1,4,7,10,13,16,19,22-Octaazacyclotetracosane-1,4,7,10,13,16,19,22-octaacetic Acid (H_8OTEC) and 1,4,7,10,14,17,20,23-Octaazacyclohexacosane-1,4,7,10,14,17,20,23-octaacetic Acid (H_8OHEC): Synthesis and Characterization of Two Large Macrocyclic Polyamine Polycarboxylic Ligands and Some of Their Copper(II) and Lanthanide(III) Complexes

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The optimized synthesis of two new macrocyclic polyamine polycarboxylic ligands, 1,4,7,10,14,17,20,23-octaazacyclohexacosane-1,4,7,10,14,17,20,23-octaacetic acid (H_8OHEC) (**10**) and 1,4,7,10,13,16,19,22-octaazacyclotetracosane-1,4,7,10,13,16,19,22-octaacetic acid (H_8OTEC) (**12**), is presented. The key step in the synthesis of both is the high yield carboxymethylation of the corresponding macrocyclic amines using *tert*-butyl bromoacetate followed by acidic hydrolysis of the acetate protecting groups. The molecular structures of the intermediates 1,4,7,10,14,17,20,23-octaazacyclohexacosane (OHEC-amine) (**8**), and octa-*tert*-butyl 1,4,7,10,13,16,19,22-octaazacyclotetracosane-1,4,7,10,13,16,19,22-octaacetate (OTEC-ester) (**11**) are determined by X-ray crystal structure analysis. OHEC-amine **8** reacts with 2 equiv. of $CuSO_4$ yielding the dinuclear complex $[Cu_2(OHEC\text{-amine})](SO_4)_2$ (**13**). Complex **13** crystallizes with 16 molecules of water. **13** · 16 H_2O contains two copper atoms, which are coordinated in a strongly distorted octahedral fashion by four nitrogen atoms, one oxygen atom from the sulfate dianion and one oxygen atom from a water molecule. The new ligands **10** and **12** are fully characterized by 1D- and 2D-NMR spectroscopy. Both ligands form dinuclear lanthanide(III) chelates (Ln = Y, Sm, Eu, Gd, Yb, Lu), which are stable and highly water soluble. With lanthanum(III) only mononuclear complexes are formed.

Introduction

Chelate complexes used as contrast enhancement agents are becoming more and more important as diagnostic drugs for nuclear magnetic resonance imaging. There are several agents used clinically for MRI including the acyclic chelates[1] $[Gd(DTPA)]^{2-}$ and the neutral[2] Gd(DTPA-BMA), as well as the kinetically stabilized macrocyclic[3] chelates $[Gd(DOTA)]^-$ and [Gd(HP-DO3A)][4]. DOTA turned out to be a suitable ligand for the formation of both the gadolinium(III) and yttrium(III) complexes; the latter are used for radioimmunotherapy[5]. There is still a high demand for new ligands which will lead to complexes with improved proton relaxation enhancing properties and an even higher in vivo stability. A great variety of functionalized derivatives of DOTA[6–14] and DTPA[11,12,15–19] has been synthesized for medical applications and some of the corresponding gadolinium(III) chelates are in the phase of clinical testing. The following points are of special interest with respect to the design of new contrast agents: (i) minimization of the osmolality of the complexes in solution by preparation of neutral compounds, (ii) slowing down of the molecular tumbling of the complexes in order to achieve enhanced proton relaxivity by increasing of the ligand bulk, (iii) introduction of hydrophilic groups on the ligands to attract more water molecules via hydrogen-bonding in order to increase the "outer-sphere" contribution to relaxivity, (iv) synthesis of ligands which allow a coupling of the ligand or the complex to molecules with a specific biodistribution (e.g. proteins or monoclonal antibodies).

To date, only a few macrocyclic dinuclear lanthanide chelate complexes have been reported[20,21]. In this contribution we present the synthesis and characterization of two new macrocyclic polyamine polycarboxylic ligands and some of their homodinuclear lanthanide(III) chelates (Ln =

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Y, Sm, Eu, Gd, Lu). Our studies are aimed at the synthesis of hexadecadentate ligands based on the DOTA or DTPA backbone, which can bind at least two trivalent lanthanide ions, to study their coordination chemistry and to determine the stability of such complexes in solution.

In addition, the coordination chemistry of a ligand precursor amine with Cu^{II} ions is described.

Results and Discussion

1. Synthesis and Characterization of the Ligands

The general route used for the preparation of H_8OHEC is shown in Scheme 1. The synthesis of the macrocyclic octaamine **8** follows a modification of the well-known procedure for the synthesis of 1,4,7,10,13,16,19,22-octaazacyclotetracosane (OTEC-amine) by Richman and Atkins[22]. A modified synthesis and the characterization of this macrocyclic octaamine and its dinuclear copper(II) complex have been published by Bianchi et al.[23]. The critical step in the synthesis of both ligands, OTEC-amine and OHEC-amine **8** is the detosylation of the protected amines. Several methods known for the cleavage of sulfonamides[24–26] are unsuccessful for the two compounds due to their insolubility in the published reaction media. Satisfactory yields (50% up to 75%) of the amines are obtained by heating the tosylated compounds in concentrated sulfuric acid (3 h, 110°C), or in an 1:1.5 mixture of glacial acetic acid and concentrated sulfuric acid (2 h, 110°C)[27]. Varying amounts of water-insoluble side products are formed during treatment with sulfuric acid, which can be easily separated. They are also insoluble in organic solvents. The amount of these precipitated side products increases upon increasing the duration of treatment.

Direct synthesis of the ligands, involving the alkylation of the amines with chloroacetic acid[28] followed by ion-exchange chromatography, does not provide a high yield of the octaalkylated product. Analysis of the products so obtained reveals that mixtures of partially alkylated species are produced, with the desired ligand detected by FAB^+MS only in very small amounts.

Carboxymethylation of the octaamines with *tert*-butyl bromoacetate[9], followed by hydrolysis gives high yields of the octaacetic ligands H_8OTEC **12** and H_8OHEC **10**. The carboxymethylation requires careful control of the stoichiometry and reaction conditions. Otherwise, mixtures of quaternary products are obtained, especially in the reaction using OHEC-amine **8**.

All products were characterized by elemental analysis, FAB^+MS, IR, and NMR spectroscopy. ^1H- and ^{13}C-NMR spectra of most of the compounds were measured and a 2D-NMR study of H_8OHEC **10** was performed in order to assign all the peaks. The HMBC spectrum shows long range connectivities which clearly identifies the different CH_2 groups. ^1H- and ^{13}C-NMR assignments of the octaacetic ligands H_8OHEC and H_8OTEC are summarized in Table 1.

Interestingly, three sharp bands of medium intensity are found in the solid-state IR spectrum of the neutral OHEC-amine **8** at 3325, 3280, and 3190 cm^{-1}. This provides evidence for a strong interaction between the N atoms via an N–H···N hydrogen-bond pattern within the molecule in the crystalline state. Hydrogen-bonding between closely neighboured molecules is also likely. A similar observation has been made for the smaller cyclam analogue (1,4,8,11-tetraazacyclotetradecane)[29a]. The two bands observed at 3270 cm^{-1} ad 3190 cm^{-1} in the solid-state IR spectrum of the compound were attributed to an intramolecular hydrogen-bond pattern[29a,b]. However, attempts to confirm this fact in cyclam by other methods were unsuccessful[29c].

