ORGANIC LETTERS

2004
Vol. 6, No. 26
4805−4808

Effect on pK_a of Metal-Bound Water Molecules in Lanthanide Ion-Induced Cyclen "Cavities"

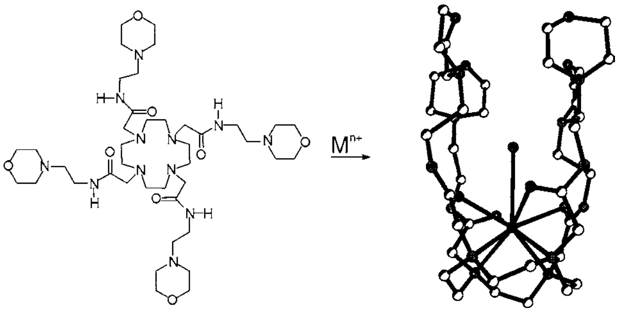
**Thorfinnur Gunnlaugsson,*,† Dermot F. Brougham,‡ Ann-Marie Fanning,†
Mark Nieuwenhuyzen,§ John E. O'Brien,† and Romain Viguier†**

*Department of Chemistry, Trinity College Dublin, Dublin 2, Ireland, National Institute
for Cellular Biotechnology, School of Chemical Sciences, Dublin City University,
Dublin 9, Ireland, and School of Chemistry, Queen's University of Belfast,
Belfast BT9, 5AG, Northern Ireland*

gunnlaut@tcd.ie

Received July 16, 2004 *(Revised Manuscript Received November 6, 2004)*

ABSTRACT



The macrocyclic cyclen conjugates 1–4 were synthesized with the aim of forming lanthanide ion-based macrocyclic conjugates possessing deep cavities, formed upon complexation to various lanthanide ions. These complexes all possess metal-bound water molecules, where the pK_a of the water molecules depends on the nature of the cavity.

Currently, there is a great interest in the development of lanthanide-responsive macrocyclic systems within the field of supramolecular chemistry.[1] Cyclen, or 1,4,7,10-tetraazacyclododecane, functionalized macrocyclic conjugates are extensively used in the development of MRI contrast agents[2] and as luminescent devices.[3] One of the driving forces for the use of tri and tetrasubstituted cyclen ligands and conjugates, is that their corresponding complexes are structurally well defined and stable, adopting either monocapped square aniprismatic and or trigonal planar geometry in solution and the solid state.[1,2,4] We have used the cyclen framework to develop Eu(III) and Tb(III) complexes as luminescent chemosensors,[5] switches,[6] and logic gate mim-

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† Trinity College Dublin.
‡ Dublin City University.
§ Queen's University of Belfast.

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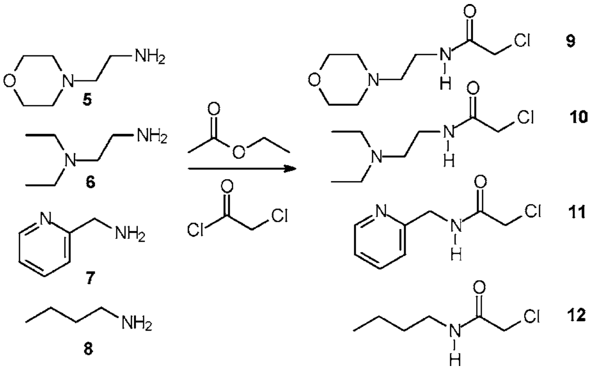
10.1021/ol048628s CCC: $27.50 © 2004 American Chemical Society
Published on Web 12/03/2004

