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Macrobicyclic and Macrotricyclic Tetralactams with 1,10-Phenanthroline Units. Dinuclear Eu^{3+} Cryptate of the Macrotricyclic Ligand

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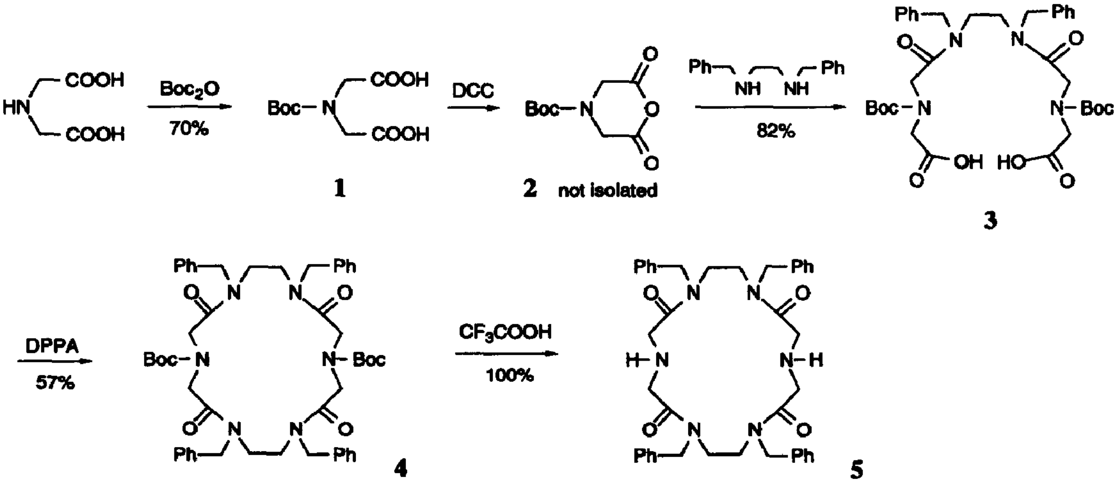
Abstract : The synthesis of a key 18-membered diazatetralactam and of subsequent macrobicycle and macrotricycle with 1,10-phenanthroline units is described. The predominant macrotricyclic cryptand gives a dinuclear europium cryptate characterized by MS techniques and luminescence emission.

The recent description of the first dinuclear lanthanide complexes of polypyridine-type ligands [1] prompts us to report our results about the obtention of the dinuclear complex of a macrotricyclic compound containing amide groups and 1,10-phenanthroline moieties. The usefulness of amides as coordinating ligands for lanthanide ions has been recently demonstrated [2] and Eu^{3+} or Tb^{3+} complexes of phenanthroline ligands are attractive targets for their luminescence properties [3] and biological applications.[4]

Herein, we describe the synthesis of the key 18-membered diazatetralactam (scheme 1) and the subsequent preparation of macrobicyclic and macrotricyclic derivatives (scheme 2). The preferential formation of the macrotricyclic cryptand and of its dinuclear Eu^{3+} cryptate is emphasized.