2. Molecular Structures of the Ligands

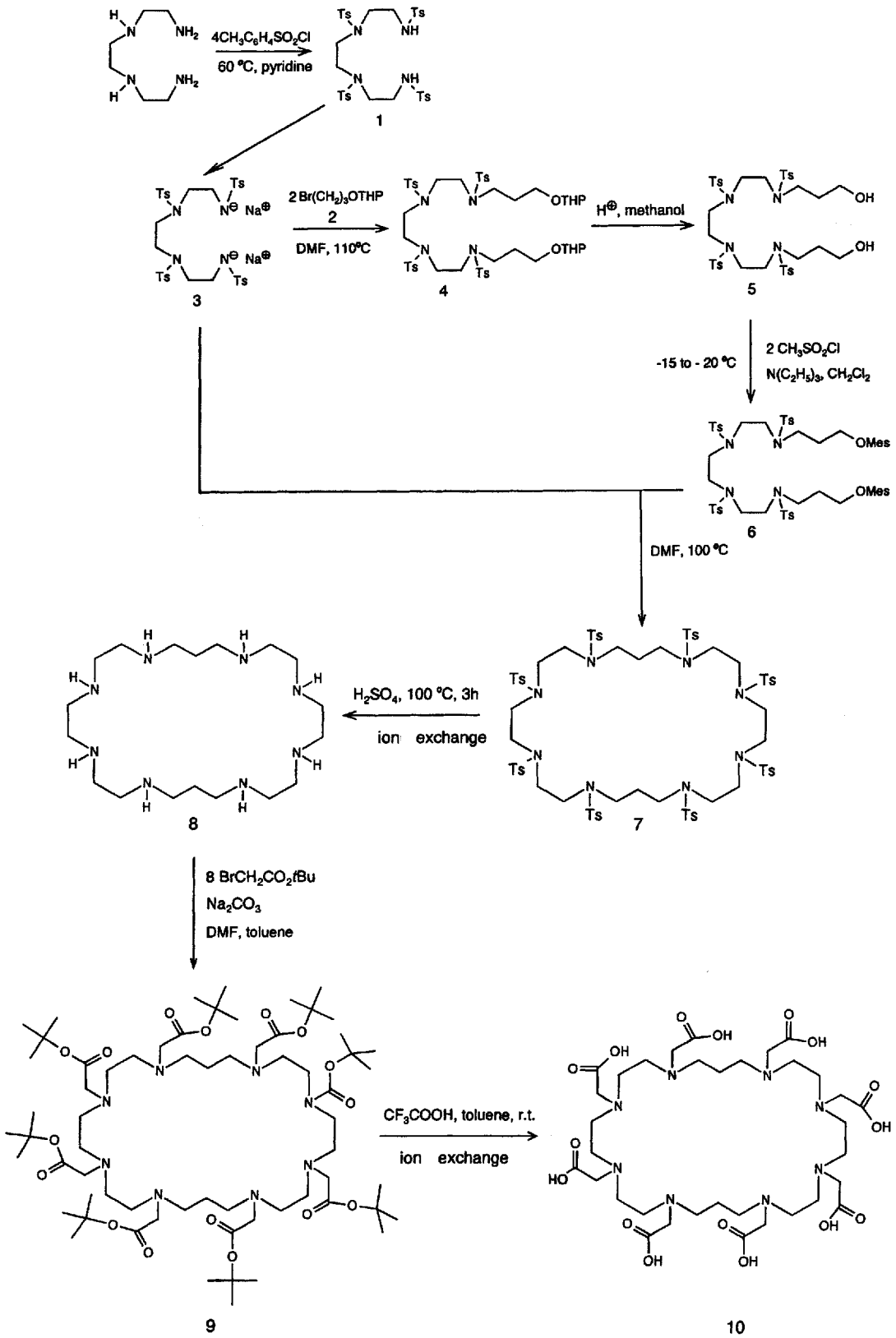
The molecular structures of the OHEC-amine **8**, its dinuclear copper complex **13** · 16 H_2O and the OTEC-ester **11** were established by single-crystal X-ray structure analysis.

Structure of OHEC-amine **8**: Single crystals of **8**, obtained from a saturated ethyl acetate solution, proved to be suitable for crystal-structure analysis. The asymmetric unit of the triclinic unit cell was found to contain one formula unit of **8** (Figure 1). The center of the macrocyclic ring resides on a crystallographic center of inversion. The four nitrogen atoms of one asymmetric unit are almost coplanar and the conformation of the macrocyclic ring corresponds to the chair shape. The cyclic amine exists in its neutral, base-free form. No counterion of a possible ammonium salt could be detected. Furthermore, the crystals were found not to contain any water. All hydrogen atoms reside on calculated positions.

However, hydrogen-bonding was detected in crystalline samples of **8** by IR spectroscopy. The presence of hydrogen bonds was also indicated by the observed (Figure 1) N–N contact distances in **8**. Typical N–N separations for N–H···N hydrogen bonds are below 300 pm. In fact, based on this assumption, all nitrogen atoms within the ring are intramolecularly hydrogen-bonded forming two six-membered and four five-membered rings (Figure 1). The presence of a weak intermolecular hydrogen-bonding is also likely because the small N–N separations between nitrogen atoms of neighbouring molecules only slightly exceed 300 pm. In Figure 2 a packing diagram is presented and hydrogen bonds are indicated by broken lines. The values of the C–N and C–C bond lengths are identical, within statistical limits, to those found in other polyazamacrocyclic compounds.

Structure of OTEC-ester **11**: Surprisingly, **11** was obtained as a white solid. Esters of macrocyclic polyamines in pure form are expected to be isolated as viscous, non-crystallizing oils. The ester was crystallized by slow evaporation of the solvent from a solution of **11** in a methanol/water mixture or by storing the solution in a refrigerator (ca. 4°C) to give colourless crystals which were suitable for X-ray structure analysis. The macrocyclic ring is sterically very crowded by the eight bulky *tert*-butyl acetate pendant arms, four of which are situated above and four below the ring. The macrocycle minimizes the steric strain by adopting a twisted configuration, which is best described as crown-shaped (Figure 3).

Scheme 1. Reaction sequence for the synthesis of the macrocycle H_8OHEC **10**

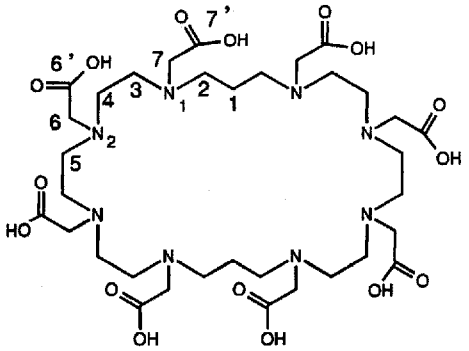


3. Synthesis and Characterization of the Complexes

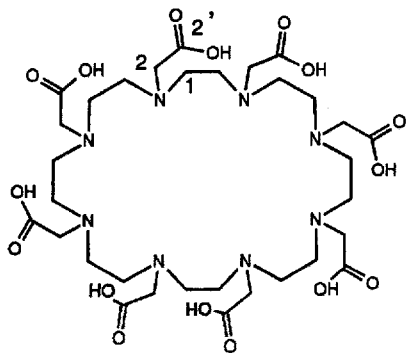
Synthesis and X-ray Structure of [Cu_2(OHEC-amine)](SO_4)$_2$ · 16 H_2O (**13** · 16 H_2O): The complex can be easily obtained by treating equimolar amounts of the cyclic octaamine **8** with $CuSO_4$ in water. The formation of the complex leads to a deep-blue aqueous solution. Needle-

Table 1. ^1H- and ^{13}C-NMR data of the synthesized ligands H_8OHEC **10** and H_8OTEC **12** in D_2O (with designation of carbon and hydrogen atoms for clarity in NMR-signal assignment)

ligand	signal	^1H δ	^{13}C δ
H_8OHEC **10**	1	2.27 (m, 4 H)	19.7
	2	3.33 (m, 8 H)	53.1
	3	3.56 (t, 8 H)	51.7
	4	3.37 (t, 8 H)	50.7
	5	3.26 (s, 8 H)	52.5
	6	3.67 (s, 8 H)	55.2
	6'		172.9
	7	3.82 (s, 8 H)	55.7
	7'		170.1
H_8OTEC **12**	1	3.29 (s, 32 H)	54.0
	2	3.65 (s, 16 H)	59.2
	2'		169.5



10



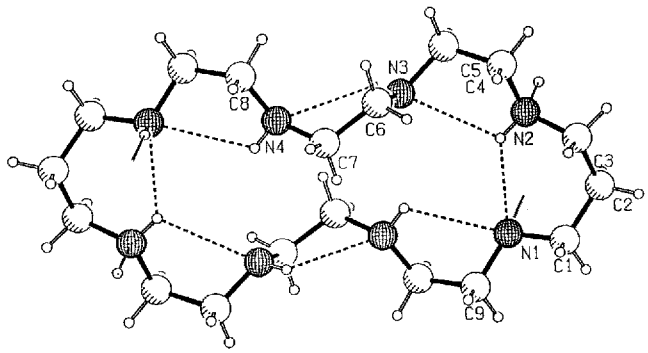
12
(**11**: octa-*tert*-butyl ester of **12**)

shaped crystals suitable for X-ray analysis are obtained by slow concentration of an aqueous solution of the complex at room temperature.

