energies. We note that a pronounced "alternation effect" is apparent in that the differences in ionization energies between P_4O_6 and As_4O_6 are much less pronounced than those between As_4O_6 and Sb_4O_6. Similar effects are found in PE spectra of the group 5 hydrides[23] and halides.[24,25]

We turn attention now to discussion of fine structure apparent in the first band in PE spectra of As_4O_6 and Sb_4O_6. In their study of the arsenic compound Cannington and Whitfield[26] assumed that the first band represented three distinct ionization processes involving arsenic and oxygen lone pairs, although they failed to venture an assignment in terms of symmetry labels appropriate to tetrahedral systems. However there is no marked change in the profile of this band on switching from He I to He II excitation, as would be expected if it were associated with molecular subshells having very different ionization cross-section profiles. We prefer the alternative view that the first band relates uniquely to the t_2 lone-pair combination. Consistent with this idea, there is a marked decrease in the intensity of the first band in the spectrum relative to the third band (the latter feature being associated with an O 2p lone-pair combination) on switching from He I to He II excitation.

The fine structure in the spectra could in principle arise from either spin–orbit coupling or vibronic (Jahn–Teller) distortion in the molecular ion or from both. The absence of fine structure in the spectrum of P_4O_6 certainly invites the speculation that spin–orbit coupling is of major importance in mediating appearance of the fine structure. However, spin–orbit coupling can assume significant proportions only if there is substantial mixing between the t_2 lone-pair combination and a t_2 combination containing a significant contribution from As p orbitals directed perpendicular to the lone pairs. Our calculations indicate that mixing of this sort is not of major importance and we therefore come to the alternative view that the structure is due largely to Jahn–Teller distortion. Vibronic structure of this sort is quite common in PE spectra of high-symmetry cage systems including P_4,[12,13] adamantane,[27–29] and bullvalene.[30]

Concluding Remarks. Our combined experimental and theoretical investigation confirms the conventional description of the bonding in the group 5 oxides. In particular it appears that cross-cage interactions are of minor importance for the molecules studied in the present work. This contrasts with the situation found in N_4S_4[31] where cross-cage bonding is significant. Investigations of the electronic structure of other group 5 chalcogenides are already at hand, a particular aim of the work being to explore the limitations of "classical" descriptions of bonding in cage molecules. These matters will be the subject of future publications.

Registry No. P_4O_6, 10248-58-5; As_4O_6, 36533-93-4; Sb_4O_6, 72926-13-7; P_4O_{10}, 16752-60-6; P_4, 12185-10-3.

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Contribution from the Department of Analytical Chemistry and Radiochemistry, University of Liège, Sart Tilman, Liège, B-4000 Belgium

Nuclear Magnetic Resonance Spectroscopy of Lanthanide Complexes with a Tetraacetic Tetraaza Macrocycle. Unusual Conformation Properties[1]

J. F. DESREUX

The ^1H and ^{13}C NMR spectra of diamagnetic and paramagnetic lanthanide complexes with 1,4,7,10-tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetraacetic acid (DOTA) are analyzed in terms of the stereodynamic behavior of the macrocycle and of the lability of the acetate groups. Below room temperature, the ethylenic groups are rigid on the NMR time scale. Rapid ring inversion is achieved at elevated temperature, the energy barrier being very high. The following kinetic parameters are obtained by line-shape analysis in the case of LaDOTA: $\Delta G^*_{300} = 60.7 \pm 1.2$ kJ mol^{-1}, $\Delta H^* = 59.4 \pm 0.8$ kJ mol^{-1}, and $\Delta S^* = -4.6 \pm 3.3$ J K^{-1} mol^{-1}. Similar energy barriers are measured for paramagnetic complexes. All the ethylenic groups of the macrocycle adopt the same conformation at low temperatures. This spatial arrangement leads to a new type of temperature-dependent asymmetry which appears in the NMR spectra of the labile acetate groups. The structure of the Eu(III), Pr(III), and Yb(III) complexes with DOTA is deduced from the relative magnitude of the large paramagnetic shifts exhibited by these compounds. The nitrogen–lanthanide distance is approximately 2.85 Å, and the metal is located under the macrocycle.

