

Complexation of Thorium(IV) and Uranium(IV) by a Hexaacetic Hexaaza Macrocycle: Kinetic and Thermodynamic Topomers of Actinide Chelates with a Large Cavity Ligand

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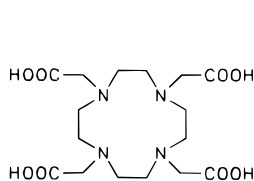
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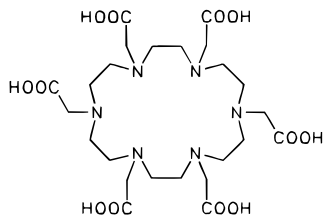
The solution behavior of the Th(IV) chelate with a polyaza polycarboxylic ligand, HEHA (1,4,7,10,13,16-hexaazacyclooctadecane-*N,N',N'',N''',N''''',N''''''*-hexaacetic acid), is investigated by one- and two-dimensional NMR spectroscopy. $[\text{Th}(\text{HEHA})]^{2-}$ exhibits a very unusual irreversible topomerization process from a kinetically stable topomer of C_2 symmetry to a thermodynamically stable topomer of remarkably high symmetry (S_6). The metal ion appears to be 12-coordinated in both geometries with a pseudoicosahedral arrangement of the chelating groups. The activation energy of the irreversible topomerization is exceedingly high (199 $\text{kJ}\cdot\text{mol}^{-1}$), and the slow kinetics of conversion is assigned to a complete reorganization of the chelate. U(IV) forms directly a stable entity of C_2 symmetry with HEHA and no reorganization of the complex is observed. The unusual topomerization phenomenon undergone by HEHA, is thus strongly dependant on the ionic radius of the encapsulated metal ion. The corresponding lanthanide chelates are totally asymmetric.

Introduction

Lanthanide complexes with polyaza polycarboxylic macrocyclic ligands such as DOTA, 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid (**1**), or TETA, 1,4,8,11-tetraazacyclotetradecane-*N,N',N'',N''',N''''*-tetraacetic acid (**2**) are known for their unusual properties.^{1,2}



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Unlike the lanthanide chelates of linear ligands, the complexes of **1** and **2** with the 4f trivalent ions are extremely rigid and display a strong kinetic inertness towards metal release.^{1,2} These properties have been the major impetus behind the use of the gadolinium complexes of DOTA and its analogues for improving the contrast of *in vivo* magnetic resonance images.³ The chelation properties of the actinide and the lanthanide ions are similar in that they form mostly kinetically labile complexes because the 4f and 5f cations have little or no stereochemical requirements. It is thus not surprising that actinide chelates adopt several geometries that are rapidly exchanging in solution and that give rise to only one set of NMR peaks. This fluxional behavior strongly limits the amount of structural information that can be extracted from the NMR spectra of actinide chelates. To our knowledge, there is only one exception to this general

rule. Evans and Jakubovic⁴ reported that a tris-complex of Th(IV) with an asymmetrical tridentate Schiff base adopts a tricapped trigonal geometry with the three ligands in a symmetrical or an asymmetrical arrangement. A conformational analysis proved possible because the two isomers are stereochemically rigid and exhibit distinct ¹H NMR peaks at 500 MHz and at room temperature. Evans and Jakubovic's report⁴ remains to date the only known example of a rigid Th(IV) chelate, and it is certainly worthwhile to find other nonlabile actinide derivatives, for instance for separation purposes. To this end, we have examined whether the unusual properties displayed by the lanthanide complexes with polyaza polycarboxylic macrocyclic ligands can also be observed with 5f ions. We analyzed the dynamic behavior of the Th(IV) and U(IV) chelates of the large polyaza polycarboxylic macrocycle HEHA, 1,4,7,10,13,16-hexaazacyclooctadecane-*N,N',N'',N''',N''''',N''''''*-hexaacetic acid (**3**). For comparison purposes, the NMR spectra of lanthanide HEHA complexes were also recorded.⁵ To our surprise, we found that the Th(IV) chelate with HEHA exhibits a most unusual dynamic behavior.

Experimental section

Syntheses. The ligand HEHA was synthesized as described previously.⁶ HEHA partially deuterated in the acetate positions was prepared following the same reaction scheme but with chloroacetic-*d*₂ acid¹ instead of chloroacetic acid. The ligand was further purified by elution with 0.1 M formic acid from a strong anion exchange resin (Dowex) in the formate form. ¹H NMR of the eluted deuterated HEHA showed a 75% deuteration yield after complete elimination of formic acid as a water azeotrope. Stock solutions of the chelating agents were made and standardized by NaOH titration.

