Solution Chemistry of Lanthanide Macrocyclic Complexes

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1 Introduction

Macrocyclic receptors define a hydrophilic cavity in which an ionic substrate like a metal ion can nest and be shielded from the environment by its lipophilic envelope.[1] Accordingly, they can mediate cation transfer from an aqueous medium to a lipophilic phase and were first designed as synthetic models to mimic the ionophoric properties of natural antibiotics towards alkali and alkaline-earth cations. They have been extensively studied with these cations and it has been shown that the main factor affecting complexation selectivity is the size match between the cavity and the metal ion. The variety of macrocycles prepared, which has increased greatly over the past two decades, includes the coronands with the well-known and studied crown-ethers,[2] cryptands,[1] spherands,[3] and amongst the last synthesized, the calixarenes and their chemically modified derivatives.[4]

The success of numerous studies on the complexation of alkali and alkaline-earth cations by macrocycles led to similar studies with a related series of cations, the lanthanides. These cations have a common +3 oxidation state (Ln^{3+}), although samarium, europium and, ytterbium can also exist as Ln^{2+}, and cerium as Ce^{4+}. They behave as hard acids with a strong affinity for hard bases like oxygen and negatively charged groups, and they form essentially non-directional electrostatic bonds. The size of Ln^{3+} cations decreases with increasing atomic numbers (lanthanidic contraction) and the achievement of high coordination numbers is an important requirement which can be met with macrocyclic ligands. Initial interest in these studies was academic, *viz.* the investigation of the coordination properties of lanthanides and the understanding of the factors governing the complexation ability and selectivity, the solvent effects, and the stabilization of unusual oxidation states – but the increasing industrial development of lanthanides in the fields of catalysts, glasses, ceramics, magnets, optics, and electronics now requires continuous improvement in separation processes. More recently, owing to their paramagnetic and luminescence properties, the possible applications of lanthanide macrocyclic complexes in chemistry, biology, and medicine, as relaxation agents for imaging techniques, structural and analytical probes, as well as labels (fluoroimmunoassays) have provided additional reasons for their extensive study.[5]

Françoise Arnaud-Neu is presently Research Director at the Centre National de la Recherche Scientifique – in the laboratory of Physical Chemistry of the Higher Institute of Chemistry of Strasbourg, France. She graduated in Chemistry in 1968 from the University of Strasbourg, where she also received her Ph.D. in 1973, studying the photochromic behaviour of amine molybdates. After her thesis, she turned her research interest towards the thermodynamics of complexation of metal ions in solution by macrocyclic receptors such as coronands, cryptands, and catenands. Since 1988, her research activity has been mainly focused on the study of the binding properties of calixarenes. She has some 60 publications to her credit.

In the following sections, a non-exhaustive report of the solution thermodynamic properties of lanthanide macrocyclic complexes will be given, associated with the different fundamental or more applied interests cited above. First, the basic question of the factors governing the complexation selectivity within the lanthanide series will be addressed, where results concerning lanthanide coronates and cryptates will be presented. Secondly, the properties of lanthanide complexes with anionic macrocycles will be reviewed. Finally, the last section will describe recent results on the complexing properties of calixarenes towards lanthanides.

The binding of lanthanides by various macrocycles, which is presented in this survey, has been established mostly through stability constant determinations in homogenous media, performed mainly by absorption spectrophotometry, potentiometry, and calorimetry. In some cases, other thermodynamic parameters such as the enthalpy (ΔH_c) and entropy (ΔS_c) of complexation have also been determined as well as biphasic extraction data of lanthanide cations, from water to an organic phase. These results will be reported and illustrated graphically. However the latest results, *i.e.* log β values pertaining to the complexation of lanthanide cations by calixarenic receptors and which are so far unpublished are given in Table 1. They correspond to the concentration ratios, $\beta = [LnL]/[Ln][L]$ where the charges are omitted and L is a neutral calixarene or the fully deprotonated form of the ligand in the case of calixarene-acids. Until 1986, references will be made throughout the text only to the exhaustive review by J. C. G. Bünzli on lanthanide complexation by synthetic ionophores.[6]

2 Lanthanide Complexes with Neutral Macrocycles

2.1 Complexes with Coronands. Influence of the Nature of the Heteroatoms

A large variety of coronands – some of which are represented in Figure 1 – are able to complex lanthanide cations, as demonstrated by the great number of complexes isolated in the solid state.[6] For instance, complexes of crown-ethers, diazapolyoxamonocycles, and even polyazamonocycles are readily obtained, whereas the synthesis of lanthanide complexes with ligands containing the softer sulfur atoms is less straightforward because of their lower affinity for hard cations. The stoichiometries of the solid complexes formed with the crown-ethers depend on different factors, such as the nature of the medium, the anion present, and the respective size of the cation and the ligand cavity. Some of these stoichiometries have been confirmed in solution. The mononuclear 1:1 complexes, the only ones which form with diazapolyoxamacrocycles, are more stable than their homologues with crown ethers. For instance, in propylene carbonate (PC), the difference in stability between 21 and 15C5 complexes of lanthanum is around 8 log units (Figure 2).[6] Although both ligands are monocycles with the same size and number of donor atoms, they differ only through the substitution of two ether oxygen atoms by two secondary amines. The same situation holds for 22 and 18C6. The presence of the nitrogen atoms in 21 and 22 should be partly responsible for the increase of stability, owing to the higher polarizability and the higher flexibility of these ligands. This explanation is further supported by the examples of A$_6$18C6, in which all the