Introduction

Current interest in the complexing properties of macrocycles[2] has stimulated the synthesis and study of a large number of new cyclic polyoxa and polyaza ligands. A variety of macrocycles of different cavity size and rigidity is now available to the coordination chemist, but most of these compounds still suffer from the absence of ionizable functions, a deficiency which is not presented by more classical ligands. However, a macrocycle featuring ionizable functions should combine two decided advantages: a selectivity gained from the steric requirements of the internal cavity and a pH-sensitive complexation. So far, only a few members of this new class of cyclic ligands are known. Recent reports describe the preparation and properties of macrocycles containing one or

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several β-diketone functions[3] or of polyaza cycles substituted with diphenols[4] or acetate groups.[5,6] Among these ligands, the new complexone 1,4,7,10-tetraazacyclododecane-N,N',-N'',N'''-tetraacetic acid (**1**) should be singled out for special

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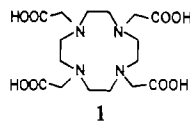
note because Stetter and Frank[5] reported that it forms the most stable Ca^{2+} complex known to date. For the sake of brevity, this chelating agent will be designated as DOTA, in line with the usual nomenclature of the polyamino polyacetic acids.

Lanthanide and alkaline-earth or alkali ions are prone to form similar electrostatic nondirectional bonds. It is thus not surprising that several lanthanide–macrocycle complexes have been recently described.[7] In view of the similarity between the ionic radius of calcium and of the trivalent rare earths, it was anticipated that the spiderlike DOTA would be an excellent sequestering agent of the rare earths. In agreement with this assumption, a stability constant of about 10^{28} was measured[8] for the formation of GdDOTA at room temperature. DOTA is thus the most powerful chelating agent of the lanthanides reported so far, the stability constant being some 10 orders of magnitude larger than the corresponding constant for EDTA. However, DOTA proved fairly difficult to use because of the exceedingly slow kinetics of formation of its complexes. The research work proposed herein indicated that this slow kinetics could be attributed at least partially to the unusual stereodynamic behavior of the lanthanide–DOTA complexes.

The properties of the DOTA complexes in aqueous solution are investigated in the present work by dynamic NMR, a technique the potentialities of which have been largely demonstrated in the analysis of exchange processes.[9] Moreover, the approximate structure of the DOTA complexes is deduced by taking advantage of the large paramagnetic shifts induced by the lanthanide ions. This procedure has been widely used not only with shift reagents[10] but also for the structural analysis of lanthanide chelates.[11,12]

Experimental Section

Chemicals and Solutions. 1,4,7,10-Tetraazacyclododecane tetrakis(hydrochloride) was synthesized according to Richman and Atkins.[13] For preparation of the ligand DOTA, the tetrakis(hydrochloride) (34.5 g, 0.11 mol) dissolved in 25 mL of ice-cooled water was neutralized by a stoichiometric amount of NaOH (4.34 g in 10 mL of water). Another solution was prepared of chloroacetic acid (46.1 g, 0.49 mol) in water (50 mL) to which was slowly added NaOH (19.50 g, 0.49 mol in 50 mL of water) while the temperature was maintained below 5 °C. The two solutions were mixed together, and the temperature

was elevated to 80 °C. A concentrated solution of NaOH (19.5 g, 0.49 mol in 6 mL of water) was then added dropwise over 24 h while the pH was monitored continuously by means of a combined pH electrode (Ingold). For most of the reaction time, the pH was maintained between 9 and 10. After the reaction mixture was cooled, it was acidified to pH 2.5, whereafter an important precipitation occurred. The resulting suspension was then loaded on a Dowex 50W-X4 cation-exchange resin in the H^+ form and eluted with water followed by 0.5 M NH_3. The purified tetraacid was isolated by addition of ethanol after concentration of the solution to near dryness.[8,14] After the compound was dried under vacuum, the purity was checked by pH titration; total yield 82%.

The ligand DOTA partially deuterated in the acetate position (DOTA-d_8) was synthesized as described above from the tetraaza cycle and from chloroacetic-d_2 acid. The latter was obtained from chloroacetonitrile which was first equilibrated with D_2O at 100 °C in the presence of a small amount of Na_2CO_3. The reaction mixture was hydrolyzed by concentrated HCl at 100 °C during 4 h. Water was then stripped off on a rotary evaporator, and chloroacetic-d_2 acid was distilled under vacuum in a Kugelrohr distillation apparatus. DOTA-d_8 was found by NMR to be 70% deuterated in the acetate position.

Solutions (0.1 M) for NMR studies were prepared in water with a 1:1 ligand-to-metal ratio or with a slight excess of ligand by mixing appropriate aliquots from stock solutions of lanthanide chlorides and DOTA. Each mixture was then heated to 80 °C, and the pH was adjusted between 10 and 11 with NaOH. Failure to perform the complexation at high temperature leads to the precipitation of lanthanide hydroxides because of the very slow kinetics of complexation. Each mixture was taken to dryness on a rotatory evaporator and redissolved in enough D_2O to yield a solution 0.1 M in lanthanide. The process was repeated two times to decrease the water NMR peak. Dioxane and *tert*-butyl alcohol were used simultaneously as internal references.