ThO₂ was dissolved in concentrated HCl with the addition of a crystal of ammonium fluoride. The solution was brought to dryness and a stock solution was prepared from the acid residue (pH ≤ 3). UCl₄ was

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prepared according to a literature procedure,⁷ and a stock solution was freshly made just before complexation by dissolution of the tetrachloride in acidic (pH ≤ 2) degassed deionized water. The $[\text{Th}(\text{HEHA})]^{2-}$ chelate was synthesized by mixing equimolar amounts of ThCl_4 solution and HEHA. The pH was adjusted to about 5.0 by very slow addition of a dilute NaOH solution. The reaction mixture was taken to dryness under reduced pressure without heating (see text). The white solid residue was dissolved in D_2O in order to obtain a 0.1 M solution of chelate. $[\text{U}(\text{HEHA})]^{2-}$ was prepared by mixing equimolar amounts of degassed solutions of UCl_4 and HEHA. All manipulations were carried out in a glovebox under argon. The pH of the green solution was slowly increased to about 3.0 by addition of a degassed solution of NaOH. Water was evaporated under reduced pressure and the green residue was dissolved in deuterated DMSO ($\text{DMSO}-d_6$). Any insoluble material was filtered off before further analysis. Any attempt to dissolve the complex in D_2O resulted in the formation of a green precipitate of uranium(IV) hydroxide that was also observed when the pH of the solution was raised. The complex $[\text{U}(\text{HEHA})]^{2-}$ featuring partially deuterated acetate groups was obtained following the same procedure.

NMR Measurements and Calculations. Both one- and two-dimensional NMR spectra were recorded on a Bruker AM400 Fourier transform spectrometer operating at 400 MHz for ^1H NMR and at 100 MHz for ^{13}C NMR. The variable-temperature unit was calibrated using a 100% ethylene glycol sample. Each calibration was repeated three times, and the reported temperatures are accurate to ± 1 °C. ^{13}C longitudinal relaxation times T_1 were determined with the classical inversion-recovery sequence. The ^1H - ^1H double quantum filtered COSY spectra (DQF-COSY) and the ^1H - ^{13}C heteronuclear shift correlation spectra (HETCOR) were recorded using standard pulse sequences from the Bruker library of microprograms. Computer simulations of the ^1H NMR spectra of $[\text{Th}(\text{HEHA})]^{2-}$ were carried out with the PANIC program (Parameter Adjustment in NMR by Iteration Calculation) supplied by Bruker. Geometries of the $[\text{Th}(\text{HEHA})]^{2-}$ chelates in keeping with the NMR spectra were generated with the Alchemy III program from Tripos Assoc. and with locally written programs.¹

Results and Discussion

Th(IV) Chelates. $[\text{Th}(\text{HEHA})]^{2-}$ is very soluble in water at pH ≈ 5.0 and its ^1H spectrum features very well resolved peaks at room temperature as shown in Figure 1. Peak broadenings were observed when the temperature of a solution of this chelate was increased, indicating that a conformational exchange was taking place. If the sample was kept at a high temperature (about 60 °C) for several hours, the broadened peaks slowly disappeared while very few well resolved sharp multiplets appeared. A very simple spectrum (see Figure 2) symptomatic of a highly symmetrical species was finally obtained. Surprisingly, this simple spectrum remained unchanged when the temperature was lowered back to 25 °C. This observation leads to the conclusion that the $[\text{Th}(\text{HEHA})]^{2-}$ chelate exists in solution as two different stable topomers, i.e. two molecules that differ only in the three-dimensional arrangement of their atoms.⁹ One species is formed when Th(IV) and HEHA are mixed and when the pH is brought to 5.0. It is a kinetically stable topomer that is formed rapidly at room temperature. A second topomer ensues from a rearrangement of the kinetically stable species when the temperature is high enough to overcome the activation energy of the transformation. The new species that is formed is a thermodynamically stable topomer as it is the only species that is found in solution at every temperature once it is formed.

The thermodynamically stable topomer of $[\text{Th}(\text{HEHA})]^{2-}$ should be a very symmetrical molecule as its ^1H and ^{13}C NMR