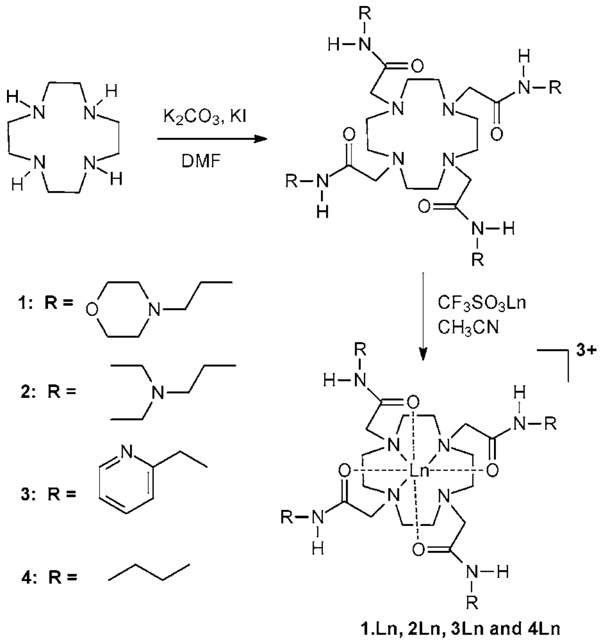
Scheme 1. Synthesis of the α-Chloroamides **9**−**12**



ics.[7] We have also developed ribonuclease mimics for the hydrolytic cleavage of phosphodiesters.[8,9] We have found that the use of small peptides, in conjunction with the Lewis acid character of the lanthanide ion and metal-bound water molecules, gave rise to a bowl-shaped structure that induced hydrophobic cavities, mimicking the active site of many ribonucleases. With this in mind we set out to design other lanthanide ion complexes where the aim was to use the lanthanide ion to *induce* the formation of more structurally defined systems that would resemble cylindrical cavities. We have chosen to call these first-generation cavitands, as the walls of the cavities (the four pendant arms of the cyclen structure) are, unlike that of cyclodextrins, calxarines and hemicacerands, etc.,[10] not covalently linked at the upper rim (the top phase) but only at the cyclen moiety. Here we describe the synthesis of ligands **1**−**4** and their corresponding metal ion complexes and demonstrate that, in the lanthanide complexes of these ligands, the cavity formation has a substantial effect on the pK_a of the metal-bound water molecules.

The synthesis of **1**−**4**, Scheme 2, began with the synthesis of the four α-chloroamides **9**−**12**. The four products were obtained in 75, 71, 86, and 79% yields, respectively, for **9**−**11** as their hydrochloride salts by reacting, in cold ethyl acetate (0 °C), the corresponding amines **5**−**8** with chloroacetyl chloride, Scheme 1. All were isolated as white powders. Reacting **9**, **10**, **11**, or **12** with cyclen in a ratio of 5:1 in the presence of K_2CO_3 (5 equiv) in dry DMF under an inert atmosphere resulted in the formation of ligands **1**−**4**.

Scheme 2. Synthesis of the Four Cyclen Ligands **1**−**4** and the Formation of Their Corresponding Lanthanide Ion Complexes



In the case of **1** and **4**, the reaction was kept at 60 °C for 48 and 18 h, respectively. The resulting off-white products were crystallized from hot CH_3CN to give **1** in 66% yield as white crystals and **4** in 90% yield as powder. In the case of **2** and **3**, longer reaction times were required, and both were formed after 2 weeks.[11] Whereas, the X-ray crystal structures of both **1** and **3** were obtained, we were unable to grow crystals suitable for X-ray crystallography studies of either **2** or **4**. The structure of **1** is shown in Figure 1.[12] It clearly shows that the cyclen moiety has four pendant arms and that these arms do not give rise to any cavity formation. The lanthanide complexes **1.Ln**, **2.Ln**, **3.Ln**, and **4.Ln** (where Ln = La(III), Eu(III), Gd(III), and Tb(III) for **1.Ln**; Ln = La(III), and Eu(III) for **2.Ln**; Ln = La(III), Eu(III), Tb(III), and Gd(III) for **3.Ln**, and Ln = La(III), Eu(III), Gd(III), and Tb(III) for **4.Ln**) were formed by refluxing **1**, **2**, **3**, or **4** with the appropriate lanthanide triflate $[Ln(SO_3CF_3)_3]$ in dry CH_3-

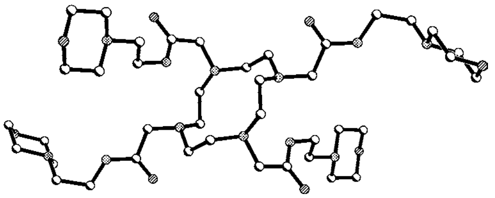


Figure 1. Diagram of the X-ray crystal structure of **1**. Hydrogen atoms have been removed for clarity.