Spectral Measurements. ^1H and proton-decoupled Fourier transform ^{13}C NMR spectra were determined on a Bruker HFX-90 with a deuterium lock respectively at 90 and 22.6 MHz. All paramagnetic shifts were referenced to the corresponding resonances recorded for the diamagnetic complex LaDOTA. The variable-temperature accessories were calibrated either with an ethylene glycol sample or with a copper–constantan thermocouple which was immersed directly in a pure water sample. It is estimated that the quoted temperatures are accurate to ± 1 °C. Before recording of the spectra, all NMR tubes were allowed to equilibrate in the probe for 15 min.

Rate constants were determined by visual comparison of experimental spectra with theoretical spectra calculated for a two-site exchange mechanism with use of a total line-shape equation as described by Binsch.[15] When ΔG^* was deduced from the coalescence of proton peaks recorded for paramagnetic complexes, the shifts at the coalescence temperature T_c were obtained from extrapolation of plots of δ vs. temperature using data collected below and above T_c. Calculations of the geometric factors of the pseudocontact equation[10] were performed with the program CONF, details of which have been reported elsewhere.[11]

In the discussion which follows, negative shifts are downfield shifts while positive shifts are upfield shifts.

Results and Discussion

Because of their complexities, the spectral features of the peaks attributed to the ethylenic and acetate groups will be addressed separately.

NMR Peaks of the Tetraaza Cycle—Diamagnetic Complexes. The proton spectra of the diamagnetic complexes LaDOTA and LuDOTA recorded at various temperatures are reproduced in Figure 1. For both complexes, two broad peaks are observed around ordinary temperature. Cooling down the NMR samples yields a large number of poorly resolved peaks. Their assignment was carried out by comparison with the spectra recorded for the corresponding complexes with DOTA-d_8. The acetate protons exhibit an AB quartet while the resonances of the ethylenic protons occur as a complicated

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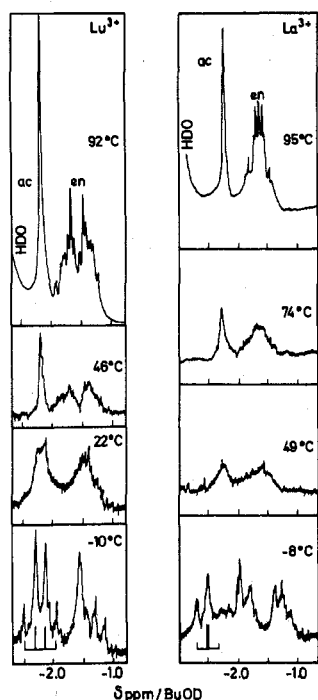(15) G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

Figure 1. 90-MHz ^{1}H NMR spectra of LaDOTA and LuDOTA at various temperatures. The symbols en and ac denote throughout the ethylenic and acetate peaks.

splitting pattern which cannot be interpreted because of peak overlappings. With an increase in the temperature, the acetate protons coalesce into a sharp single peak and a symmetrical AA′BB′ splitting pattern is observed for the ethylenic groups. As illustrated in Figure 2, two ethylenic peaks appear at low temperatures in the ^{13}C spectra of LaDOTA. These peaks coalesce into a single line at elevated temperature. LuDOTA presents the same spectral characteristics, but the separation of the ethylenic doublet is much smaller.

Both the ^{1}H and ^{13}C spectral features are taken as evidence for the rigidity of the tetraaza cycle. Indeed, the 12-membered macrocycle is too small to accommodate a lanthanide ion in its internal cavity (radius 0.56 Å[16]). The macrocycle is thus assumed to be situated above the metallic ion as illustrated schematically in **2** and **3**. In conformation **2** or **3**, all the

2   **3**
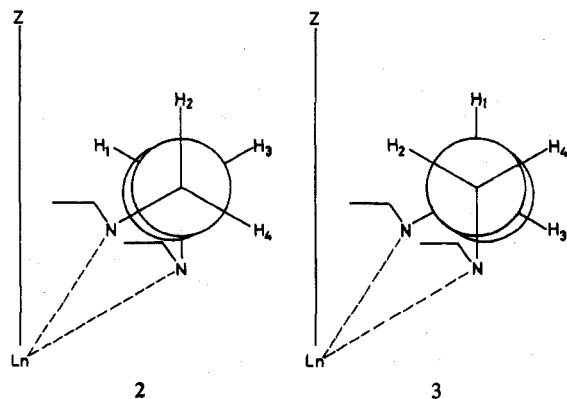
carbon and hydrogen nuclei are inequivalent relative to the lanthanide. The rigidity acquired by the ethylenic groups near 0 °C thus leads to a doublet in the ^{13}C spectra and an ABCD pattern in the ^{1}H spectra. The poor resolution achieved at low temperatures precludes even a qualitative analysis of this
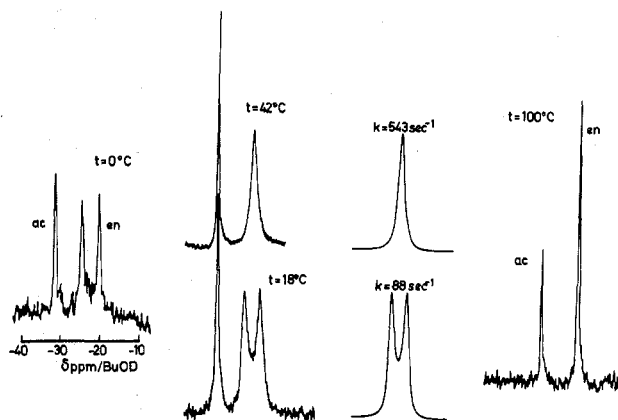