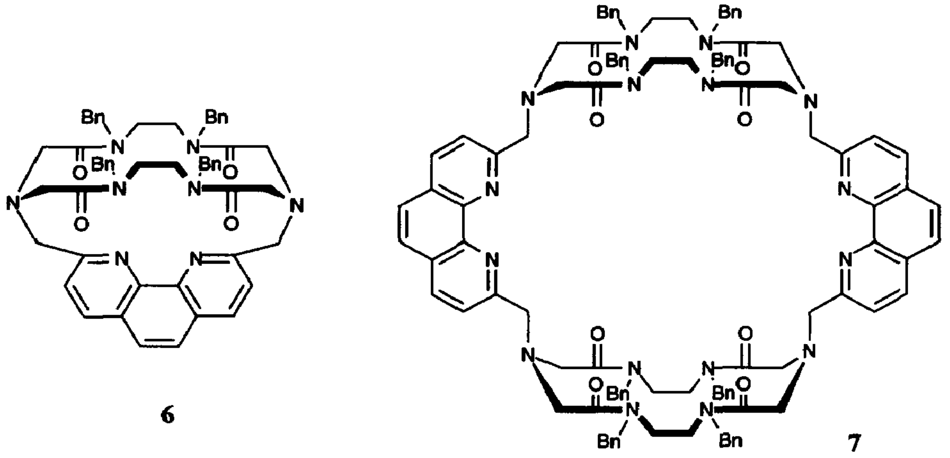
Scheme 1

The synthesis of the key diazatetralactam **5** was accomplished by a stepwise approach. Iminodiacetic acid was first converted to its Boc derivative **1** [5] and then dehydrated to its cyclic anhydride using the 1,3-dicyclohexylcarbodiimide (DCC) method. Compound **2** was not isolated, owing to its instability, and was reacted with N,N'-dibenzylethylenediamine to afford the intermediate diamide diacid **3** in 82% yield. The cyclization reaction between **3** and N,N'-dibenzylethylenediamine was carried out in THF solution under low dilution conditions (10^{-2} M) by using diphenylphosphoryl azide (DPPA) as *in situ* activating-coupling agent following the procedure described by Mertes et al.[6] The macrocyclic tetralactam **4** was thus obtained in 57% yield after purification by chromatography on silica gel.

It is noteworthy that in the same experimental conditions the DPPA mediated direct macrocyclization between N-Boc iminodiacetic acid and N,N'-dibenzylethylenediamine failed for preparing **4** ; polymeric materials were only obtained.

Removal of the Boc protecting groups of **4** by CF_3COOH-CH_2Cl_2, followed by an aqueous base treatment led to the key diazatetralactam **5** (overall yield 33%).

Condensation of the key macrocycle **5** with 2,9-bis(bromométhyl)-1,10-phenanthroline using the Na_2CO_3/CH_3CN procedure [7] gave the NaBr complexes of the macrobicycle **6** [8] and the macrotricycle **7** [9] in 6% and 45% yield respectively.



6

7

Scheme 2

The orientation of this reaction essentially towards the macrotricyclic compound is clearly different from the predominant macrobicycle formation observed by Lehn [7] for analogous cryptands following the same procedure. This may result from a different conformational behaviour of the initial macrocycle **5** with respect to the [2.2] ([18]-N_2O_4) macrocycle used by Lehn in relation with a template effect of the Na^+ ion.

The macrotricyclic tetralactam **7** forms a stable Eu^{3+} complex when treated with $EuCl_3$ in methanol.[10] The characterization of this complex by mass spectrometry and microanalysis [11] unambiguously shows complexation of two cations per molecule of **7**. FAB^+ mass spectrometry carried out with the complex in methanolic solution indicated the presence of the characteristic molecular peaks [1] at m/z 2202.4 (M - 2 Cl) and 2167.4 (M - 3 Cl) (the most abundant). For this latter peak, the two isotopes of Eu^{3+} could be distinguished and the simulated isotopic pattern was superposable to the measured one. On the other hand, it is noteworthy that no peak ascribed to the free ligand was observed in the FAB mass spectrum of the complex. The electrospray ionisation (ES-MS) was also used to characterize the dinuclear complex. The ES mass spectrum of the complex displayed only the doubly and triply charged species corresponding to the [M - 3Cl] entity, previously observed under FAB ionization.

Homo- and hetero-dinuclear lanthanide (III) complexes have been yet described particularly with lariat-type ligands [1] or with macrocyclic Shiff bases,[12] anyone, at our knowledge, with macrotricyclic compounds. So, structure and photophysical properties of supermolecules like $[Eu_2(7)Cl_6]$ are of a great interest.