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(11) Synthesis of **2** has proven to be quite troublesome, and we have had difficulties in obtaining **2** in high yield and purity.

CN, followed by precipitation from dry ether. All complexes were characterized using conventional methods. In the case of the paramagnetic ions, the resonance corresponding to the axial and the equatorial protons of the cyclen rings and the α-methtylene spacer in the ^1H NMR was substantially shifted. In the case of **1.Eu**, these appeared at δ 28.9, 3.7, 3.45, 2.74, 2.51, 1.76, −5.78, −7.8, −12.7 ppm, when recorded in CD_3CN, indicating that the structure adopted a square antiprismatic geometry in solution as the major isomer. Similar results were observed for the other complexes. This would suggest that the four arms of the cyclen complexes would all be lining the "wall" of a cavity as the lanthanide ions would be coordinated to the four nitrogens of the cyclen ring and to the four oxygens of the carboxy amides. Unfortunately, we were unable to grow crystals of any of these lanthanide ion complexes that were suitable for X-ray crystallographic analysis, despite attempting different crystal growth techniques. However, we were able to obtain the sodium complex of **1**, **1.Na**.[12]

The structure of **1.Na** is shown in Figure 2, viewed from the top phase, showing the high organization of the ion-induced cavity. The use of Na^+ as a substitute for lanthanide ions in X-ray crystallography has previously been demonstrated, as the ion is of similar size and has a similar coordination requirement.[13] The structure **1.Na** has C_4 symmetry, adopting a monocapped square antiprismatic conformation.[3] The side view of this complex is shown in the graphical abstract, demonstrating that the morpholine arms, indeed, line the wall of the cavity, with the ion placed in the center.[14] Furthermore, the ninth coordination site is occupied by a water molecule[15] as would be expected from the analogues Eu(III), Gd(III), and Tb(III) complexes of **1**, giving rise to monocapped square antiprismatic geometry. The depth of this cavity is 7.99 Å (distance from Na to the center of morpholine oxygen atoms), and the width is 6.46 Å.

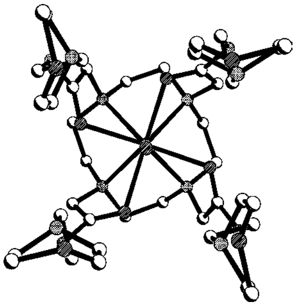

Figure 2. X-ray crystal structure of the Na^+ complex of **1**, when viewed from the top of the cavity.

The presence of the metal-bound water molecules in the above lanthanide complexes was also observed by evaluating the hydration number (q) for the Eu(III) and the Tb(III) complexes of **1**−**4**. Table 1 ($q \pm 0.3$) lists these values, which were obtained by using a luminescent method, where the rate constant for the radiative decay (k) of the $^5D_0$ excited state of Eu(III) and the $^5D_4$ excited state of Tb(III) are measured in H_2O and D_2O, respectively.[1,3,5,16]

Table 1. Hydration Numbers (q) for Eu(III) and Tb(III) Complexes of **1**−**4**

no.	k (H_2O) [ms]	k (H_2O) [1/ms]	k (D_2O) [ms]	k (D_2O) [1/ms]	q (±0.3)
1.Eu	0.41	2.47	1.26	0.79	**1.34**
1.Tb	1.40	0.72	2.00	0.50	**0.77**
2.Eu	3.06	3.27	0.54	1.86	**1.04**
3.Eu	0.57	1.77	2.18	0.46	**0.91**
3.Tb	1.62	0.61	2.69	0.37	**0.91**
4.Eu	0.49	2.02	1.82	0.55	**1.12**
4.Tb	1.59	0.63	2.64	0.38	**0.94**

