$)[5] had the unusual ketonic[8] carbonyl binding mode (structure A) but that the analogous complexes $[Ir_2Cl_2(CO)(\mu\text{-RC}_2R)(DPM)_2]$[9] (**2**) contained normal terminal CO groups (structure B). This difference is consistent with the known preference of carbonyl groups to bridge metals higher up in a triad and seems to be related, at least in part, to the increasing size of

---

† Present address: Centro di Studio sulle Metodologie Innovative di Sintesi Organiche del CNR, Dipartimento di Chimica, Università di Bari, 70126 Bari, Italy.

[1] Muetterties, E. L.; Rhodin, T. N.; Band, E.; Brucker, C.; Pretzer, W. R. *Chem. Rev.* **1979**, *79*, 91.

[2] Cotton, F. A.; Hunter, D. L. *Inorg. Chem.* **1974**, *13*, 2044.

[3] (a) Cotton, R.; McCormick, M. J.; Pannan, C. D. *J. Chem. Soc., Chem. Commun.* **1977**, 823. (b) Colton, R.; McCormick, M. J.; Pannan, C. D. *Aust. J. Chem.* **1978**, *31*, 1425.

[4] Brown, M. P.; Keith, A. N.; Manojlovic-Muir, Lj.; Muir, K. W.; Puddephatt, R. J.; Seddon, K. R. *Inorg. Chim. Acta* **1979**, *34*, L223.

[5] (a) Cowie, M.; Southern, T. G. *J. Organomet. Chem.* **1980**, *193*, C46. (b) Cowie, M.; Southern, T. G. *Inorg. Chem.* **1982**, *21*, 246.

[6] Kullberg, M. L., Kubiak, C. P. *Organometallics* **1984**, *3*, 632.

[7] Mague, J. T. *Inorg. Chem.* **1983**, *22*, 45.

[8] We refer to ketonic carbonyls as bridging carbonyl ligands in which there is no accompanying metal–metal bond.

[9] Sutherland, B. R.; Cowie, M. *Organometallics* **1984**, *3*, 1869.