

Kinetically and thermodynamically stable isomers of thorium chelates of polyaza polycarboxylic macrocycles

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Abstract

The solution conformation of the thorium(IV) complexes of two polyaza polycarboxylic macrocycles, DOTA and HEHA (1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid and 1,4,7,10,13,16-hexaazacyclooctadecane-*N,N',N'',N''',N''''*-hexaacetic acid), was investigated by one- and two-dimensional nuclear magnetic resonance spectroscopy. ThHEHA²⁻ forms a kinetically stable topomer of C₂ symmetry and a thermodynamically stable topomer of S₆ symmetry. Both complexes are assigned an icosahedral geometry. The activation energy for the intermolecular exchange is very high (214 kJ mol⁻¹). The behavior of ThHEHA²⁻ contrasts with the properties of the other Th(IV) chelates that are known to be fluxional.

1. Introduction

Most lanthanide(III) and thorium(IV) chelates are known to be labile species because the 4f and 5f ions have no stereochemical requirements. These chelates can adopt several geometries which interconvert rapidly in solution. Thus, only one set of peaks is observed in the nuclear magnetic resonance (NMR) spectrum of each complex. Evans and Jakubovic [1] reported on a rare exception to this rule: an asymmetric tridentate Schiff base forms a tris-complex with Th(IV) which adopts a tricapped trigonal geometry with the three ligands in a symmetric or in an asymmetric arrangement. The two forms exhibit separate NMR peaks at 500 MHz and at room temperature. These two forms are thus stereochemically rigid, in contrast to all other known chelates of thorium(IV). Polyaza polycarboxylic macrocycles are known to form kinetically inert highly rigid lanthanide complexes [2] and it seems reasonable to assume that the thorium(IV) chelates of some of these ligands could also exhibit a conformational preference. The present paper reports on a thorough analysis of the NMR spectra of the thorium(IV) chelates of two macrocyclic ligands, 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid (DOTA) and 1,4,7,10,13,16-hexaazacyclooctadecane-*N,N',N'',N''',N''''*-hexaacetic acid (HEHA, see structures in Fig. 1). The ThHEHA²⁻ complex shows an astounding preference for a highly symmetric configuration.

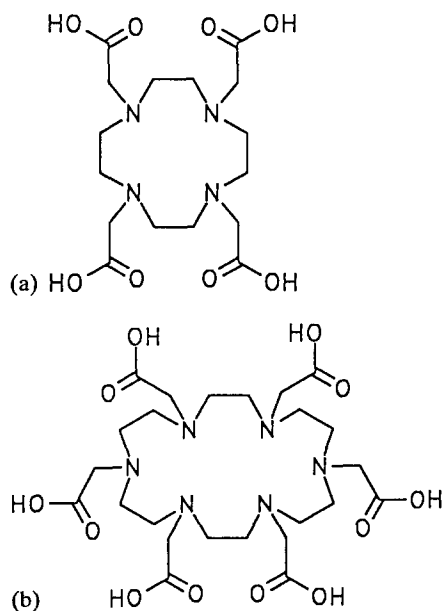


Fig. 1. Structures of (a) DOTA and (b) HEHA.

2. Experimental details

The DOTA and HEHA ligands were synthesized as reported earlier [2, 3]. The ThDOTA and ThHEHA²⁻ complexes were prepared in water by mixing equimolar solutions of ThCl₄ and of each ligand in the acid form. The pH was adjusted slowly to 5.0 with an NaOH solution and the reaction mixture was brought to dryness under vacuum. For reasons that become obvious below, water should be eliminated without heating. The remaining white solid was dissolved in

D₂O. All ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM spectrometer at 400 MHz and 100.6 MHz. The probe temperature was calibrated with an ethylene glycol sample. Longitudinal relaxation times *T*₁ were obtained by the classical inversion–recovery pulse sequence. The ¹H–¹H double-quantum-filtered phase-sensitive DQF-COSY spectra and the ¹H–¹³C heteronuclear shift correlation (HCORR) spectra were acquired using standard methods. Computer simulations of the ¹H spectra were carried out with the PANIC program supplied by Bruker and calculations of the geometries of the HEHA complexes were performed with the ALCHEMY III package and with locally written programs.