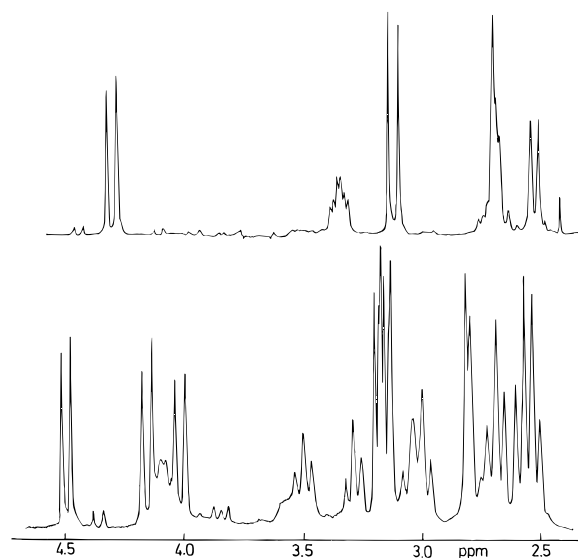


Figure 1. ^1H NMR spectra of the kinetically stable (bottom) and the thermodynamically stable topomer (top, obtained after heating a fresh solution of $[\text{Th}(\text{HEHA})]^{2-}$ at 70 °C during 24 h of $[\text{Th}(\text{HEHA})]^{2-}$ at room temperature). The chemical shifts of the proton peaks are listed in Table 1.

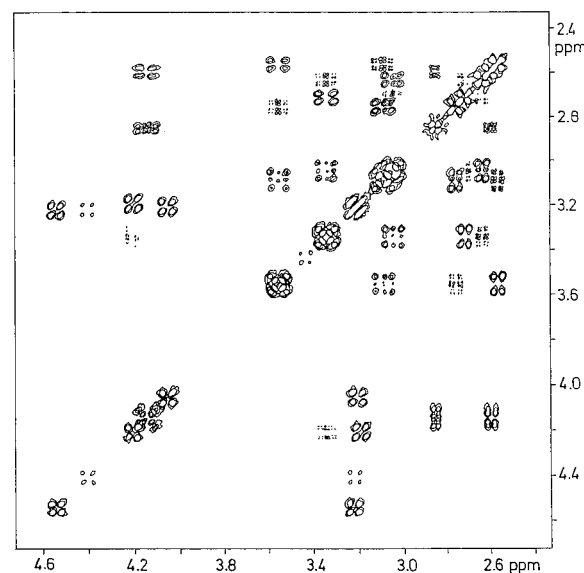


Figure 2. 400 MHz two-dimensional DQF-COSY NMR spectrum of the kinetically stable topomer of $[\text{Th}(\text{HEHA})]^{2-}$.

spectra are exceedingly simple (see Figure 1 and Table 1). The symmetry of the kinetically stable species is obviously lower since its ^1H and ^{13}C spectra are more complex as shown in Figure 1. The behavior of $[\text{Th}(\text{HEHA})]^{2-}$ contrasts significantly with the properties of all other known actinide complexes which are highly fluxional. Each topomer of $[\text{Th}(\text{HEHA})]^{2-}$ is a rigid structure as no broadening was observed when the temperature was increased or lowered, besides the broadening due to the topomerization. The unusual rigidity displayed by the topomers of $[\text{Th}(\text{HEHA})]^{2-}$ allows a quantitative analysis of their NMR spectra. The 3J coupling constants between hydrogen nuclei in a molecule are related to the torsion angle ϕ between the two C-H bonds by the Karplus equations

$$^3J = A_1 \cos^2 \phi \quad 0^\circ < \phi < 90^\circ \quad (1)$$

$$^3J = A_2 \cos^2 \phi \quad 90^\circ < \phi < 180^\circ \quad (2)$$

where A_1 and A_2 are constants that are specific of the system

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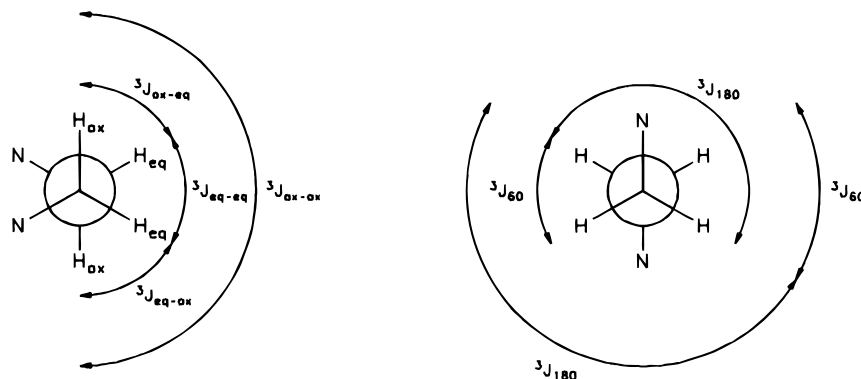
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Table 1. ^1H and ^{13}C Correlations for the Two Topomers of $[\text{Th}(\text{HEHA})]^{2-}$