$$2\,CuSO_4 + \mathbf{8} \rightarrow [Cu_2(OHEC\text{-}amine)](SO_4)_2$$
13

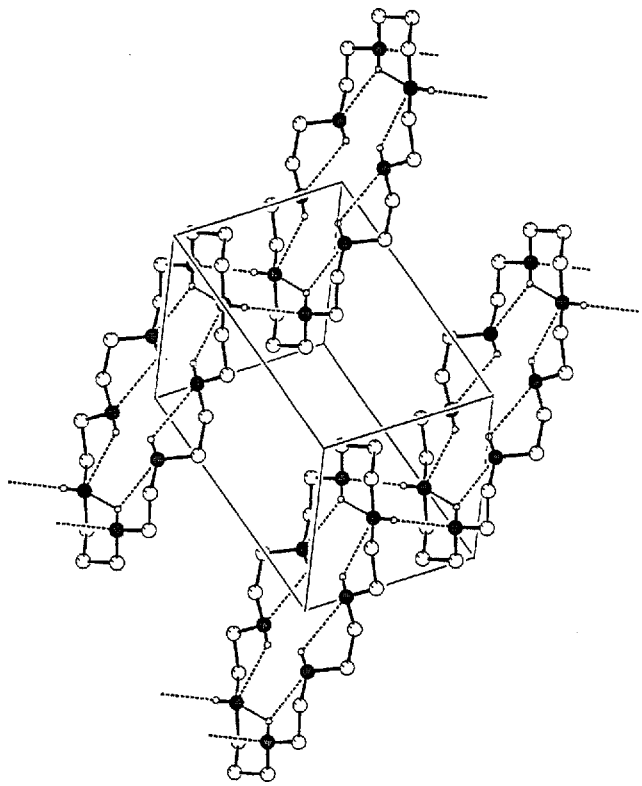
Crystals of **13** · 16 H_2O contain centrosymmetric dinuclear [Cu_2(OHEC-amine)] units (Figure 4). In the dinuclear complex each copper atom is coordinated by four nitrogen atoms of the macrocyclic ligand, one oxygen atom of a sulfate dianion and one oxygen atom of one water molecule, forming a strongly distorted octahedral coordination environment around the copper atoms. The nitrogen atoms of

Figure 1. PLUTON plot of the molecular structure of OHEC-amine **8** with the numbering scheme; selected interatomic distances [pm] and bond angles [°] in **8** with estimated standard deviations in parentheses



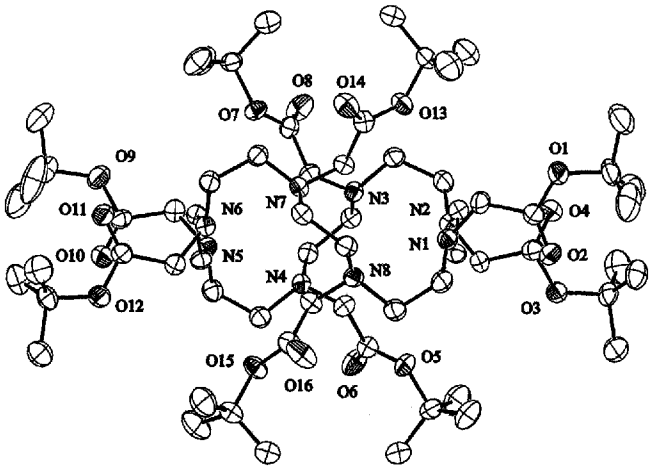
C1–C2	150.3(12)	C4–C5	150.1(11)	C6–N3	145.2(10)
C1–N1	145.1(9)	C4–N2	144.8(10)	C7–N4	145.5(9)
C2–C3	150.7(13)	C5–N3	145.3(10)	C8–N4	145.0(10)
C3–N2	146.3(10)	C6–C7	149.2(11)	C9–N1	145.3(10)
non-bonding distances					
N4–N1	288.0	N3–N2	293.0	N3–N4	291.4
N2–N1	297.8				
C1–N1–C9	112.8 (6)	C3–N2–C4	113.8 (6)	N3–C6–C7	111.2 (6)
N1–C1–C2	112.7 (6)	N2–C4–C5	110.7 (6)	C6–C7–N4	112.8 (6)
C1–C2–C3	114.9 (7)	C4–C5–N3	112.4(6)	C7–N4–C8	114.7 (6)
C2–C3–N2	112.0 (7)	C5–N3–C6	113.6 (6)		

Figure 2. Solid-state conformation of OHEC-amine **8** in the unit cell; broken lines show possible N–H···N contacts



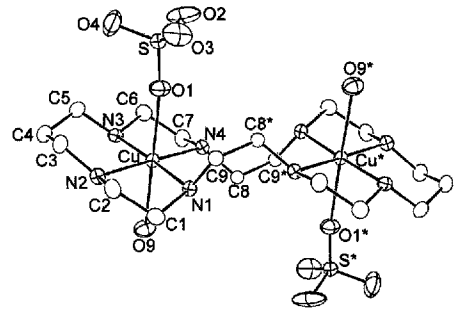
the asymmetric unit lie approximately in one plane, as they do in the ligand **8**, with a maximum deviation from the plane of 2.6 pm. The copper atoms occupy the center of the plane with a shift of only 3.8 pm towards the coordi-

Figure 3. ORTEP plot of the molecular structure of OTEC-ester **11** with the numbering scheme; thermal ellipsoids are 30% probability level; selected bond lengths [pm] and angles [°] in **11** with estimated standard deviations in parentheses



C1–C2	150.9(7)	C4–N3	146.5(6)	C8–N5	145.9(6)
C1–N1	146.4(7)	C5–N3	146.1(6)	C9–C10	152.0(7)
C2–N2	147.3(7)	C6–N4	146.3(6)	C9–N5	146.6(6)
C3–N2	146.7(7)	C7–N4	145.5(6)	C10–N6	147.8(6)
C3–C4	153.8(7)	C7–C8	151.6(7)		
C2–C1–N1	113.2(5)	C4–C3–N2	112.2(4)	N4–C6–C5	114.5(4)
N2–C2–C1	112.8(5)	N3–C4–C3	114.2(4)	C7–N4–C6	114.6(4)
C3–N2–C2	113.6(4)	C5–N3–C4	113.5(4)	C8–C7–N4	114.4(4)
C2–C3–N2	112.5(2)	C6–C5–N3	113.9(4)	N5–C8–C7	112.8(4)

Figure 4. Solid-state conformation of $[Cu_2(OHEC\text{-amine})](SO_4)_2$ 16 H_2O (**13** · 16 H_2O); only copper-bound water molecules are shown; selected bond lengths [pm] and angles [°] in **13** · 16 H_2O with estimated standard deviations in parentheses[a]



Cu–N1	207.7(3)	Cu–O9	243.7(2)	N3–C6	146.2(4)
Cu–N2	202.4(3)	Cu–Cu[b]	582.0(1)	N4–C7	148.5(4)
Cu–N3	203.3(3)	N1–C1	149.1(4)	N4–C8	148.9(4)
Cu–N4	205.7(2)	N2–C3	147.3(4)	N1–C9	149.1(4)
Cu–O1	238.6(2)	N3–C5	147.9(4)		
N1–Cu–N2	85.12(10)	N3–Cu–N4	84.88(10)	Cu–N4–C7	106.6(2)
N1–Cu–N3	176.93(10)	N3–Cu–O1	90.09(10)	Cu–N4–C8	120.4(2)
N1–Cu–N4	98.09(10)	N3–Cu–O9	87.88(10)	C7–N4–C8	111.2(2)
N1–Cu–O1	91.71(10)	O1–Cu–O9	176.35(10)	Cu–N1–C1	104.2(2)
N1–Cu–O9	91.55(10)	C2–N2–C3	111.0(3)	Cu–N1–C9	118.0(2)
N2–Cu–N3	91.87(11)	Cu–N3–C5	118.2(2)	C1–N1–C9	110.5(2)
N2–Cu–N4	175.21(10)	Cu–N3–C6	107.2(2)	Cu–N2–C2	108.0(2)
N2–Cu–O1	93.85(10)	C5–N3–C6	111.1(2)	Cu–N2–C3	118.1(2)
N2–Cu–O9	88.22(10)				

[a] Atoms labelled with (*) represent symmetry-equivalent positions of the type $(-x, -y, -z)$. – [b] This is the distance between the copper atoms within the ring.

nated sulfate anion. This "in plane" coordination of the copper ions is favoured by the low energy chair configuration of the six-membered chelate rings involving the propylene bridged nitrogen atoms. The bond angles N–Cu–N involving the propylene bridged nitrogen atoms are more relaxed (91.87°, Figure 4) in comparison to those with ethylene bridged nitrogen atoms (84.88, 85.12°). On the other hand, the dinuclear copper complex of OTEC-amine[23] exists in an "out-of-plane" coordination with a maximum deviation of 360 pm of the copper ions from the center of the N_4 planes. This significant difference in the molecular structures of these complexes leads to the presumption that **13** · 16 H_2O must be the complex of higher stability. This is in accordance with the rule of ligand design established by Hancock[30], which relates complex stability to the size of both the chelate ring and the metal ion. According to this rule, small metal ions such as Cu^{2+} should give more stable complexes with **8** which allows the formation of two six-membered rings in comparison to OTEC-amine which can onyl form five-membered chelate rings.