3. Results

The ¹H spectrum of ThDOTA at 95 °C is reproduced in Fig. 2. At room temperature, the spectrum features only exceedingly broad NMR bands. Three poorly resolved peaks were observed at high temperature and were assigned by comparison with the spectra of LaDOTA[−] and LuDOTA[−] [2]. By contrast, well resolved NMR peaks were observed in the ¹H spectrum of ThHEHA^{2−} at room temperature as indicated in Fig. 3 (bottom). As the temperature was increased, all ¹H signals appeared to undergo broadening at approximately the same rate. A conformational exchange is thus taking place in the HEHA ligand. If the temperature was maintained at 45 °C for several hours, the broadened peaks progressively disappeared and the spectrum evolved into a very simple, well resolved pattern (see Fig. 3, top). This pattern did not change if the temperature was brought back to 25 °C. It thus

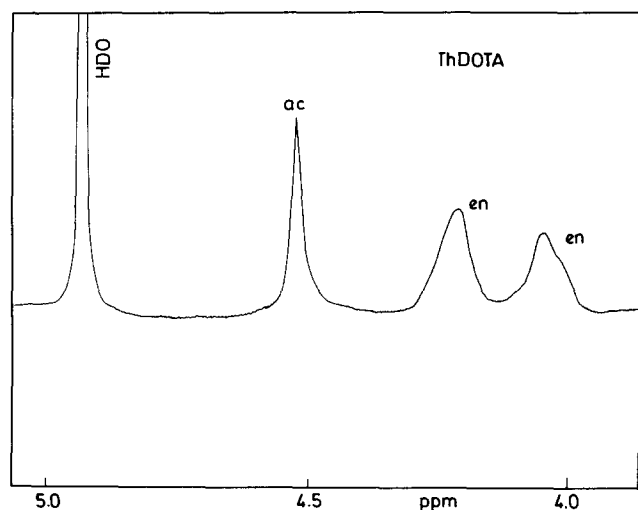


Fig. 2. 400 MHz proton NMR spectrum of ThDOTA at 95 °C. The symbols en and ac denote the ethylenic and acetate protons respectively.

appears that ThHEHA^{2−} adopts two different geometries: a kinetically stable topomer which is obtained at room temperature when the pH of an equimolecular mixture of thorium(IV) and HEHA is adjusted to 5.0, and a thermodynamically stable topomer which results from a rearrangement of the kinetic species when the temperature is high enough to overcome an energy barrier. As expected, the thermodynamically stable topomer is the only species which is found at all temperatures once it is formed.

The two-dimensional DQF-COSY and HCORR spectra of each topomer of ThHEHA^{2−} were used to determine which protons belong to the same –CH₂–CH₂– moiety and also to the same –CH₂– unit within each ethylene group. The coupling pattern of each proton was then simulated by computer until the best agreement between the experimental and the calculated spectra was reached. The coupling pattern assigned to each ethylenic group was simulated accurately by taking into account two ²*J* and four ³*J* constants. Two ³*J* constants were found to be systematically larger (12.5–14.0 and 1.9–4.7 Hz) than the two others (2–3 Hz). Finally, the longitudinal relaxation times *T*₁ of all the ¹³C nuclei of the two forms of ThHEHA^{2−} were measured in order to verify that there are no differences between the dynamic behavior of the topomers or of certain groups within each topomer. The *T*₁ values ranged between 0.16 and 0.19 s and the two forms of ThHEHA^{2−} can thus be regarded as compact structures.

4. Discussion

As expected for an uncharged complex, ThDOTA is poorly soluble in water. The NMR proton spectrum of this complex features three broad featureless peaks (Fig. 2) and is similar to spectra of the corresponding chelates of the diamagnetic lanthanides at 40–60 °C [4]. It is thus assumed that ThDOTA adopts a square antiprismatic structure of C₄ symmetry and that a conformational exchange takes place in the chelate ring and brings about a rapid interconversion between the axial and the equatorial protons (Fig. 4). Judging from the band width of the NMR peaks at various temperatures, ThDOTA appears to be approximately as rigid as the lanthanide DOTA chelates.