kinetically stable topomer					thermodynamically stable topomer				
	$\delta(^{13}\text{C})^a$	$\delta(^1\text{H})$		type (and coupling)		$\delta(^{13}\text{C})^a$	$\delta(^1\text{H})$		type (and coupling)
1	65.4	4.55	3.21	acetate	1	63.6	2.97	4.15	acetate
2	63.9	4.19	3.18	acetate	2	62.7	2.37	3.17	ethylenic (with 3)
3	62.8	4.13	2.58	ethylenic (with 7)	3	58.3	2.55	2.55	ethylenic (with 2)
4	62.6	3.33	2.69	ethylenic (with 9)					
5	61.9	4.06	3.18	acetate					
6	60.3	3.05	2.78	ethylenic (with 8)					
7	58.2	2.84	2.84	ethylenic (with 3)					
8	56.5	3.53	2.54	ethylenic (with 6)					
9	55.7	3.01	2.62	ethylenic (with 4)					

^a The $\delta(\text{C}=\text{O})$ values are 185.7, 185.6, and 185.1 ppm for the kinetically stable topomer and 184.4 ppm for the thermodynamically stable topomer.

Scheme 1

investigated. Constants A_1 and A_2 were deduced from the NMR spectrum of $[\text{LaDOTA}]^-$, a compound known to have all its ethylenic groups fully staggered both in solution¹ and in the solid state.⁸ Values of 11.5 and 12.65 Hz were obtained for A_1 and A_2 respectively. The acetate peaks of either topomer of $[\text{Th}(\text{HEHA})]^{2-}$ can be fully analyzed as they contain only 2J constants. However, 3J coupling constants cannot be extracted directly from the multiplets assigned to the ethylenic groups as these are obviously second order. It is therefore necessary to perform computer simulations in order to determine the useful coupling constants from the spectra. An ethylenic group is characterized by a maximum of two 2J and four 3J coupling constants as indicated in Scheme 1 (in this scheme, the ax and eq symbols denote axial and equatorial protons respectively).

We were able to isolate all the spin systems and to identify the 3J coupled spins in each system as the HETCOR ^1H - ^{13}C spectrum provides a way of knowing which hydrogen atoms are bound to the same carbon atom and as the DQF-COSY shows all the homonuclear coupling (2J and 3J). The COSY spectrum of the kinetically stable topomer is shown in Figure 2 and the other spectra are available with the Supporting Information. The ^1H and ^{13}C chemical shifts of the two topomers are listed in Table 1. The spectrum of each ethylenic group was simulated with the PANIC software until the best agreement between the calculated and the experimental spectra was reached. The resulting theoretical spectra for each isolated spin system were then superposed to give the simulated spectra that are available in the Supporting Information. As expected, two 2J and four 3J coupling constants had to be taken into account for each ethylenic moiety and only one 2J constant for each acetate arm (see Supporting Information). The 3J coupling constants that were obtained by simulation were then used in the Karplus equation to compute the torsion angles ϕ shown in Table 2. Two torsion angles may be obtained for each coupling constant as the Karplus equations are degenerate and cannot distinguish between the angles below 90° and above 90° .

Table 2. Torsion Angles ϕ for the Ethylenic Groups of the Two Topomers of $[\text{Th}(\text{HEHA})]^{2-}$ As Obtained by the Karplus Equations

	kinetically stable topomer			thermodynamically stable topomer
ax-ax	180 ± 3	180 ± 3	180 ± 2.5	177 ± 12
a	66 ± 3	60.5 ± 2.5	63 ± 5	73 ± 8
a	66.5 ± 3	64 ± 2.5	59.8 ± 10	50 ± 5
a	69 ± 1	59.5 ± 3	75.4 ± 10	74 ± 8

^a These torsion angles are related to the ax-eq, eq-ax, and eq-eq coupled protons of each ethylenic group (ax and eq denote axial and equatorial protons respectively).

However, it is very easy to isolate the correct value as shown in Scheme 1. Only two structures can be drawn for the ethylenic groups if one assumes a fully staggered conformation. One of these conformations requires that two torsion angles be equal to 180° . This is impossible for the topomers of $[\text{Th}(\text{HEHA})]^{2-}$ as the simulation generated for each ethylenic group yields only one 3J coupling constant that is compatible with a 180° angle. Furthermore it is impossible to generate a three-dimensional structure for the HEHA complex with the two nitrogen atoms of an ethylenic group at 180° from each other. As indicated in Table 2, the computations show that in both topomers the angles $\phi_{\text{ax-ax}}$ are close to 180° and the angles $\phi_{\text{eq-ax}}$, $\phi_{\text{ax-eq}}$, and $\phi_{\text{eq-eq}}$ are all close to 60° (axial and equatorial refer here to the position of the hydrogen atoms with respect to the mean plane of the five-membered ring that is formed by the metal ion, two nitrogen and two carbon atoms). The torsion angles listed in Table 2 are in keeping with fully staggered ethylenic groups in both topomers. This arrangement is the most stable conformation for ethylenic groups and it could account for the rigidity of the $[\text{Th}(\text{HEHA})]^{2-}$ topomers. Furthermore all the longitudinal relaxation times T_1 of the methylene carbons of both topomers have been determined and were found to be nearly identical (0.16–0.19 s). We assumed that the two forms of $[\text{Th}(\text{HEHA})]^{2-}$ are compact structures with fully coordinated acetate groups and that the metal ion is 12-coordinated in both isomers although