The long intramolecular Cu–Cu separation (582 pm), which is the shortest Cu–Cu contact found in this structure, excludes any electronic interaction. This is in agreement with the magnetic moment of the complex, measured on a powdered sample by means of a Faraday magnetic susceptibility balance over the temperature range 78–325 K. The corrected effective magnetic moment is 1.80 (±0.10) B.M. This corresponds to mononuclear Cu^{II} complexes with temperature independent magnetic moments[31]. The mean Cu–N distance [205(3) pm] is comparable to that in other hexacoordinated Cu^{II} complexes[32]. Bond lengths and angles are similar to those of the free ligand. In contrast to the free ligand OHEC-amine, the complex **13** · 16 H_2O is wrapped in a water matrix. The crystal contains sixteen molecules of water per molecule of complex. Only one molecule is definately coordinated to each copper atom. In the solid state complex **13** · 16 H_2O, the macrocyclic ring of the ligand adopts a chair conformation, similar to that in **8**, with all five- and six-membered rings in the gauche configuration.

Lanthanide Complexes: Mono- and dinuclear lanthanide(III) complexes were obtained by treating the ligands H_8OTEC and H_8OHEC with lanthanide oxides Ln_2O_3 (Ln = La, Eu, Gd) or with lanthanide(III) hydroxides, freshly prepared from the corresponding chlorides or triflates (Ln = Y, Sm, Yb, Lu) under basic conditions (pH adjusted to 8.5 with NaOH) in aqueous solution. The large La^{3+} ion gives only mononuclear complexes with both ligands.

$$Lu(OH)_3 + \mathbf{10} + 5\ NaOH \rightarrow [Na_5Lu(OHEC)] + 8\ H_2O$$
14f

$$2\ Ln(OH)_3 + \mathbf{10} + 2\ NaOH \rightarrow [Na_2Ln_2(OHEC)] + 8\ H_2O$$
15a (Ln = Y), **15c** (Sm)

$$Ln_2O_3 + \mathbf{10} + 2\ NaOH \rightarrow [Na_2Ln_2(OHEC)] + 5\ H_2O$$
15d (Ln = Eu), **15e** (Gd)

$$Y(OH)_3 + \mathbf{12} + 5\ NaOH \rightarrow [Na_5Y(OTEC)] + 8\ H_2O$$
16a

$$La_2O_3 + 2\ \mathbf{12} + 10\ NaOH \rightarrow 2\ [Na_5La(OTEC)] + 13\ H_2O$$
16b

$$2\ Y(OH)_3 + \mathbf{12} + 2\ NaOH \rightarrow [Na_2Y_2(OTEC)] + 8\ H_2O$$
17a

$$Ln_2O_3 + \mathbf{12} + 2\ NaOH \rightarrow [Na_2Ln_2(OTEC)] + 5\ H_2O$$
17d (Ln = Eu), **17e** (Gd)

The dinuclear complexes with Ln = Sm, Eu, and Gd were characterized by means of FAB$^+$MS. All complexes proved to be highly soluble in water.

Single crystals of the complexes could be obtained by very slow evaporation of the aqueous solutions of the sodium salts. However, despite the good optical shape of the crystals obtained, they were found to have grown in layers and to date all attempts to investigate their solid-state structures have been unsuccessful.

Compared to those of the free ligands, the NMR spectra of the mononuclear chelates show broad lines indicating the presence of dynamic processes (diamagnetic complexes). For the dinuclear chelates, room-temperature NMR spectra consist of very complex lines. To study the solution behaviour of these chelates, variable temperatue NMR investigations are currently in progress.

4. Electrochemical Studies

Detailed results of this study are reported separately[33]. Polarograms on DME and cyclic voltammetry plots on GC of mono- and dinuclear Eu^{III} complexes with H_8OHEC, prepared without addition of base (pH = 3.4–5.6), revealed the presence of free or only loosely bound metal ions in the aqueous solution. This is presumably caused by dissociation or uncomplete chelation. Within this pH range, the acidic protons bonded to nitrogen are responsible for the poor coordination ability of the macrocycle. Free Eu^{3+} ions are incorporated completely into the complex after constant potential electrolysis whereas the acidic protons are irreversibly removed by their reduction to H_2. The current for reduction of free Eu^{3+} ions is absolutely absent, and in turn the current density for the complex increases. Thus it seems that electrochemically prepared dinuclear Eu^{III} complexes are surprisingly resistant towards dissociation in water. According to the large shifts in reduction potentials for complexed Eu^{III}, the metal ions are bound to the ligand both by carboxylate groups as well as by nitrogen donors. This accounts for the high stability of these complexes.

5. ^{89}Y-NMR Investigations

^{89}Y-NMR chemical shifts of the complexes investigated are summarized in Table 2. Firstly, ^{89}Y-NMR studies of mono- and dinuclear Y^{III} chelates, prepared by treating equimolar amounts of the ligands H_8(OTEC) and H_8(OHEC) with $Y(OH)_3$ under acidic (pH = 3.4–5.6) and basic (pH = 8–9) conditions, show results consistent with the aforementioned electrochemical investigations. Although yttrium is not a lanthanide metal, it has a trivalent effective ionic radius comparable to those of the second half of the lanthanides. Hence it is a potentially useful candidate for testing the binding of lanthanide ions in amino carboxylates. Primarily, our objective was the detection of signals for coordinated and free metal ions. For comparison, the Y^{III} chelates of EDTA, DTPA, and DOTA were prepared under identical conditions and also investigated by NMR. For the complex prepared by reacting H_8OTEC with $Y(OH)_3$ in the molar ratio 1:1, three types of ^{89}Y-NMR signals appeared in the spectrum. This reveals the existence of an equilibrium between different Y^{III} species: (i) one intense upfield resonance signal for uncomplexed $^{89}Y^{III}$ (δ = 0), caused by dissociation of loosely bound metal ions or incomplete chelation, (ii) one lowfield resonance signal for $^{89}Y^{III}$ in the mononuclear complex of approximately half the intensity (δ = 97.7), and (iii) two signals attributable to $^{89}Y^{III}$ in the dinuclear chelate with shifts at higher field (δ = 71.9, 64.7) and nearly the same intensity as free $^{89}Y^{III}$ (Table 2). After adjusting the solution to pH = 8.5, no equilibrium between the mono- and dinuclear complexes was detectable. Only the ^{89}Y resonance at δ = 114.0 was observed. Interestingly, in the NMR spectrum of the dinuclear complex, prepared by treating H_8OTEC with $Y(OH)_3$ in the molar ratio 1:2, no ^{89}Y signal for the mononuclear complex could be observed. Thus the equilibrium between the Y^{III} species must favour the more stable dinuclear complex, as already found by polarography for $[H_2Eu_2(OHEC)]$[3]. The intensities of the signals for free and complexed $^{89}Y^{III}$ in this spectrum were approximately the same. Similar observations were made for the corresponding complexes with H_8OHEC. With the exception of $[H_2Y(DTPA)]$, in all chelates studied a significant signal for free Y^{3+}(aq) was observed under these conditions, although in considerably lower intensity than in the complexes with **10** and **12**. After adjusting the solutions of these complexes to pH = 8.5, no signal for the free Y^{III} was observed for any of the complexes investigated. Generally, chemical complexation under basic conditions (pH $\approx$ 8.5) should ensure (i) deprotonation of the ligand leading to strong chelation of metal ions by carboxylate groups as well as by the non-charged nitrogen donors, (ii) removal of excess metal ions by their precipitation as hydroxide, thereby minimizing the detectable amount of free metal ions.

The distinct ^{89}Y-NMR chemical shifts measured for mono- and dinuclear complexes indicate that the metal ions in these chelates have different coordination environments. The two ^{89}Y-NMR signals found in the spectrum of the dinuclear complex **15a**, which were detectable in the pH range 3.4–8.5, may be caused by two different species in solution.