Figure 2. 22.6-MHz ^{13}C spectra of the ethylenic and CH$_2$ acetate carbons of LaDOTA at various temperatures compared with spectra calculated by line-shape analysis.
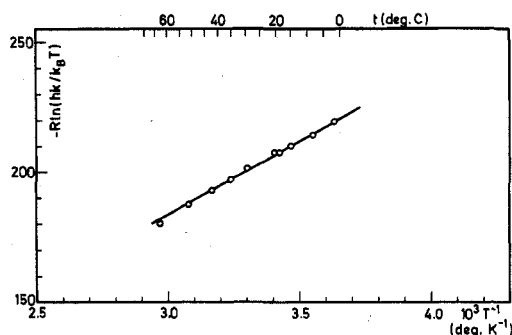

Figure 3. Eyring plot for ethylenediamine ring inversion in LaDOTA.

Table I. Kinetic Data for Ethylenediamine Group Interconversion in LaDOTA[a]

$k_5{}^\circ{}_C$, s^{-1}	23	$\Delta S^\ddagger$, J K^{-1} mol^{-1}	-4.6 ± 3.3
$k_{80}{}^\circ{}_C$, s^{-1}	6.8×10^3	E_a, kJ mol^{-1}	61.9 ± 1.2
$\Delta G^\ddagger$, kJ mol^{-1} [b]	60.7 ± 1.2	log A^b	13.0 ± 0.4
$\Delta H^\ddagger$, kJ mol^{-1}	59.4 ± 0.8		

[a] 0.1 M solution in D$_2$O at pH 11. All errors are random errors estimated at the 95% level. [b] At 25 °C.

splitting pattern. On the other hand, the interconversion between the two staggered conformations **2** and **3** brings about the replacement of the axial proton H$_1$ by the equatorial proton H$_2$ and vice versa and, also, the replacement of the axial proton H$_4$ by the equatorial proton H$_3$ and vice versa. At high temperatures, two proton peaks with an AA′BB′ splitting pattern are thus expected for the H$_1$–H$_2$ and the H$_3$–H$_4$ pairs in agreement with the observed spectra. A parallel NMR investigation[17] with the related tetraoxa ligand 12-crown-4 indicated that this macrocycle forms sandwich-type lanthanide complexes which also exhibit two ethylenic proton peaks. In this case however, the conformational interchange is fast on the NMR time frame at room temperature. The data reported here for small macrocycles differ from those of nickel mono-(ethylenediamine) complexes[10] for which one single ethylenic peak is observed.

As indicated in Figure 2, the barrier to interconversion of the ethylenediamine groups can be obtained by a band-shape analysis of the ^{13}C peaks exhibited by LaDOTA. The relaxation time T_2 in the absence of exchange was calculated from the bandwidth at half-height of the acetate peak. No exchange effect occurs for this peak, the bandwidth of which was found to be independent of temperature within the limits of the errors. The rate constant k at temperatures between 0 and 60 °C was

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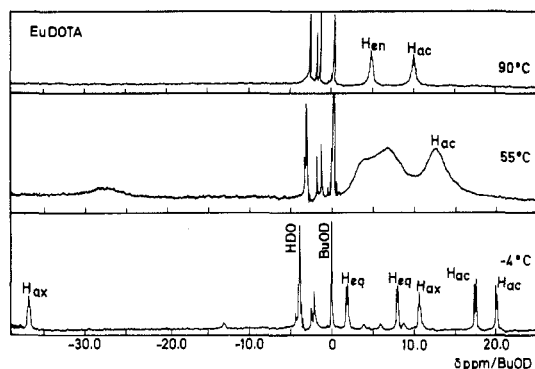
Figure 4. 90-MHz spectra of EuDOTA at various temperatures. The symbols ax and eq denote throughout the axial and equatorial ethylenic peaks.