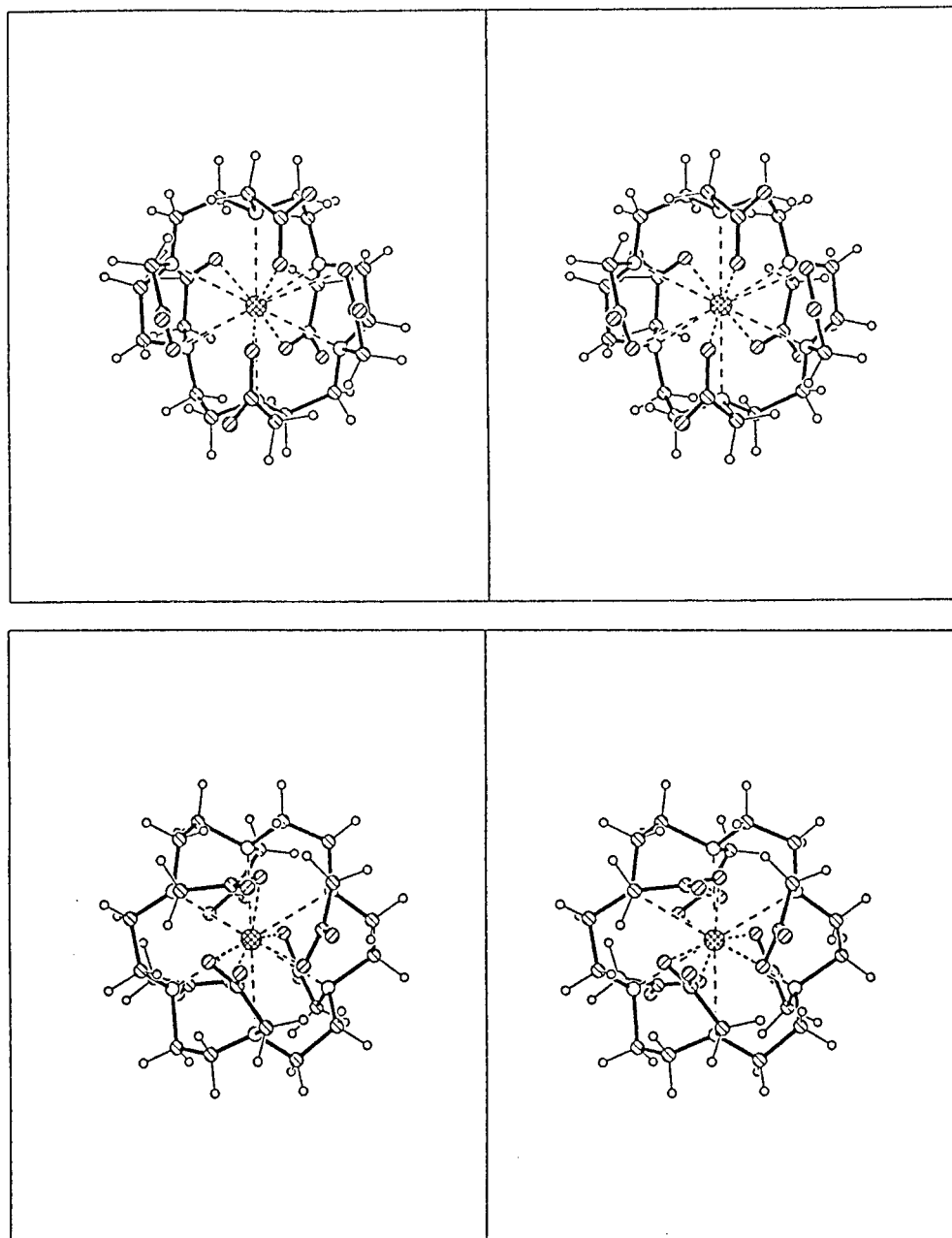


Figure 3. Proposed conformations for $[\text{Th}(\text{HEHA})]^{2-}$. Top: kinetically stable topomer (stereoscopic view down the C_2 axis). Bottom: thermodynamically stable topomer (spectroscopic view down the S_6 axis). Atoms: N, open circles; O, bottom left–top right dashed circles; C, bottom right–top left dashed circles; Th, cross-hatched circles; H, small open circles.