6. FAB$^+$MS Measurements

The characterization of the complexes $[Na_2Ln_2(OTEC)]$ and $[Na_2Ln_2(OHEC)]$ (Ln = Sm, Eu, Gd) by FAB$^+$ mass

Table 2. ^{89}Y-NMR chemical-shift (δ values) assignment of different yttrium complexes

complex	pH (± 0.1)	^{89}Y δ
$[Y(EDTA)]^-$	2.0	129.5 (129.6/pH 5.9)[a]
$[Y(DTPA)]^{2-}$	2.1	82.5 (82.2/pH 5.8)[a]
$[Y(DOTA)]^-$	1.9	118.2
reaction of H8OTEC with $Y(OH)_3$ in molar ratio 1 : 1		
Y(OTEC)[b]	3.4	97.7
Y_2(OTEC)[b]	3.4	64.7; 71.9
Y(OTEC)[b]	8.5	114.0
reaction of H8OTEC with $Y(OH)_3$ in molar ratio 1 : 2		
Y_2(OTEC)[b]	5.0	64.7; 71.9
Y_2(OTEC)[b]	8.5	63.7; 70.2
reaction of H8OHEC with $Y(OH)_3$ in molar ratio 1 : 2		
Y_2(OHEC)[b]	5.6	85.2
Y_2(OHEC)[b]	8.5	83.5

[a] Literature value (see ref.[34]). – [b] Part of the species.

spectrometry unambiguously showed complexation of two cations per ligand molecule by the presence of an intense molecular ion $[M + H]^+$. Other peaks of lower intensity were observed which could be assigned to the molecular species $[M + Na]^+$, $[M - Na + 2H]^+$, and $[M - 2Na + 3H]^+$. The molecular ions showed the typical isotopic pattern of the corresponding lanthanides.

The FAB$^+$ mass spectrum of $[H_2Gd_2(OHEC)]$, prepared without addition of base, showed not only the molecular ion $[M + H]^+$ but also another intense peak at m/z = 1301.5, probably corresponding to the fragment $[M - 2H + Gd]^+$, which contains a loosely bound third Gd^{III} ion. This peak was not found in the FAB spectrum of $[Na_2Gd_2(OHEC)]$.

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Experimental Section

1. General: Organic and inorganic reagents were purchased from Merck or Aldrich and were used without further purification (unless otherwise noted). The reactions were followed by TLC which was carried out on precoated TLC plates (Merck silica gel 60 F-254) with an ethyl acetate/dichloromethane (20:1) mixture as eluent. Purification of the octaacid ligands was carried out by reversed-phase column chromatography (Europrep silica gel 60–60 C18, 35–70 μ irregular). A water/methanol mixture was used as eluent. Ion-exchange resins were purchased from Merck (Amberlyst 15, macroporous, H^+ form; Amberlite IRA-410, obtained in Cl^- form, used in OH^- form). – Elemental analyses: Perkin-Elmer 2400 Series CHNS/O Analyzer. – IR (KBr pellets; range $\tilde{\nu}$ = 4000–400 cm^{-1}). Perkin-Elmer 560 B spectrometer. – MS: Double-focusing ZAB instrument, VG company (FAB, positive ions). – ^{1}H, ^{13}C, and ^{89}Y NMR: Bruker WP 80 SY, WH 270, AM 300, ARX 400, and AMX 600 instruments. The compounds **8**, **9**, and **11** were dissolved in $CDCl_3$ and the spectra were measured at room temp. with respect to the internal standard of the solvent. The spectra of the ligands **10** and **12** and of the complexes **16b** and **14f** were recorded in D_2O solution at room temp. and are reported with respect to an external standard ($CHCl_3$). Based on one-dimensional ^{1}H-NMR and ^{13}C-NMR spectra, ^{1}H–^{1}H homo- and ^{13}C-^{1}H heteronuclear shift correlations were measured[35]. The inverse detected ^{1}H–^{13}C correlation via heteronuclear zero and double quantum coherence (HMBC) was carried out with shaped gradient pulses. The pulse sequence contained a low-pass J filter to suppress one-bond correlations [^1J(CH) = 130 Hz] and was optimized on the long-range coupling constants [^{LR}J(HC) = 5.5 Hz]. The gradient pulses had a sine shape and a gradient ratio of 5:3:4. The other experimental parameters were used as follows: spectral width in F2 3817 Hz and in F1 29412 Hz, number of experiments 512 and relaxation delay 3 s. ^{89}Y-NMR chemical shifts are reported versus a 1.0 M solution of YCl_3 in D_2O as external standard. The spectra required 14000–30000 pulses for satisfactory signal-to-noise ratio. The magnetic susceptibility of $[Cu_2(OHEC\text{-amine})](SO_4)_2$ **13** was measured from 78–325 K by using a Faraday magnetic susceptibility balance. Diamagnetic corrections were estimated by using the semiempirical increment system by Haberditzl[36].

2. Crystallographic Studies[37]: Compound **13** crystallizes with 16 molecules of water. Crystals of **13** · H_2O are temperature sensitive (loss of solvent), while **8** and **11** are stable at room temp. Suitable specimens of **8** and **13** · 16 H_2O were selected at −100 °C using a device similar to that described by Veith and Bärnighausen[38] and mounted in the cold stream [−100(2) °C] of an Enraf-Nonius CAD-4 diffractometer. A crystal of **11** was selected in air and mounted at 20(2) °C on a Syntex $P2_1$ diffractometer. Important crystal and data-collection details are listed in Table 3. Data for all three compounds were collected by using ω-2Θ scans. Raw data were reduced to structure factors (and their esd's) by correcting for scan speed, Lorentz and polarization effects[39]. No crystal decay was detected during data collection. Empirical absorption corrections were applied to the data for **8** and **11**[40]. The space group was found to be $P\bar{1}$ for **8** and **11** and was unambiguously determined from systematic absent reflections to be $P2_1/c$ for **13** · 16 H_2O. All three structures were solved by direct methods. The positional parameters for all non-hydrogen atoms were refined by using first isotropic and later anisotropic thermal parameters. Difference Fourier maps calculated at this stage showed the positional parameters of the hydrogen atoms for all three molecules. All hydrogen atoms were added to the structure models at calculated positions (no water hydrogen atom positions were calculated for **13** · 16 H_2O) and are unrefined. The isotropic temperature factors for hydrogen atoms were fixed. The asymmetric unit in **13** · 16 H_2O contains 1/2 molecule, which is related to the other half by an inversion

Table 3. Summary of crystallographic data for OHEC-amine **8**, OTEC-ester **11**, and $[Cu_2(OHEC\text{-amine})](SO_4)_2$ · 16 H_2O (**13** · 16 H_2O)

	8	**11**	**13** · 16 H_2O
crystal size [mm]	0.20×0.20×0.20	0.70×0.60×0.45	0.30×0.40×0.65
formula	$C_{18}H_{40}N_8$	$C_{64}H_{120}N_8O_{16}$	$C_{18}H_{76}Cu_2N_8O_{24}S_2$
mol wt [amu]	368.58	1257.70	980.05
a [pm]	803.7(2)	1124.6(2)	891.0(4)
b [pm]	857.8(4)	1820.5(6)	1400.4(4)
c [pm]	907.7(4)	1994.1(6)	1690.4(4)
α [°]	84.57(3)	82.36(2)	—
β [°]	68.17(3)	77.62(2)	101.94(3)
γ [°]	72.25(3)	76.32(2)	—
V [Å^3]	553.1(4)	3860(2)	2063(2)
Z	1	2	2
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
ρ [g/cm^3]	1.119	1.082	1.577
μ [cm^{-1}]	0.70	0.77	12.17
radiation, λ [Å]		Mo-K_α, 0.71073	
2 Θ-range, [°]	5 ≤ 2 Θ ≤ 45	1 ≤ 2 Θ ≤ 45	2 ≤ 2 Θ ≤ 50
unique data	1363	10151	3626
observed data	1313 $F_o^2 \geq 4\sigma(F_o^2)$	5570 $F_o^2 \geq 4\sigma(F_o^2)$	3225 $F_o^2 \geq 3\sigma(F_o^2)$
R [%]	3.83	7.23	4.38
GOF	0.844	1.21	—
no of variables	122	793	235

center (see Figure 4, symmetry code $-x, -y, -z$). Calculations were carried out with SHELX-86[41] and SHELX-93[42] for **8** and **11** and with MolEN package for **13** · 16 H_2O[43]. ORTEP[44] was used for all molecular drawings. Table 3 gives a summary of the crystallographic data for OHEC-amine **8**, OTEC-ester **11**, and $[Cu_2(OHEC\text{-amine})](SO_4)_2 \cdot 16\ H_2O$ **13** · 16 H_2O.

3. Synthesis of the Ligands

1,4,7,10-Tetrakis-(p-tolylsulfonyl)-1,4,7,10-tetraazadecane (**1**): To a stirred solution of 514.73 g (2.70 mol) of *p*-tolylsulfonyl chloride in 1.5 l of pyridine, 165.00 g (0.68 mol) of 1,4,7,10-tetraazadecane (60%, Aldrich) was added slowly, with the temperature kept strictly in the range 50−60 °C. An orange precipitate was formed and the reaction mixture was stirred for further 30 min within the same temperature range. After cooling to room temp., 700 ml of water was added, the mixture was stirred overnight and then cooled at 0 °C for 2 h. The precipitated crude yellow product was filtered and washed several times with hot ethanol. The slightly yellow solid was then dried in vacuo at 50 °C. Yield 389.00 g (85%), m.p. 219−220 °C. − $C_{34}H_{42}N_4S_4O_8$ (762.65): calcd. C 53.52, H 5.55, N 7.34, S 16.81; found C 53.55, H 5.65, N 7.56, S 15.91.