deduced from a fit between the experimental spectra and spectra calculated for a two-site exchange. The activation parameters were derived from the Eyring plot reproduced in Figure 3. The equation of the straight line is

$$-R \ln (kh/k_B T) = (\Delta H^{\ddagger}/T) - \Delta S^{\ddagger} \qquad (1)$$

where k_B denotes the Boltzmann constant and where the other symbols have their usual meaning. The transmission factor was set equal to unity. The activation parameters together with the Arrhenius parameters are listed in Table I. The barrier to ring inversion is the highest reported to data for a lanthanide complex, thereby implying that, once formed, the DOTA cage is very tight with little flexibility. The literature abounds with examples of lanthanide complexes involved in fast intramolecular rearrangements due to the nondirectional nature of their coordination bonds. A rare case of a slow rearrangement of a lanthanide chelate was recently reported by Evans and de Villardi.[18] By cooling down well below 0 °C solutions of adducts between a shift reagent, Pr(fod)$_3$, and substituted diamines such as N,N,N',N'-tetraethylenediamine, these authors were able to "freeze" the ring inversion. The barrier $\Delta G^{\ddagger}$ reported here for LaDOTA is around 12 kJ mol^{-1} higher than the corresponding values given for various Pr(fod)$_3$ adducts. This barrier is also significantly higher than activation barriers ($\Delta G^{\ddagger}_{300} = 40.6$ kJ mol^{-1}) measured[19] for transition-metal complexes with a substituted diamine and is very near to the activation energy of racemization[20] of NiEDTA^{2-}. The entropy of activation $\Delta S^{\ddagger}$ is small, in keeping with earlier findings on simple unimolecular processes such as conformational interconversions or internal rotations.[9,19]

NMR Peaks of the Tetraaza Cycle—Paramagnetic Complexes. Further confirmation of the rigidity of the DOTA complexes is provided by the analysis of the NMR spectra of paramagnetic species. Representative proton spectra of Eu-DOTA recorded at various temperatures are shown in Figure 4. The slight excess of ligand which gives peaks around -2.5 ppm does not exchange with the complex at any temperature and has no influence on the paramagnetic shifts. At low temperatures, the spectrum of EuDOTA consists of a total of six peaks of equal intensity: four ethylenic and two acetate protons. Two ethylenic peaks also occur in the ^{13}C spectra. The proton peaks are readily assigned with the help of the partially deuterated DOTA but also because of the spectrum exhibiting various coupling patterns. The studies of ethylenediamine complexes of transition-metal ions[21] indicate that
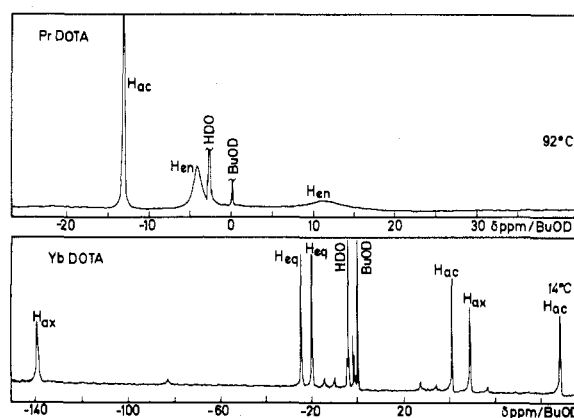

Figure 5. 90-MHz spectra of YbDOTA at 14 °C (slow-exchange limit, no interconversion of the ethylenic groups) and of PrDOTA at 92 °C (fast-exchange limit).

staggered ethylenic groups have large trans and geminal coupling constants but small gauche coupling constants. The two triplets which appear in the spectrum of EuDOTA are thus attributed to the axial protons (ax) because their splitting pattern arises from two large coupling constants. The equatorial proptons (eq) constitute two doublets ($J = 13$ Hz) which occur at $+2$ and $+8$ ppm, their general appearance resulting from a large geminal coupling and an unresolved small gauche coupling constant. As the temperature is increased, the proton peaks start to broaden, and at 90 °C (see Figure 4), the two acetate protons have merged into a singlet. The fast-exchange limit is also reached for the axial proton at high fields and one of the equatorial protons. By contrast, coalescence of the axial proton which occurs at low fields is not yet fully achieved at 100 °C because of the very large shift exhibited by this nucleus. From the coalescence temperature of one of the H_{eq}–H_{ax} pairs, the barrier to ring inversion $\Delta G^{\ddagger}_{330}$ is estimated at 61.9 kJ mol^{-1} and compares well with the corresponding value deduced for LaDOTA. The analysis of the spectral features exhibited by EuDOTA thus fully supports the previously forwarded assumption of a high rigidity of the tetraaza cycle at low temperatures.