one cannot exclude a rapid coordination-decoordination process of the carboxylic groups that would take place while maintaining the overall symmetry of the chelates. A coordination number of 12 has already been found for Th(IV) complexes such as $[\text{Th}(\text{NO}_3)_6]^{2-10}$ and $[\text{Th}(\text{dedecmp})_2(\text{NO}_3)_4]^{11}$ (dedecmp = diethyl(*N,N*-diethylcarbamoyl) methylene phosphonate). These complexes are regular or distorted icosahedral polyhedra as can be expected since the icosahedron has been shown to be by far the most stable structure¹² of the 12-coordinate compounds. We attempted to generate a geometry for the two topomers by combining all of the information deduced from the NMR spectra, namely, rigidity, 12-coordination of the metal ion,

appropriate symmetry, fully staggered ethylenic groups, and also reasonable Th–N and Th–O distances (2.6–2.7 and 2.3–2.5 Å respectively) and van der Waals radii.

The ^1H and ^{13}C spectra of the thermodynamically stable topomer are extremely simple as shown in Figure 1 and Table 1. All the acetate groups are equivalent (one C=O peak and one CH_2 peak at 184.4 and 63.6 ppm) and all the ethylenic moieties of the hexaazacyclooctadecane macrocycle are also equivalent (two CH_2 peaks at 62.7 and 58.3 ppm). The small number of NMR peaks points to a very symmetrical icosahedral geometry with an S_6 axis of symmetry. Figure 3 shows the structure that fulfills these requirements. In this arrangement, the metal ion is located at the center of the polyhedron, and the 12 coordinating atoms occupy the 12 vertices. The nitrogen atoms of the macrocycle are located alternately in two parallel planes and form two large equilateral triangles located below and above the central metal ion. The

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acetate arms point alternately above and below the two nitrogen planes with the oxygen atoms forming two of the parallel triangular faces of the icosahedron. The S_6 axis is perpendicular to all the nitrogen and oxygen planes. Finally, the 18-membered tetraaza ring is in a chair conformation that allows all the ethylenic bridges to be fully staggered.

It is also possible to suggest a structure for the kinetically stable topomer. The ^1H and ^{13}C spectra of this isomer (see Figure 1 and Table 1) are indicative of a 2-fold symmetry. The ^1H spectrum could only be computer simulated if three different acetate substituents and three different ethylenic groups were considered. The ^{13}C spectrum shows exactly the same features (three different $\text{C}=\text{O}$ peaks and nine CH_2 peaks, i.e. three acetate and six ethylenic CH_2 groups). The 2-fold symmetry plus a coordination number of 12 and the requirement that the ethylenic moieties be fully staggered can be combined to give the structure shown in Figure 3. The macrocyclic ligand is again encapsulating completely the central metal ion, and the coordinated heteroatoms (nitrogens and oxygens) still occupy the vertices of an icosahedron although the latter is less regular than in the preceding case. Two acetate arms substituting the nitrogen atoms 1 and 10 are now pointing above the mean nitrogen plane and define the top edge of the icosahedron. The four other acetate groups are pointing below the mean nitrogen plane and form the bottom edge and two vertices. The top and bottom edges are parallel but form an angle of 57° instead of 0° . The lower part of the icosahedron no longer contains equilateral triangles. The nitrogen atoms in the 4, 7, 13, and 16 positions are located in one plane and the remaining two nitrogen atoms are located at the same distance above that plane. The C_2 axis bisects all the oxygen–oxygen edges and is perpendicular to the central nitrogen plane. In this structure, the macrocyclic ring is no longer in a chair conformation but adopts a boat geometry with all its ethylenic groups fully staggered. This structure may not be the only one that matches all the experimental data collected for the kinetic topomer, but the proposed geometry is favored because the icosahedron is the most stable arrangement for a coordination number of 12¹² and because boat conformations of 18-membered polyaza polyoxa macrocycles have already been reported for lanthanide crown ether complexes.¹³