3-Bromopropyl Tetrahydro-2 H-pyran-2-yl Ether (**2**): 14.33 g of cation-exchange resin Amberlyst H 15 was added to 238.50 g (1.72 mol) of 3-bromo-1-propanol at −15 °C, with stirring. Then, 151.42 g (1.80 mol) of dihydropyran was added dropwise while keeping the temperature below 10 °C. The reaction mixture was then allowed to reach room temp. and stirring was continued overnight. The ion-exchange resin was separated and the remaining brownish-green liquid was distilled in vacuo, yielding a colourless oil. Yield 325.42 g (85%), b.p. 59 °C/0.01 mbar. − $C_8H_{15}O_2Br$ (223.09): calcd. C 43.07, H 6.80; found C 42.98, H 6.77.

Disodium 1,4,7,10-Tetrakis(p-tolylsulfonyl)-1,4,7,10-tetraazadecane-N,N‴-diide (**3**): A suspension of 130.00 g (0.17 mol) of **1** in 1.5 l of absolute ethanol was refluxed under nitrogen. The heat source was removed and a solution of sodium ethoxide, prepared by dissolving 10.00 g (0.43 mol) of sodium in 300 ml of absolute ethanol, was added as rapidly as possible. The suspension changed to a clear solution, which was decanted from undissolved residues while still hot. The solution was stirred overnight, whereupon the product crystallized. The product was filtered, washed with absolute ethanol and dried in vacuo at 100 °C. Yield 130.30 g (95%). − $C_{34}H_{40}N_4S_4O_8Na_2$ (806.61): calcd. C 50.61, H 4.99, N 6.94, S 15.89; found C 50.22, H 5.18, N 6.99, S 14.77.

Bis(tetrahydro-2 H-pyran-2-yl) 4,7,10,13-Tetrakis(p-tolylsulfonyl)-4,7,10,13-tetraazahexadecane-1,16-diyl Ether (**4**): 73.18 g (0.33 mol) of **2** was added dropwise over a period of 3 h to a stirred solution of 133.14 g (0.16 mol) of **3** in 650 ml of anhydrous dimethylformamide at 100 °C under N_2. When the addition was complete, the solution was stirred for 1 h and then one third of the solvent was removed under reduced pressure. 200 ml of water was added and the mixture was extracted with CH_2Cl_2 (3 × 200 ml). The organic fractions were combined, washed with water, and dried with anhydrous $MgSO_4$. The solution was filtered, and the solvent removed in a rotary evaporator to afford a sticky yellow solid, which was recrystallized from hot methanol. Yield 103.70 g (60%), m.p. 145 °C. − FAB^+MS (3-nitrobenzyl alcohol) *m/z*: 1047.5 $[M + H]^+$, 963.4 $[M + 2H - THP]^+$, 879.4 $[M + 3H - 2\ THP]^+$. − $C_{50}H_{70}N_4O_{12}S_4$ (1047.00): calcd. C 57.34, H 6.74, N 5.35, S 12.24; found C 58.21, H 6.59, N 5.33, S 12.08.

4,7,10,13-Tetrakis(p-tolylsulfonyl)-4,7,10,13-tetraazahexadecane-1,16-diol (**5**): 5.20 g of cation-exchange resin Amberlyst H 15 was added to a suspension of 243.00 g (0.23 mol) of **4** in 500 ml of methanol and the mixture was refluxed. After 2 h, a clear solution was obtained. Refluxing was continued overnight yielding a suspension of a white product in methanol. After cooling, the product was filtered, dissolved in CH_2Cl_2 and separated from the ion-exchange resin. The solvent was removed in a rotary evaporator to afford a white solid. Yield 146.85 g (72%), m.p. 178−180 °C. − FAB^+MS (thioglycerine); *m/z*: 879.3 $[M + H]^+$, 725.3 $[M + 2H - Ts]^+$. − $C_{40}H_{54}N_4O_{10}S_4$ (750.87): calcd. C 54.65, H 6.19, N 6.37, S 14.59; found C 54.68, H 6.20, N 6.26, S 14.21.

4,7,10,13-Tetrakis(p-tolylsulfonyl)-4,7,10,13-tetraazahexadecane-1,16-bis(methanesulfonate) (**6**): 55 ml of triethylamine was added to a solution of 147.69 g (0.17 mol) of **5** in 825 ml of anhydrous CH_2Cl_2. The solution was allowed to stand overnight over molecular sieves (4 Å) to remove traces of water. After filtering from the molecular sieve, the stirred solution was maintained at −20 to −15 °C in a dry-ice/acetone bath and 48.11 g (32.60 ml, 0.42 mol) of methanesulfonyl chloride was added over a period of 10 min. The dry-ice/acetone bath was replaced by an ice bath and the solution was stirred for an additional 30 min. It was then poured into a mixture of 550 ml of crushed ice and 275 ml of 10% aqueous HCl solution and shaken. The layers were separated, the organic layer was washed with two 300-ml portions of water and 300 ml of a saturated NaCl solution and then dried with anhydrous $MgSO_4$. Removal of the solvent in a rotary evaporator gave a white solid which was dried in vacuo. Yield 156.54 g (90%), m.p. 160 °C. − FAB^+MS (3-nitrobenzyl alcohol) *m/z*: 1035.3 $[M + H]^+$. − $C_{42}H_{58}N_4O_{14}S_6$ (1034.80): calcd. 48.72, H 5.65, N 5.41, S 18.58; found C 48.87, H 5.56, N 5.18, S 18.18.

1,4,7,10,14,17,20,23-Octakis(p-tolylsulfonyl)-1,4,7,10,14,17,20,23-octaazacyclohexacosane (**7**): 140.80 g (0.14 mol) of **6** dissolved in 480 ml of dimethylformamide was added dropwise over a period of 3 h to a stirred solution of 109.74 g (0.13 mol) of **3** dissolved in 1140 ml of dimethylformamide at 100 °C. The solution was stirred for an additional 30 min, then the heat source was removed, and 480 ml of water was added. After cooling to room temp. and stirring overnight, the suspension was kept for 2 h in an ice bath. The precipitated product was collected by filtration, washed several times with ethanol and dried in vacuo. Yield 154.43 g (71%), m.p. 245−248 °C. − IR spectra indicated that cyclization had occurred since no bands in the N−H region ($\tilde{\nu}$ = 3060−3500 cm^{-1}) were observed. − FAB^+MS (3-benzyl alcohol); *m/z*; 1605.6 $[M + H]^+$, 1449.5 $[M + 2H - Ts]^+$. − $C_{74}H_{92}N_8O_{16}S_8$ (1605.42): calcd. C 55.34, H 5.63, N 6.81, S 15.98; found C 55.22, H 5.63, N 6.78, S 15.55.

1,4,7,10,14,17,20,23-Octaazacyclohexacosane (OHEC-amine) (**8**): 78.40 g (48.80 mmol) of **7** were dissolved in 190 ml of concentrated sulfuric acid. The stirred mixture was kept at 100 °C under N_2 for 3 h and was then allowed to cool to room temp. Subsequently, the mixture was cooled to 0 °C and 500 ml of anhydrous diethyl ether was added dropwise. The precipitated grey polydrosulfate salt was collected by filtration and washed with anhydrous diethyl ether and methanol. The salt was dissolved in 700 ml of water to obtain a clear, acidic solution. Insoluble, precipitated materials were removed by filtration. The clear solution was stirred and treated with anion-exchange resin IRA 410 in a beaker until the pH was constant (pH ≈ 11). The ion exchanger was added in portions and filtered off after use. The solvent was then evaporated yielding a white solid which was dried in vacuo and recrystallized from ethyl acetate/diethyl ether. Crystals suitable for X-ray structure analysis were obtained by cooling a hot solution of **8** in ethyl acetate to room temp. Yield 13.45 g (74%), m.p. 122−126 °C. − IR: $\tilde{\nu}$ = 3325 cm^{-1}, 3280, 3190 (ν_{N-H}). − FAB^+MS (magic bullet/

methanol, H_2O); *m/z*: 373 $[M + H]^+$. – ^1H NMR ($CDCl_3$, 25°C): δ = 1.69 (m, 4H, $NCH_2CH_2CH_2N$), 2.26 (s, 8H, NH), 2.72 (m, 24H, NCH_2N and 8H, $NCH_2CH_2CH_2N$). – ^{13}C NMR ($CDCl_3$, 25°C): δ = 29.5 (s, $NCH_2CH_2CH_2N$), 48.4, 48.7, 48.9, 49.2 (4s, NCH_2CH_2N and $NCH_2CH_2CH_2N$). – $C_{18}H_{44}N_8$ (372.59): calcd. C 58.02, H 11.90, N 30.07; found C 57.60, H 11.55, N 29.58.