The intramolecular rearrangement of the ethylenic groups is also noted for other paramagnetic DOTA complexes. The NMR spectrum of YbDOTA at low temperatures is depicted in Figure 5. Noteworthy are the remarkably large paramagnetic shifts toward both high and low fields. The peaks were assigned by analogy with the spectra of YbDOTA-d_8 and of EuDOTA. The spectra of YbDOTA do not lend themselves easily to a dynamic analysis because coalescence is not achieved below 100 °C in the case of most protons or because there is excessive broadness of the peaks at high temperatures. On the contrary, as illustrated in Figure 5, the fast-exchange limit is achieved at high temperatures for all proton peaks exhibited by PrDOTA. As anticipated, the ethylenic protons appear as two singlets respectively for the eq–ax proton pairs H_1–H_2 and H_3–H_4 (see structures **2** and **3**). The barrier to interconversion $\Delta G^{\ddagger}_{334}$ is 60.7 kJ mol^{-1}. Errors on the values of conformational barriers deduced from coalescence temperatures can be very large.[15] However, in the limits of these errors, the consistency of the $\Delta G^{\ddagger}$ values obtained with LaD-OTA, PrDOTA, and EuDOTA suggests that the barrier to interconversion of the ethylenic groups is insensitive to the size of the encapsulated ion.

NMR Peaks of the Acetate Groups. As shown in Figure 1, the proton peaks attributed to the acetate groups of the diamagnetic complexes LaDOTA and LuDOTA appear at low

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Table II. Experimental Proton NMR Shifts and Shift Ratios for Some Lanthanide–DOTA Complexes

Ln-(III)	δ-$(H_{ax1})^{a,b}$	shift ratio^c					
		H_{ax1}	H_{ax2}	H_{eq1}	H_{eq2}	H_{ac1}	H_{ac2}
Pr	+31.6	+10.0	−3.74	+0.42	+1.31	−3.06	−6.06
Eu	−35.3	+10.0	−3.48	−1.01	−2.75	−5.58	−6.29
Yb	−144.2	+10.0	−3.66	+1.33	+1.68	−3.13	−6.59
calcd^d		+10.0	−3.75	+2.04	+2.58	e	e

^{a} Paramagnetic shifts in ppm at −2 °C (Pr), +3 °C (Eu), or +7 °C (Yb) referenced to LaDOTA. ^{b} A negative shift represents a shift to low fields. ^{c} Normalized to shifts of H_{ax1}, the most shifted axial proton. ^{d} Calculated by the computer program CONF[11] for a lanthanide–nitrogen distance equal to 2.85 Å. ^{e} See text.

temperatures as an AB quartet ($J = 17.1$ Hz for LaDOTA and $J = 16.3$ Hz for LuDOTA). With an increase in the temperature, the quartet coalesces into a single line. Furthermore, both diamagnetic complexes exhibit a single $^{13}CH_2$ acetate peak over the entire temperature range investigated (see Figure 2). \Two acetate ^1H peaks also appear in the spectra of the paramagnetic complexes (see Figures 4 and 5). EuDOTA is the only complex for which signal broadening is weak: the coupling constant of the AB quartet is 17 Hz.

It is well-known that the ^1H acetate peak of aminopolycarboxylate complexes can occur as a singlet or can be resolved into an AB quartet. Day and Reilley[22,23] interpreted the appearance of the acetate protons in terms of the relative lifetimes of the metal–amine and metal–oxygen bonds. Both lifetimes may be short on the NMR time scale; the acetate spectrum then consists of a singlet. On the contrary, if the metal–nitrogen bond is not labile while the lifetime of the metal–oxygen bond is short, the acetate groups occur as an AB quartet. Indeed as indicated in structure 4 which is a Newman pro-