The measurements described above clearly show that the thermodynamically stable topomer is formed by the rearrangement of the kinetically stable species when the temperature of the solution is raised. This rearrangement is irreversible in the sense that, once formed, the thermodynamic topomer remains the only species in solution at all temperatures. The energy, enthalpy, and entropy of activation of this process were deduced from the rate of topomerization at different temperatures. The integrated intensity of the 2.97 ppm ^1H acetate doublet assigned to the thermodynamically stable topomer was measured vs time at four temperatures. The obtained values were fitted to the equation

$$T_t = K_0(1 - e^{-kt}) \quad (3)$$

where T_t is the concentration of the thermodynamically stable topomer at time t (integrated doublet), K_0 is the initial concentration of the kinetically stable isomer and k is the first-order rate constant of the irreversible process. Both K_0 and k were parameters in the fitting that was performed for each set of data at each temperature. The rate constants obey very well the Arrhenius law (see Supporting Information). Values of 199

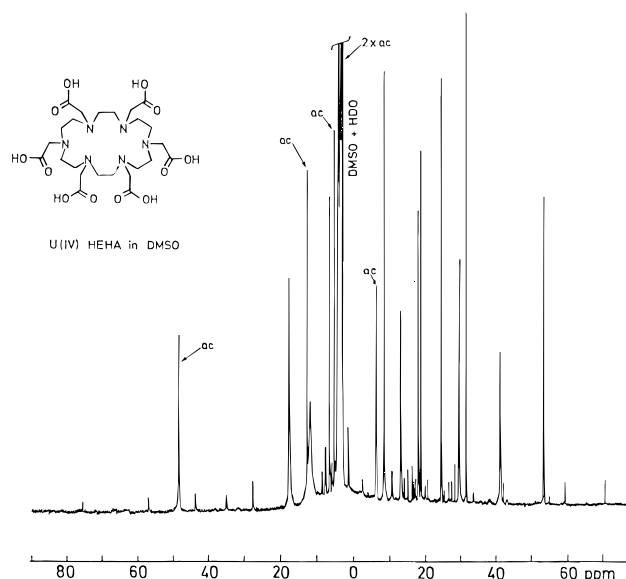


Figure 4. ^1H NMR spectrum of $[\text{U}(\text{HEHA})]^{2-}$ at 400 MHz in $\text{DMSO}-d_6$ (ac denote the NMR peaks corresponding to acetate group hydrogens).

$\text{kJ}\cdot\text{mol}^{-1}$, $196 \text{ kJ}\cdot\text{mol}^{-1}$ and $233 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ were obtained for the energy, enthalpy, and entropy of activation respectively. A kinetic constant of $4 \times 10^{-10} \text{ s}^{-1}$ was calculated at 25°C . The very high activation energy and the very slow kinetics of rearrangement indicate that both topomers are extremely rigid. They are even more rigid than the corresponding lanthanide-(III) DOTA complexes that are known for their inertness¹ and that have been shown¹⁴ to adopt two conformations in slow exchange with an activation energy of about $80 \text{ kJ}\cdot\text{mol}^{-1}$. The astounding inertness of the $[\text{Th}(\text{HEHA})]^{2-}$ topomers is in keeping with the three dimensional structures presented in Figure 3 as the rearrangement from the kinetically stable topomer of C_2 symmetry to the thermodynamically stable one of S_6 symmetry requires a complete concerted reorganization of the chelating agent around the metal ion. The hexaaza ring has to undergo a rearrangement from a boat to a chair conformation while acetate arms have to move from one side of the icosahedral structure to the other and to adopt new conformations. These simultaneous processes are difficult presumably because of the tight packing of the HEHA chelate and could require the decoordination of some of the donor atoms. This complete rearrangement of the ligand is in keeping with the fairly high value of the entropy of activation.

U(IV) Chelates. The ^1H spectrum of $[\text{U}(\text{HEHA})]^{2-}$ at room temperature in $\text{DMSO}-d_6$ features 18 major NMR peaks as shown in Figure 4. The paramagnetism of the U(IV) ion induces large chemical shifts that cover a 150 ppm range, and it is responsible for peak broadenings that mask the coupling patterns. In addition, 18 minor peaks are observed in the spectrum, and it thus appears that the $[\text{U}(\text{HEHA})]^{2-}$ chelate adopts two conformations that are in slow exchange at room temperature. The shifted peaks could not be assigned on the basis of a geometrical model as the U(IV) cation induces both contact and dipolar shifts.⁴ These induced shifts cannot be separated in any simple way in the absence of a crystallographic structure. It was therefore necessary to record the NMR spectrum of the complex of U(IV) with HEHA deuterated in the acetate positions in order to gain some structural information. The intensity of six peaks labeled "ac" in Figure 4 was decreased by deuteration. A totally asymmetric and rigid structure would