Octa-tert-butyl 1,4,7,10,14,17,20,23-Octaazacyclohexacosane-1,4,7,10,14,17,20,23-octaacetate (**9**): 5.85 g (15.70 mmol) of **8** was suspended in 40 ml of anhydrous dimethylformamide under N_2 and cooled to 2°C. Then, 24.50 g (125.62 mmol) of freshly distilled *tert*-butyl bromoacetate was added to the stirred milky suspension over a period of 13 min. The reaction mixture was kept at room temp. for 35 min, then 13.31 g (125.62 mmol) of anhydrous Na_2CO_3, dissolved in 135 ml of water, was added over a period of 8 min to obtain a clear, colourless solution from which a thick white precipitate soon settled. The resulting mixture was stirred for 30 min, 50 ml of toluene was added, and the stirring of the slurry was continued for a further 3.5 h. The reaction mixture was transferred together with 30 ml of toluene to a separatory funnel, and the layers were separated. The toluene layer was extracted three times with 20 ml of a 1 M Na_2CO_3 solution, once with 50 ml of 0.8 M HCl, and once with 30 ml of water. The HCl and H_2O layers were combined, extracted with 30 ml of toluene and transferred to an Erlenmeyer flask, along with 100 ml of CH_2Cl_2. The solution was adjusted to pH = 9.4 by the careful addition of solid Na_2CO_3 in small portions and then transferred to a separatory funnel to separate the layers. The aqueous layer was extracted twice with CH_2Cl_2, then the organic layer were combined and extracted with 30 ml of water and dried with anhydrous $MgSO_4$. The solvent was removed in vacuo at room temp. to yield 16.55 g (82%) of a clear, colourless, viscous oil. Purification of the crude product via column chromatography on silica gel [CH_3OH/CH_2Cl_2 (10:1)] led to a considerable loss of substance due to partial hydrolysis of the ester. Yield 8.88 g (44%). – FAB^+MS (thioglycerine/methanol); *m/z*: 1286 $[M + H]^+$, 1230 $[M + 2H - tBu]^+$, 1172 $[M + 2H - CH_2CO_2tBu]^+$. – ^1H NMR ($CDCl_3$, 25°C): δ = 1.20 [s, 72H, $C(CH_3)_3$], 1.45 (t, 4H, $CH_2CH_2CH_2$), 2.50 (br. s, 32H, ring-CH_2), 3.04 [s, 8H, N-2-$CH_2CO_2C(CH_3)_3$], 3.10 [s, 8H, N-1-$CH_2CO_2C(CH_3)_3$]. – ^{13}C NMR ($CDCl_3$, 25°C): δ = 24.0 (s, $CH_2CH_2CH_2$), 27.5 [s, $C(CH_3)_3$], 51.8 (s, N-1-CH_2CH_2-N-2), 52.2 (s, N-2-CH_2CH_2-N-2), 53.3 [s, N-2-$CH_2CO_2C(CH_3)_3$], 53.5 [s, N-1-$CH_2CO_2C(CH_3)_3$], 79.8 [s, $CO_2C(CH_3)_3$], 170.3 [s, $CO_2C(CH_3)_3$]. – $C_{66}H_{124}N_8O_{16}$ (1285.58): calcd. C 61.65, H 9.72, N 8.70; found C 61.13, H 9.81, N 8.59.

1,4,7,10,14,17,20,23-Octaazacyclohexacosane-1,4,7,10,14,17,20,23-octaacetic Acid (H_8OHEC) (**10**): 7.57 g (5.88 mmol) of **9** was suspended in 30 ml of toluene and added slowly, with vigorous stirring, to 80 ml of CF_3COOH under nitrogen. Following the addition, the mixture was stirred for a further 24 h at room temp. After removing the solvent under reduced pressure, the residue was dissolved in 20 ml of water, filtered, and evaporated in a rotary evaporator. This procedure was repeated three times to remove traces of free CF_3COOH. The aqueous solution of the trifluoroacetate salt was treated with anion-exchange resin IRA 410 to produce the free octaacetic acid ligand as a slightly yellow solid, which was purified by RP 18 reversed-phase chromatography [H_2O/methanol (10:4)]. Yield 4.18 g (75%), m.p. 230–235°C. – FAB^+MS (magic bullet/H_2O); *m/z*: 837 $[M + H]^+$, 859 $[M + Na]^+$, 875 $[M + K]^+$ (Na^+ and K^+ are from impurities of the water used). – $C_{34}H_{60}N_8O_{16}$ (836.73): calcd. C 48.80, H 7.23, N 13.39; found C 49.01, H 7.44, N 13.43.

Octa-tert-butyl 1,4,7,10,13,16,19,22-Octaazacyclotetracosane-1,4,7,10,13,16,19,22-octaacetate (OTEC-ester) (**11**): 2.70 g (7.84 mmol) of 1,4,7,10,13,16,19,22-octaazacyclotetracosane (OTEC-amine), prepared according to the procedure of Richman and Atkins[22], was suspended in 20 ml of DMF under nitrogen, and the stirred mixture was cooled to 2°C. Then, 12.23 g (62.69 mmol) of freshly distilled *tert*-butyl bromoacetate was added over a period of 10 min, thereby producing a clear solution. This was allowed to warm to room temp. and stirring was continued for a further 35 min. To the slightly yellow solution, 6.64 g (62.69 mmol) of anhydrous Na_2CO_3 dissolved in 63 ml of water was added over a period of 8 min, whereupon a thick, white precipitate was formed. The resulting mixture was stirred for 35 min and then 30 ml of toluene was added. The mixture was stirred for 4 h so that the product accumulated in the organic phase. The isolation procedure was analogous to that for **9**. After evaporation of the treated organic layers, a colourless, viscous oil was obtained which soon started to crystallize producing a white solid, which was recrystallized from a mixture of methanol and water. Yield: 8.28 g (84%), m.p. 88–89°C. – FAB^+MS (thioglycerine/methanol); *m/z*: 1258 $[M + H]^+$. – ^1H NMR ($CDCl_3$, 25°C): δ = 1.36 [s, 72H, $C(CH_3)_3$], 2.66 (s, 32H, ring-CH_2), 3.23 [s, 16H, $CH_2CO_2C(CH_3)_3$]. – ^{13}C NMR ($CDCl_3$, 25°C): δ = 28.1 [s, $C(CH_3)_3$], 51.4 (s, ring-CH_2), 55.1 [s, $CH_2CO_2C(CH_3)_3$], 81.7 [s, $CO_2C(CH_3)_3$], 169.6 [s, $CH_2CO_2C(CH_3)_3$]. – $C_{64}H_{120}N_8O_{16}$(1257.53): calcd. C 61.11, H 9.60, N 8.90; found C 60.73, H 9.64, N 8.56.

1,4,7,10,13,16,19,22-Octaazacyclotetracosane-1,4,7,10,13,16,19,22-octaacetic Acid (OTEC) (**12**): 36 ml of trifluoroacetic acid was added slowly with vigorous stirring to 3.58 g (2.85 mmol) of **11** in 20 ml of toluene under nitrogen. The mixture was stirred for 24 h at room temp. The isolation procedure was the same as that described for **10**. The acid was purified by reversed-phase chromatography [water/methanol (10:4)]. Yield 1.50 g (65%), m.p. 225°C. – FAB^+MS (thioglycerine/H_2O); *m/z*: 809 $[M + H]^+$, 847 $[M + K]^+$. – $C_{32}H_{56}N_8O_{16}$ (808.68): calcd. C 47.52, H 6.98, N 13.85; found C 47.47, H 7.03, N 13.48.

4. Complexes

[Cu_2(OHEC-amine)](SO_4)$_2$ (**13**): A solution of 0.30 g (0.80 mmol) of **8** in 10 ml of ethanol and a solution of 0.40 g (0.16 mmol) of $CuSO_4(H_2O)_5$ in 10 ml of ethanol were mixed and heated to reflux. The solution turned deep-blue and a precipitate formed immediately upon heating. Water was added until the precipitate dissolved and the solution was refluxed for 15 min. After removal of the solvent, the blue complex was recrystallized from water/ethanol and dried in vacuo. Yield 0.55 g (75%). – $C_{18}H_{44}Cu_2N_8O_8S_2$ (691.51): calcd. C 31.25, H 6.41, Cu 18.37, N 16.19, S 9.27; found C 31.27, H 6.26, Cu 18.51, N 16.16, S 8.13.