4
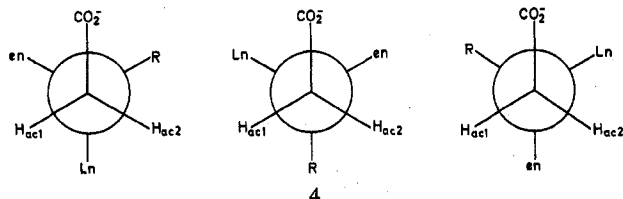
jection along the acetate CH_2–N bond, the protons H_{ac1} and H_{ac2} are nonequivalent in any of the three staggered conformations. The quaternary nitrogen is in fact asymmetric as far as one acetate is concerned. Consistent with this, LuEDTA (R = CH_2COO^- in structure 4) exhibits a quartet pattern for the acetate protons.[24] In the case of the ligand DOTA, the lifetime of the metal–nitrogen bond is expected to be long because of the rigidity of the macrocycle. The quaternary nitrogen, however, is not asymmetric because, in structure 4, R = en. The free rotation of the acetate groups should lead to a symmetrical rotamer and to two equal-energy mirror-image rotamers, a situation which is known to give rise to a single peak for both protons H_{ac1} and H_{ac2}. This reasoning, however, does not take into account the conformational preference of the tetraaza cycle at low temperatures. Indeed, Dreiding models of the DOTA complexes indicate that all the rigid ethylenediamine groups are constrained to adopt an identical conformation in order to avoid steric interactions (either δ or λ in the terminology of conformational analysis). Such a stereochemical arrangement has been reported for a tetrasubstituted 1,4,7,10-tetraazacyclododecane[16] in the solid state. Also, an oxygenated analogue of this cycle was found

to adopt the same conformation in sandwich-type solid complexes with sodium.[25] Finally, Anet and Rawdah recently carried out[26] force-field calculations on cyclododecane and demonstrated that a "square" structure of D_4 symmetry ([3333] in Dale's nomenclature[27]), with four ethylenic groups of identical conformation separated by CH_2 moieties, is markedly more stable than any other structure. This unique property of 12-membered macrocycles results in the appearance of a doublet for the acetate protons in the spectra of the DOTA complexes as illustrated schematically in structure 5 which

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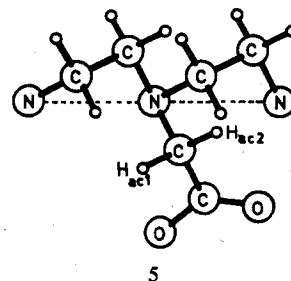
presents two ethylenic groups in the same conformation separated by one acetate group. The quaternary nitrogen is asymmetric at low temperatures because it is bonded to a metal ion (not shown), to an acetate group, and to two carbon atoms, one of which is nearer to the metal ion than the other. Protons H_{ac1} and H_{ac2} are thus nonequivalent. When the temperature is increased, the ethylenediamine groups start to interconvert rapidly on the NMR time frame and the quaternary nitrogen atom is no longer asymmetric. The two acetate protons become equivalent and occur as a singlet. The present interpretation is fully supported by the measurement of the energy of activation ΔG^*_{321} obtained from the coalescence of the acetate peaks exhibited by EuDOTA. The calculated value (63.6 kJ mol^{-1}) is in very good agreement with the value derived from the study of the ethylenic peaks as is to be expected if the nonequivalence of the acetate protons is due to the stereochemical behavior of the tetraaza cycle.[28] To our knowledge, the present work is the first example of this very unusual temperature-dependent asymmetry.

Approximate Structure of the Aza Complexes. Paramagnetic lanthanide ions are known to induce large shifts which are essentially dipolar (pseudocontact) in origin.[10,11] In the simple case where the complex is axially symmetric, the induced shift $\Delta\nu$ depends only on a magnetic susceptibility term D and on a geometric factor as indicated in eq 2, where θ and

$$\frac{\Delta\nu}{\nu} = -D\left\langle\frac{3\cos^2\theta - 1}{r^3}\right\rangle \qquad (2)$$

r are the polar coordinates of the nucleus under consideration relative to the main susceptibility axis. Equation 2 can be safely used to elucidate the structure of the DOTA complexes at low temperatures because the rigid macrocycle possesses a C_4 axis perpendicular to its main plane. ^1H NMR data recorded for DOTA complexes with Pr(III), Eu(III), and Yb(III) are collected in Table II. When these results are examined, it can be seen that the ratio of the shifts of the axial

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(28) If both the metal–nitrogen and the metal–oxygen bonds are nonlabile, up to four different AB splitting patterns may be expected in the NMR spectra for the acetate protons. Indeed the very tight packing of the DOTA complexes would probably constrain the protons of each acetate group to be located in different magnetic environments. Furthermore, the ΔG^* values would certainly be different for the acetate and the ethylenic protons. Long lifetimes for both types of bonds can thus be ruled out on the basis of the evidence at hand.
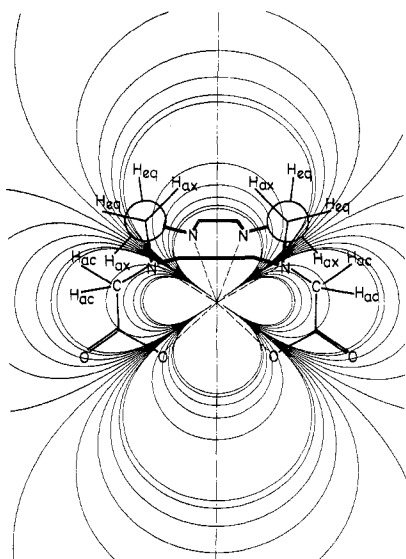
Figure 6. Schematic presentation of a portion of the DOTA ligand coordinated to a lanthanide ion with a map of the dipolar field in the background.