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give rise to 24 peaks due to the ethylenic hydrogen atoms and to 12 acetate peaks. As only half this number of NMR peaks are observed in the spectrum of $[\text{U}(\text{HEHA})]^{2-}$, it is concluded that this chelate has a 2-fold symmetry. A fast exchange between two totally asymmetric structures can be ruled out since increasing or decreasing the temperature leads only to negligible alterations of the peak widths. Moreover, varying the temperature does not lead to an exchange between the minor and the major isomers. The two $[\text{U}(\text{HEHA})]^{2-}$ solution species are thus rigid on the NMR time scale at 400 MHz, and they probably have structures similar to the geometry of the kinetically stable topomer of $[\text{Th}(\text{HEHA})]^{2-}$. The two isomers might differ because of different orientations of the acetate arms and/or the ethylenic groups and they would then be present in solution as two species of different chiralities. A slow exchange between forms that are nearly exact stereoisomers of each other with opposite arrangements of their ethylenic and/or acetate moieties has already been referred to to interpret the NMR spectra of lanthanide(III) DOTA complexes.^{14,15} The $[\text{U}(\text{HEHA})]^{2-}$ complex is the first example of a similar process taking place in an actinide chelate. It should be noted that such a process cannot be observed in the spectrum of the diamagnetic $[\text{Th}(\text{HEHA})]^{2-}$ that covers a much smaller NMR shift range. The distribution between the two forms of $[\text{U}(\text{HEHA})]^{2-}$ depends on the water content in the DMSO-*d*₆ solvent. It reaches a 1:1 ratio after the addition of 60% of water with respect to the initial volume. The solvation of the metal ion by either DMSO or water appears to favor one or the other of the two forms presumably because of differences in steric crowding of the solvating agent and/or because of changes in the dielectric constant of the solution. Moreover, new species are formed upon the addition of water, and more than 50 NMR peaks are observed in the ¹H spectra. At the present stage, these peaks cannot be assigned reliably (see Supporting Information).

The NMR spectrum of $[\text{U}(\text{HEHA})]^{2-}$ solutions in DMSO or in DMSO/water mixtures remains unaltered even after several days of heating at 80 °C. The formation of this complex does not proceed through a kinetically stable intermediate before its rearrangement into a thermodynamically stable species. This contrasts significantly with the behavior of $[\text{Th}(\text{HEHA})]^{2-}$ despite a very small difference in ionic radius between U(IV) and Th(IV) (0.05 Å for a coordination number of 12¹⁶). The thermodynamically stable topomer of $[\text{Th}(\text{HEHA})]^{2-}$ must be an exceedingly tightly packed structure since a very small decrease in the ionic radius of the encapsulated metal ion is sufficient to prevent its formation. The model of the thermo-

dynamically stable topomer as deduced from the NMR analysis (see Figure 3) is in agreement with this conclusion.

Conclusions

The cavity size of HEHA is much larger than the ionic radius of U(IV) and Th(IV) but this ligand is able to wrap completely around tetravalent actinide ions and to form rigid chelates. There are a very large number of possible conformations for a 18-membered ring,¹⁷ and it could not have been foreseen that HEHA would form a kinetic topomer of C₂ symmetry that would slowly rearrange into a highly symmetric thermodynamic topomer. This is in complete contrast with the behavior of DOTA and TETA whose 12- and 14-membered cycles are known to exhibit well-defined conformational preferences^{1,2} for a square [3333] and a quadrangular [77] geometry. The geometry of the lanthanide chelates of these ligands was predicted simply by assuming that the preferred conformation of the free macrocyclic ring was also found in the metal complexes.^{1,2} HEHA does not lend itself to such an analysis—not only when one examines the properties of its actinide complexes but also if one studies its lanthanide chelates. The NMR spectrum of $[\text{EuHEHA}]^{3-}$ displays 36 major peaks and 36 minor peaks that cannot be assigned but that are clearly due to totally asymmetric structures (see Supporting Information). Small differences in ionic charge and size of the encapsulated metal ions obviously have a drastic and unanticipated influence on the geometry of the HEHA chelates.

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Supporting Information Available: Figures giving experimental ¹H–¹H coupling constants for the two topomers, calculated ¹H spectra of the two topomers, ¹³C spectra of the two topomers, a HETCOR ¹H–¹³C 2D spectrum of the kinetic topomer of $[\text{Th}(\text{HEHA})]^{2-}$, a ¹H COSY spectrum of the thermodynamic topomer of $[\text{Th}(\text{HEHA})]^{2-}$; ¹H spectrum of $[\text{U}(\text{HEHA})]^{2-}$ in a 1:1 DMSO-*d*₆:D₂O mixture; Arrhenius plot for the topomerization of $[\text{Th}(\text{HEHA})]^{2-}$, and a ¹H spectrum of $[\text{EuHEHA}]^{3-}$ in D₂O (9 pages). Ordering information is given on any current masthead page.

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