From these results it can be seen that these complexes all have a single metal-bound water molecule. The corresponding La(III) complexes, however, would have been expected to have two such coordinated water molecules, due to their higher coordination requirements.[1−4,17] The q-values of **1.Eu**, **3.Eu**, and **4.Eu**, as well as **3.Tb** and **4.Tb**, were also determined in 0.1 M NMe_4Cl, and all gave q-values of ~1, indicating that Cl^- was not coordinating to the metal ion. On the basis of the above results, we propose that all the complexes are adopting a cavity-based conformation. We also investigated the effect these "walls" would have on the pK_a of the metal-bound water molecules. We could foresee that this could have a considerable effect on (i) the ability of these complexes to cleave phosphodiesters,[18] which is highly depended on the pK_as of any metal-bound water molecules, and (ii) the relaxivity of the Gd(III) complexes.

The pK_a values were determined by potentiometric pH titration against 0.1 M NMe_4OH aqueous solution with I = 0.1 M (NMe_4Cl) at 37 °C and analyzed using the program SUPERQUAD, which gave the deprotonation constants pK_a.

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(12) *SMART Software Reference Manual*, version 5.054; Bruker Analytical X-ray Systems, Inc.: Madison, WI, 1998. Sheldrick, G. M. *SHELXTL, An Integrated System for Data Collection, Processing, Structure Solution and Refinement*; Bruker Analytical X-ray Systems, Inc.: Madison, WI, 1998. Crystal data for **1**: monoclinic, space group $P2_1/c$, $a = 10.2041$ (12) Å, $b = 10.6133$ (12) Å, $c = 21.190$ (2) Å, $\beta = 95.937$ (2)°, $U = 2282.3$ (5) $Å^3$, $Z = 2$. A total of 25 760 reflections were measured for $4 < 2\theta < 57$, and 5298 unique reflections were used in the refinement; the final parameters were $wR_2 = 0.1742$ and $R_1 = 0.0538$ [$I > 2\sigma(I)$]. Crystal data for **1.Na**: tetragonal, space group $P4/n$, $a = b = 13.5281$ (11) Å, $c = 13.3754$ (16) Å, $U = 2447.8(4)$ $Å^3$, $Z = 2$. A total of 20 249 reflections were measured for $3 < 2\theta < 57$, and 2812 unique reflections were used in the refinement; the final parameters were $wR_2 = 0.1701$ and $R_1 = 0.0549$ [$I > 2\sigma(I)$].

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(14) ^1H NMR ($CDCl_3$) of **1** was also monitored upon titration with $NaPF_6$. These preliminary titrations showed that upon introduction of Na^+, the cyclen resonances were substantially broadened and the amide proton resonance was shifted downfield.

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(17) Ref 9: This paper has also an X-ray crystal structure of 10-coordinated La(III) tetraamide cyclen structure.

(18) This will be discussed in future publications.

Table 2. pK_{a}s for the Ln(III) Complexes of **1**, **3**, and **4**

no.	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}	pK_{a5}
1.La	**7.45 (±0.06)**	5.51 (±0.07)	5.27 (±0.07)	4.68 (±0.06)	
3.La	**10.27 (±0.02)**	**9.93 (±0.02)**	4.29 (±0.07)	3.67 (±0.07)	3.67 (±0.02)
4.La	**8.60 (±0.02)**	**8.20 (±0.02)**			
1.Eu	**7.41 (±0.02)**	5.70 (±0.07)	5.30 (±0.07)	4.55 (±0.08)	4.43 (±0.07)
3.Eu	**9.80 (±0.07)**	4.14 (±0.07)	3.57 (±0.08)	3.57 (±0.07)	
4.Eu	**7.84 (±0.04)**				
1.Gd	**7.31 (±0.03)**	5.52 (±0.04)	5.39 (±0.05)	4.39 (±0.06)	4.91 (±0.05)
3.Gd	**9.23 (±0.02)**	4.30 (±0.03)	3.54 (±0.03)	3.54 (±0.03)	
4.Gd	**7.79 (±0.04)**				
1.Tb	**6.84 (±0.03)**	5.47 (±0.06)	5.26 (±0.06)	4.19 (±0.08)	3.91 (±0.07)
3.Tb	**9.18 (±0.02)**	4.30 (±0.03)	3.61 (±0.03)	3.61 (±0.03)	