[Na_2Y(OHEC)] (**15a**): 0.44 g (1.16 mmol) of $YCl_3(THF)_{2.5}$[45] was dissolved in 5 ml of distilled water and $Y(OH)_3$ was precipitated with 0.1 M NaOH. Chloride was removed by repeated washing with distilled water, centrifuging, and decanting of the solution. The hydroxide and 0.49 g (0.58 mmol) of **10** were suspended in 40 ml of distilled water and refluxed for 3 h to obtain a clear solution. The solution was then cooled to room temp., adjusted to pH = 8.5 with 0.1 M NaOH and refluxed for a further 2 h. Subsequently, the solution was filtered to remove traces of excess Y^{III}, precipitated as the hydroxide. The solvent was removed, the residue was crystallized from water/ethanol and the white solid was dried in vacuo at 80°C. Yield: 0.46 g (76%), m.p. >300°C (dec.). – $C_{34}H_{52}N_8Na_2O_{16}Y_2$ (1052.46): calcd. C 38.79, H 4.98, N 10.64; found C 38.60, H 4.69, N 10.38.

[Na_5Y(OTEC)] (**16a**): From 0.44 g (1.16 mmol) of $YCl_3(THF)_{2.5}$ dissolved in 5 ml of distilled water $Y(OH)_3$ was precipitated with 0.1 M NaOH as described above. The hydroxide and

0.94 g (1.16 mmol) of **12** were suspended in 40 ml of water and treated as described for **15a**. Further treatment and the isolation procedure were analogous to those described for **15a**. Yield 0.93 g (80%), m.p. >300°C (dec.). – $C_{32}H_{48}N_8Na_5O_{16}Y$ (1004.47): calcd. C 38.25, H 4.82, N 11.15; found C 38.40, H 4.79, N 11.38.

[Na_2Y_2(OTEC)] (**17a**): From 0.88 g (2.32 mmol) of $YCl_3(THF)_{2.5}$ dissolved in 10 ml of distilled water, $Y(OH)_3$ was precipitated with 0.1 M NaOH as described for **15a**. The hydroxide and 0.94 g (1.16 mmol) of **12** were suspended in 40 ml of water and treated as described for **15a**. Further treatment and the isolation procedure were also analogous to those described for **15a**. Yield 0.86 g (72%), m.p. >300 cm^{-1} (dec.). – $C_{32}H_{48}N_8Na_2O_{16}Y_2$ (1024.41): calcd. C 37.51, H 4.72, N 10.94; found C 37.70, H 4.73, N 11.08.

[Na_5La(OTEC)] (**16b**): The complex was obtained by treating 0.50 g (0.62 mmol) of **12** with 0.20 g (0.62 mmol) of La_2O_3. These were suspended in 40 ml of distilled water and refluxed for 24 h to obtain a clear solution. Further treatment and the isolation procedure were the same as those described for **15a**. Yield 0.54 g (83%), m.p. >300°C (dec.). – ^{1}H NMR (D_2O, 25°C): δ = 3.38 (s, 32H, ring-CH_2), 3.72 (s, 16H, CH_2COO^-). – ^{13}C NMR (D_2O, 25°C): δ = 51.8 (ring-CH_2), 56.2 (CH_2COO^-), 173.2 (CH_2COO^-). – $C_{32}H_{48}LaN_8Na_5O_{16}$ (1054.64): calcd. C 36.44, H 4.59, N 10.62; found C 36.58, H 4.49, N 10.35.

[Na_2Sm_2(OHEC)] (**15c**): From 0.48 g (1.20 mmol) of $SmCl_3(THF)_2$[45] dissolved in 5 ml of distilled water, $Sm(OH)_3$ was precipitated with 0.1 M NaOH as described for $Y(OH)_3$ (see **15a**). The freshly prepared hydroxide and 0.50 g (0.59 mmol) of **10** were suspended in 40 ml of distilled water and refluxed for 3 h. Further treatment and the isolation procedure were the same as described above for **15a**. Yield 0.46 g (66%), m.p. >300°C (dec.). – FAB^+MS (magic bullet); *m/z*: 1169–1184 $[M + H]^+$. – $C_{34}H_{52}N_8Na_2O_{16}Sm_2$ (1175.61): calcd. C 34.73, H 4.46, N 9.53; found C 34.58, H 4.49, N 9.35.

[Na_2Eu_2(OHEC)] (**15d**): The complex was obtained by treating 0.50 g (0.60 mmol) of **10** with 0.21 g (0.60 mmol) of Eu_2O_3, both suspended in 40 ml of distilled water and heated to reflux for 4 h. Further treatment and the isolation procedure were carried out as described above for **15a**. Yield 0.55 g (78%), m.p. >300°C (dec.). – FAB^+MS (thioglycerine/methanol/H_2O); *m/z*: 1177–1183 $[M + H]^+$. – $C_{34}H_{52}Eu_2N_8Na_2O_{16}$ (1178.65): calcd. C 34.65, H 4.45, N 9.51; found C 34.83, H 4.53, N 10.00.

[Na_2Eu_2(OTEC)] (**17d**): The complex was obtained by treating 0.50 g (0.62 mmol) of **12** with 0.22 g (0.62 mmol) of Eu_2O_3 as described for **15d**. Yield 0.49 g (69%), m.p. >300°C (dec.). – FAB^+MS (3-nitrobenzyl alcohol/glycerine/DMSO); *m/z*: 1149–1154 $[M + H]^+$. – $C_{32}H_{48}Eu_2N_8Na_2O_{16}$ (1150.60): calcd. C 34.41, H 4.20, N 9.74; found C 35.83, H 4.83, N 10.07.

[Na_2Gd_2(OHEC)] (**15e**): To 0.49 g (0.58 mmol) of **10** in 25 ml of water 0.21 g (0.58 mmol) of Gd_2O_3 was added and the mixture was refluxed for 2 h with stirring to obtain a clear solution. Further treatment and the isolation procedure were the same as described above for **15a**. Yield 0.52 g (75%), m.p. >300°C. – FAB^+MS (thioglycerine/methanol/H_2O); *m/z*: 1185–1196 $[M + H]^+$. – $C_{34}]H_{52}Gd_2N_8Na_2O_{16}$ (1189.25): calcd. C 34.34, H 4.41, N 9.42; found C 34.60, H 4.41, N 9.08.

[Na_2Gd_2(OTEC)] (**17e**): The complex was obtained by treating 1.00 g (1.24 mmol) of **12** with 0.45 g (1.24 mmol) of Gd_2O_3 as described for **15e**. Yield 1.21 g (84%), m.p. >300°C (dec.). – FAB^+MS; *m/z*: 1157.4–1168.4 $[M + H]^+$, 1179.4–1190.4 $[M + Na]^+$. – $C_{32}H_{48}Gd_2N_8Na_2O_{16}$ (1161.19): calcd.C 33.10, H 4.17, N 9.65; found C 32.95, H 4.09, N 9.63.

[Na_5Lu(OHEC)] (**14f**): From 0.72 g (1.16 mmol) of $Lu(SO_3CF_3)_3$, prepared by treating Lu_2O_3 with trifluoromethanesulfonic acid[46], $Lu(OH)_3$ was precipitated as described for $Y(OH)_3$ (see **15a**). The complex **14f** was obtained by treating the pure $Lu(OH)_3$ with 0.97 g (1.16 mmol) of **10** as described for **15a**. Yield 1.08 g (83%), m.p. >300°C (dec.). – ^{1}H NMR ($CDCl_3$, 25°C): δ = 2.10 (s, 4H, N-1–$CH_2CH_2CH_2$–N-1), 3.06 (s, 8H, N-2–CH_2CH_2–N-2), 3.21 (s, 16H, N-1–CH_2CH_2–N-2), 3.37 (s, 8H, N-1–$CH_2CH_2CH_2$–N-1), 3.49 (s, 8H, N-2–CH_2COO^-), 3.71 (s, 8H, N-1–CH_2COO^-). ^{13}C NMR ($CDCl_3$, 25°C): δ = 19.8 (N-1–$CH_2CH_2CH_2$–N-1), 53.8 (N-1–$CH_2CH_2CH_2$–N-1), 52.5 (N-1–CH_2CH_2–N-2), 51.5 (N-1–CH_2CH_2–N-2), 53.0 (N-2–CH_2CH_2–N-2), 56.0 (N–CH_2COO^-), 170.5 (N-1–CH_2COO^-), 174.0 (N-2–CH_2COO^-). – $C_{34}H_{52}LuN_8Na_5O_{16}$ (1118.75): calcd. C 36.50, H 4.68, N 10.02; found C 36.58, H 4.49, N 9.95.

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