By contrast, the HEHA ligand exhibits the astounding property of forming both a kinetically stable and a thermodynamically stable topomer with Th⁴⁺ even though this metal ion is known to have little or no directing effects on the geometry of its complexes. This unusual lack of lability probably stems from the steric requirements of the HEHA ligand itself. Models purported to represent the structure of the two topomers can be built by computer on the basis of the Karplus

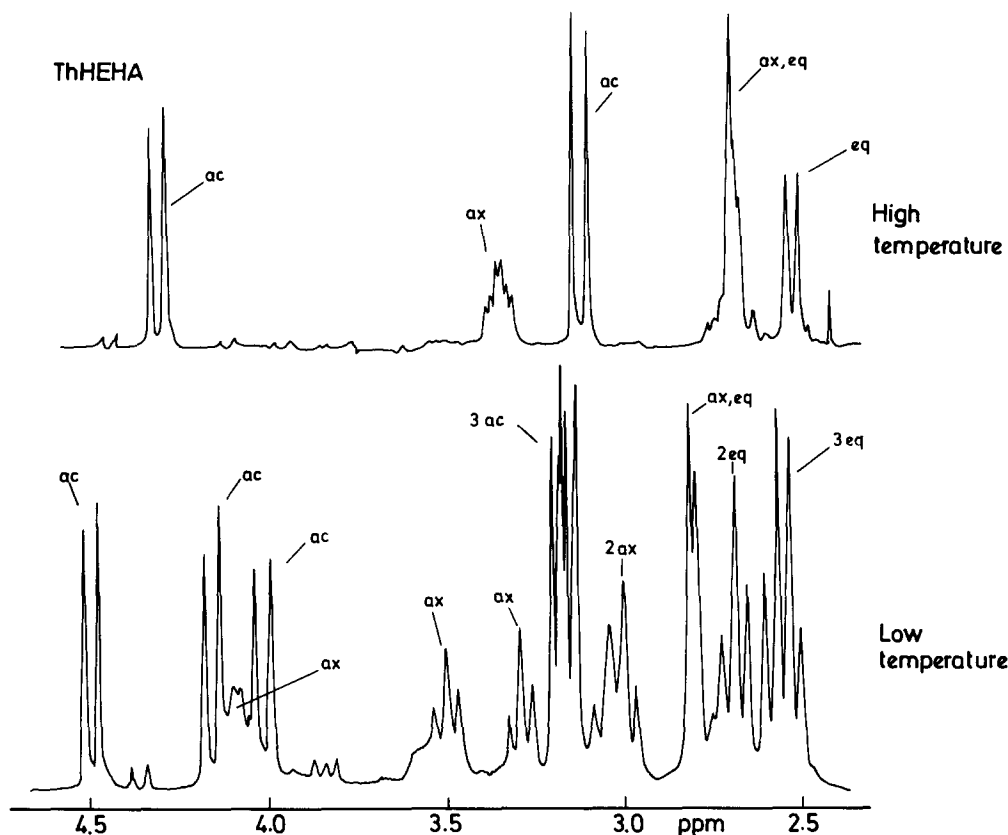


Fig. 3. 400 MHz proton NMR spectrum of ThHEHA²⁻ taken immediately after the formation of the complex (bottom) and after heating at 85 °C during 5 days (top). the symbols ax, eq and ac denote the axial and equatorial protons in the ethylenic groups and the acetate protons respectively.

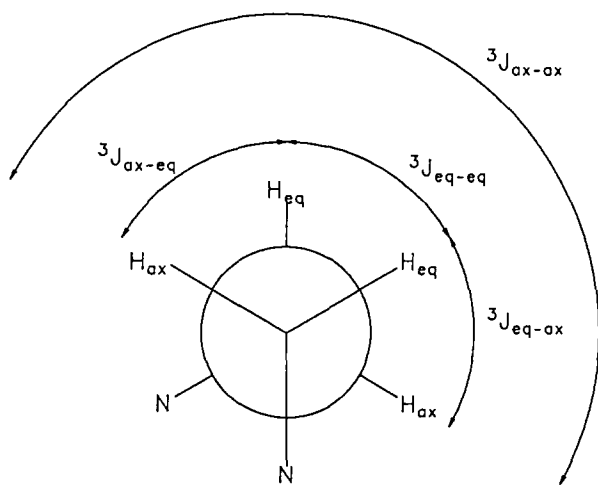


Fig. 4. Fully staggered conformation of an ethylenic group and ³J coupling constants.

equation that links the ³J coupling constants to the torsion angle ϕ between two protons in an ethylenic group

$${}^3J_{X-Y} = A_1 \cos^2 \phi \quad 0 < \phi < 90$$

$${}^3J_{X-Y} = A_2 \cos^2 \phi \quad 90 < \phi < 180$$

where A_1 and A_2 are constants that were deduced from the NMR spectrum of LaDOTA; a compound that is known to have all its ethylenic group fully staggered in solution [4] and in the solid state [2] ($A_1 = 11.5$, $A_2 = 12.65$). A Newman projection of an ethylenic group together with the appropriate ³J coupling constants is shown in Fig. 4. The calculations show that the $H_{ax}-H_{ax}$ angle is close to 180° in the two topomers while all the other H-H angles are close to 60°. Thus, the models of the two topomers of ThHEHA²⁻ must have all their -N-CH₂-CH₂-N- moieties fully staggered.