The pK_{a}s of arms **9**−**12** and ligands **1**−**4** were first measured using potentiometric titrations. Of these, the results for **9**, **11**, **12**, ligands **1**, **3**, and **4**, and the corresponding lanthanide complexes **Ln.1**, **Ln.3**, and **Ln.4** are discussed herein. For the arms **9**, a pK_{a} of 6.42 (±0.03) was determined, whereas for **11**, a pK_{a} of 4.39 (±0.03) was determined, these being assigned to the protonation of the morpholine and the pyridine nitrogens, respectively. For **1**, five pK_{a}s of 8.63 (±0.05), 6.82 (±0.05), 6.47 (±0.05), 5.76, and 5.74 were determined for the protonations of the morpholine moieties and the amino moieties of the ring. For **3**, these were determined to be 10.55 (±0.03), 8.87 (±0.02), 6.25 (±0.03), 4.63 (±0.03), and 4.42 (±0.03), respectively. In comparison, only two pK_{a}s were determined for **4**, at 8.66 (±0.03) and 5.34 (±0.08). The results of the deprotonation of **1.Ln**, **3.Ln,** and **4.Ln** are shown in Table 2, with pK_{a}s of the metal-bound water molecule(s) shown in bold. As the cyclen amines are all engaged in the binding of the lanthanide ion, these pK_{a}s are assigned to the protonation of the nitrogen moieties of the arms and the deprotonation of any metal-bound water molecules. This is best seen for **4.Ln**, where the deprotonation of the water molecules is only observed. Furthermore, the stepwise protonation of the arms is clearer here than for the ligands. Here it can be seen that the smaller the Ln(III), the lower the pK_{a} of the metal-bound water molecule. Second, and possibly more important, the pK_{a}s were dramatically affected by the nature of the pendant arm. On all occasions, **1.Ln** gave substantially lower pK_{a}s than **3.Ln**, with those of **4.Ln** occurring between the above two. Also, with the exception of **1.La**, two pK_{a}s can be determined for all the La(III) complexes, confirming the high coordination requirement of La(III). We thus propose that the cavity formation has a substantial effect on the pK_{a}, which can be tuned. This is an advantage for developing novel ribonuclease mimics,[8] as well as cellular and tumor-targeting MRI contrast agents.[19]

To investigate the potential of these macrocylic complexes as MRI contrast agents, we measured the frequency dependence of the ^{1}H spin−lattice relaxation time of **3.Gd** and **4.Gd** by nuclear magnetic resonance dispersion, NMRD[20] (Figure S1, Supporting Information). The relaxivity, r_1, was 5.30 and 5.57 s^{-1} $mmol^{-1}$, at 20 MHz, 25 °C, and pH 6.6, for **3.Gd** and **4.Gd**, respectively. These values and the shape of the profiles (Supporting Information) are consistent with low-molecular weight Gd^{3+} complexes with one innersphere water molecule.[21,22] Thus, NMRD confirms that in solution the complexes are monomeric, with intact cavities containing one water molecule that is in rapid exchange.

In summary, we have developed novel lanthanide complexes that possess deep structurally defined organized cavities, where the structure of the walls/pendant arms can be used to tune the physical properties of the complex.

Acknowledgment. We like to thank TCD, DCU, and Enterprise Ireland for financial support. We also thank Dr. Hazel M. Moncrieff for her help.

Supporting Information Available: Experimental procedure for all compounds, CIF files (in Word format) for **1** and **1.Na**, and NMRD of **3.Gd** and **4.Gd**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) ^{1}H NMRD data was recorded with a Stelar Spinmaster Fast Field Cycling Relaxometer (Stelar SRL, Mede, Italy). Sample temperature was controlled at 25.0 ±1 °C by use of a thermostated airflow system.

(21) Ref 2a: see p 45.

(22) While a fit to the data is possible, given the number of adjustable parameters, the values obtained will be questionable without corroborative measurements. Instead, NMRD studies are ongoing to study the effect of pH on the cavity formation and hence on the water exchange time.