In this complex it was observed by IR techniques that the carbonyl stretching band of 7 in KBr pellet is strongly shifted toward lower frequency (1640 → 1609 cm^{-1}). In addition, the UV absorbance in methanol undergoes a bathochromic shift (274.9 → 280.2 nm) upon complexation. These two effects can be associated to the chelation of the Eu^{3+} cation at the same time by all the carbonyl groups and the nitrogen atoms of the phenantholine moieties. Complexation related to the carbonyl groups involves that these groups converge toward the cation in each subunit. This feature was yet described [13] for macrocyclic dioxatetralactams analogous to **5** (NH replaced by O) in their Ca^{2+} complexes [14] where similar shifts of the $\nu(C=O)$ band were observed and was also confirmed by molecular modelling.[13]

Moreover, the participation of the nitrogen phenanthrolic atoms in the complexation is supported by the luminescence spectrum of $[Eu_2(7)Cl_6]$. Excitation of the methanolic solution of the complex at 300 nm gives the usual ligand-to-metal energy transfer process with $^5D_o \rightarrow {}^7Fj$ emissions at 580 (j = 0), 593 and 597 (j = 1) and at 615, 622 (shoulder) (j = 2), 650 (j = 3), 688 and 700 nm (j = 4). The excitation spectrum is in perfect agreement with the absorption spectrum.

A detailed study of dinuclear macrotricyclic cryptates with other more effective antenna groups such as 2,2'-bipyridyle and their photophysical properties in H_2O and D_2O is in progress and will be reported elsewhere.

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8. **6** : white solid, m.p. = 180°C ; IR (KBr) : ν(C=O) = 1640 ; ^{1}H NMR ($CDCl_3$) δ : 2.4-2.7 (m, 8H, CH_2N), 3.3-4.5 (m, 20H, CH_2CO, CH_2Ph, CH_2Phe), 6.7-7.4 (m, 20H, Ph), 7.49 (d, J = 8.1 Hz, 2H, H-4,7), 7.86 (s, 2H, H-5,6), 8.24 (d, J = 8.1 Hz, 2H, H-3,8) ; MS : FAB$^+$ (glycerol-thioglycerol matrix) m/z 879.1 (MH^+) (100%); Anal. calc. for $C_{54}H_{54}N_8O_4$, NaBr, $3H_2O$ (1036.03) : C, 62.60; H, 5.84; N, 10.82; found C, 62.91; H, 5.45; N 10.98.
9. **7** : white solid, m.p. > 230°C ; IR (KBr) : ν(C=O) = 1640 ; ^{1}H NMR ($CDCl_3$) δ: 2.4-2.7 (m, 16H, CH_2N), 3.3-5 (m, 40H, CH_2CO, CH_2Ph, CH_2Phe), 6.7-7.4 (m, 44H, H-4,7), 7.81 (s, 4H, H-5,6), 8.06 (d, J = 8.1 Hz, 4H, H-3,8) ; MS : FAB$^+$ (glycerol-thioglycerol-trichloracetic acid matrix) m/z 1759.8 (MH^+) (100%); Anal. calc. for $C_{108}H_{108}N_{16}O_8$, 2 NaBr, 10 H_2O (2144.12) : C 60.50, H 6.02, N 10.45; found C 60.14, H 5.58, N 10.87.
10. The [$Eu_2(7)Cl_6$] cryptate was prepared as follows : a solution of the [$Na_2(7)Br_2$] complex (1.85 x 10^{-5} M in 5 ml methanol) was added under argon to 2.2 equivalents of $EuCl_3$ in 15 ml methanol. After 15 h of reflux the solution was concentrated to a half and the cryptate precipitated by adding Et_2O. The solid was centrifugated, then chromatographed on a gel permeation column (LH20) with methanol as eluent giving the pure cryptate (yield : 40%).
11. [$Eu_2(7)Cl_6$], $7CH_3OH$, $3H_2O$: Anal. calcd for $C_{115}H_{142}H_{16}O_{18}Eu_2Cl_6$: C, 54.11; H, 5.61; N, 8.78. Found : C, 54.1; H, 5.6; N, 8.5.
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14. It is noteworthy that Ca^{2+} and Eu^{3+} ions have equivalent ionic radius.

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