protons is fairly independent of the nature of the lanthanide ion. On the contrary, the two shift ratios H_{eq}/H_{ax1} change for each metal, a large deviation being found for the Eu(III) complex. These deviations are tentatively attributed to contact contributions which are expected to be small for YbDOTA but significant for EuDOTA.[29] The approximate position of the macrocycle relative to the lanthanide can be estimated from the shift ratio of the axial protons. The geometric factor of eq 2 was deduced for each nucleus from the crystallographic structure of the tetraaza cycle[16] with the metal ion placed along the C_4 axis at various distances from the nitrogen atoms. A relatively good agreement is reached between experimental and calculated values of the shift ratio H_{ax2}/H_{ax1} for a lanthanide–nitrogen distance of around 2.85 Å. This value must be accepted with reservation as it was deduced from the paramagnetic shifts of two protons only. However, the present structural analysis suggests that the lanthanide–nitrogen distance is similar in the complexes with the macrocyclic DOTA and with EDTA.[30] The location of the acetate protons is difficult to assess because of the short lifetime of the metal–oxygen bond which allows the acetate groups to be uncoordinated for an unknown length of time. Nevertheless, as it is presented schematically in Figure 6, the sign and magnitude of all shifts are in semiquantitative agreement with the proposed structure. By referral to the dipolar interaction surface reproduced in the background of Figure 6, it is readily seen that one axial proton should exhibit a large paramagnetic shift and that the two equatorial protons should be shifted in the same direction but to a lesser extent. The other axial proton and the two acetate protons have to be shifted in the opposite direction. This ordering of the paramagnetic shifts is observed for YbDOTA and PrDOTA, with particularly large

dipolar contributions for the former (see Figure 5), but the equatorial protons of EuDOTA are shifted in the "wrong" direction, probably because of large contact interactions.[29] Furthermore, the model proposed in Figure 6 is at least qualitatively valid also at high temperatures as it predicts that one of the H_{eq}–H_{ax} pair should be shifted to low fields while the other proton pair should appear at high fields and with a larger paramagnetic shift in agreement with the experimental spectrum of PrDOTA (see Figure 5).

Concluding Remarks

The NMR data reported here for the DOTA complexes clearly demonstrate the similarities between the tetraaza cycle and other 12-membered cycles such as cyclododecane. Indeed, at low temperatures, all the ethylenic groups of DOTA are rigid on the NMR time scale and they adopt the same conformation. Dale[27] and Anet et al.[26] showed that two enantiomeric "square" {3333} conformations are favored in the case of cyclododecane: each enantiomer has four identical ethylenic groups (δ or λ) separated by CH_2 moieties which are pointing to the same side of the cycle. The exchange between the two enantiomeric conformations proceeds through a path along which the ethylenic groups are inverted one by one in a continuous sequence, the separating CH_2 moieties remaining on the same side of the ring. The inversion barrier to the conformational change of one ethylenic group[26] is 33.0 kcal mol^{-1}. The same interconversion path was used by Anet et al.[31] to interpret the NMR spectra of a lithium complex with 12-crown-4. The separating CH_2 moieties are then replaced by four oxygen atoms which do not have to dissociate from the metal ion when the conformational interconversion takes place. It is highly probable that the ligand DOTA behaves in a similar manner: at high temperatures, one ethylenic group changes its conformation after the other, either clockwise or counterclockwise along the ring.

Finally, it is tempting to associate the unusual conformational properties of the lanthanide–DOTA complexes with the exceedingly slow kinetics of formation of these compounds. Nyssen and Margerum[32] reported on the kinetics of formation of the *trans*-1,2-diaminocyclohexane-N,N,N',N'-tetraacetate of lanthanum. These authors indicated that the rate-determining step is the rearrangement of an intermediate complex in which the metal ion is not coordinated to all the carboxylic groups. The rearrangement of the ligand leads to the complete encapsulation of the lanthanum ion. A similar mechanism of formation could be valid for the DOTA complexes, the slow kinetics of complexation being accounted for, at least partially, by the tight packing and the stringent conformational requirements of the ligand. The kinetics of complexation is much faster at elevated temperatures. It is also faster in the case of tetraaza tetraacetic macrocycles possessing a larger ring.[8]

Registry No. DOTA, 60239-18-1; La, 7439-91-0; Pr, 7440-10-0; Eu, 7440-53-1; Yb, 7440-64-4; Lu, 7439-94-3.

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