The thermodynamically stable ThHEHA²⁻ species must be highly symmetric because it exhibits very simple ¹H and ¹³C NMR spectra (Fig. 3). All the acetate groups of this topomer are equivalent and give rise to only one pair of doublets (Fig. 3, top) and single C=O and CH₂ peaks at 184.4 and 63.6 ppm respectively. Moreover, all ethylenic groups are also equivalent and show a proton coupling pattern which is computer simulated accurately with only four ³J coupling constants. In addition, the ethylenic groups feature only two ¹³C peaks at 62.7 and 58.3 ppm. Finally, the relaxation time measurements do not show any significant differences between the ¹³C nuclei of the thermodynamic topomer and it is assumed that the metal ion is twelve-

coordinate. All these observations point to an icosahedral geometry with an S_6 axis as shown in the stereoscopic view reproduced in Fig. 5(a). In this geometrical arrangement, the nitrogen atoms of HEHA are disposed alternatively in two parallel planes. The acetate substituents are pointing alternatively above and below these planes and the oxygen atoms coordinated to thorium(IV) form two parallel triangular faces.

The ^1H spectrum of the kinetically stable topomer of ThHEHA^{2-} (Fig. 3) can be interpreted quantitatively if three different ethylenic groups and three different acetate moieties are taken into account. In keeping with the proton spectrum, three CO peaks and eight CH_2 peaks are observed in the ^{13}C spectra. Thus, the kinetic topomer must have a twofold symmetry. As shown in Fig. 5(b), the HEHA ligand can be arranged

around the metal ion with its heteroatoms on the vertices of an icosahedral structure while maintaining the ethylenic groups fully staggered. In this geometry, the hexaaza ring adopts a boat conformation with two carboxylic groups on one side of the complex and four carboxylic groups on the other side. Other structures are compatible with the NMR data but the geometry shown in Fig. 5 is favored because an icosahedron is by far the most stable structure for twelve-coordinate complexes [5] and because boat conformations are also found in lanthanide complexes with substituted 18-membered polyaza polyoxa macrocycles. The kinetics of rearrangement from the kinetically stable to the thermodynamically stable topomer was followed at different temperatures and an activation energy of 214 kJ mol^{-1} was obtained. At 70 °C, the kinetic constant for the intermolecular exchange is $3.0 \times 10^{-5} \text{ s}^{-2}$. This very high activation energy and very slow kinetics indicate that the two topomers of ThHEHA^{2-} are quite stable and that the rearrangement into a highly symmetric icosahedral conformation is a difficult process, as could be expected because of the tight packing of the HEHA chelates.

Acknowledgments

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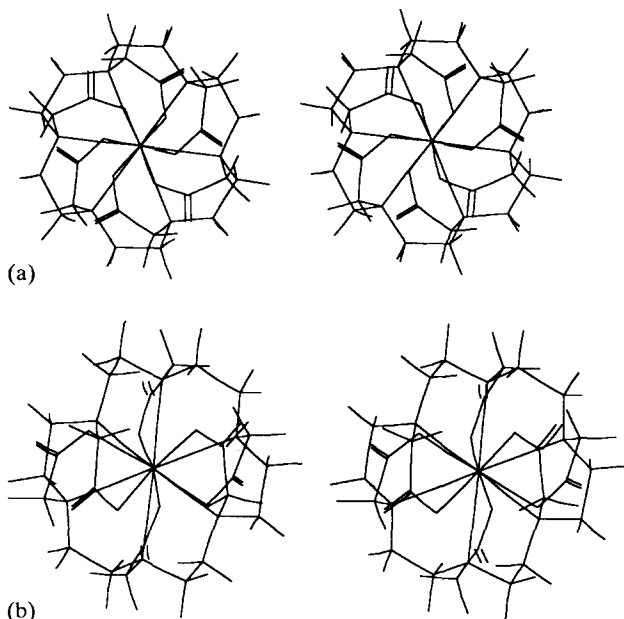


Fig. 5. Stereoscopic view of the conformation proposed for the thermodynamically stable topomer (a) and for the kinetically stable topomer (b) of ThHEHA^{2-} .