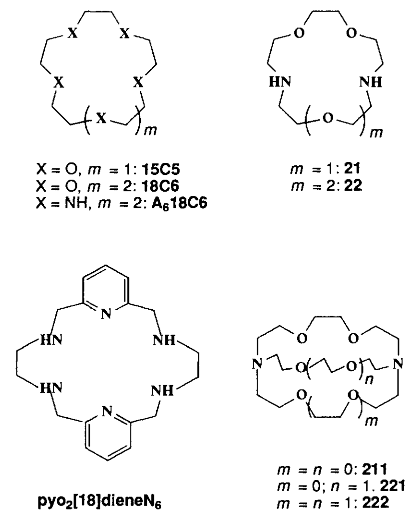

Figure 1 Chemical structures of some coronands and cryptands.

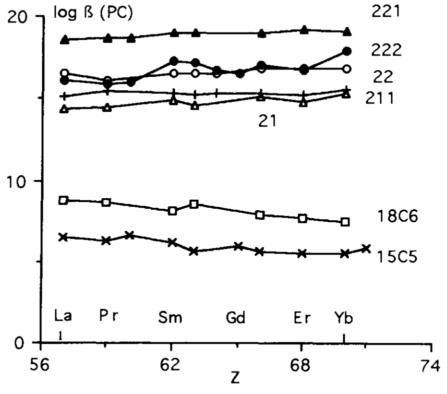

Figure 2 Variation of log β with Z for some lanthanide cryptates and coronates in propylene carbonate.

oxygens of the 18C6 are replaced by $-NH$ groups,[7] and of pyo$_2$[18]dieneN$_6$.[8] Both ligands complex the trivalent lanthanides strongly, even in water with values of log β ranging from 9.1 to 11.8 along the series for the former and values of 7.4 and 8.1 for the latter with La^{3+} and Gd^{3+}. These results show that lanthanides have a great affinity not only for oxygen but also for nitrogen atoms. No sulfur-containing ligand has been investigated in solution with lanthanides so far.

2.2 Effect of the Lanthanidic Contraction

Figure 3 shows the variation of log β of 21, 221, and 18C6 complexes in methanol (MeOH) with the atomic number Z.[6] This parameter is chosen rather than the ionic radii, because of their strong variation with the coordination number, which is unknown. Complexation by 221 and 21 occurred only after 12 and 7 days of equilibration of the solutions, respectively. A constant cryptate effect of *ca.* 1.5 log units is observed between 221 and 21 complexes. An increase in stability is found with 21 and 221 which contrasts with the behaviour of 18C6.[6] In PC, as in MeOH, the effect of the lanthanide contraction is different with cryptands and crown-ethers (Figure 2).[9] The stability of cryptates varies irregularly, but the overall trend is a slight increase in the series. Generally the increasing charge density is invoked to explain the increase in stability of lanthanide chelates along the series. The peculiar behaviour of coronates could be predicted from their inclusive nature. When going from La^{3+} to Yb^{3+}, the cations become less and less adapted to the cavity and this effect is predominent. The fact that cryptands do not exhibit the same trend should be related to the presence of nitrogen atoms which masks the expected size effect.

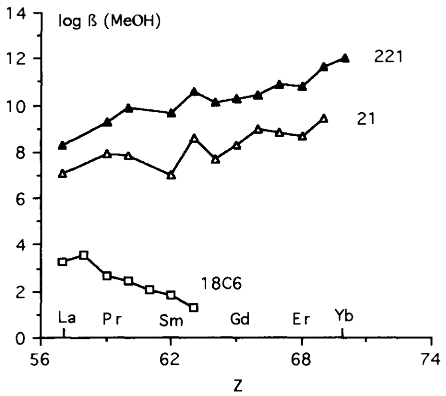

Figure 3 Variation of log β with Z for some lanthanide cryptates and coronates in methanol.

2.3 Solvent Effect – Transfer Properties

The thermodynamic properties of trivalent lanthanide cryptates have also been investigated in solvents other than MeOH and PC: water,[6] dimethylsulfoxide (DMSO),[6] *N,N*-dimethylformamide (DMF),[10] and acetonitrile (AN).[11] Their stability increases in the following order:

$$\text{DMF} < \text{DMSO} < H_2O < \text{MeOH} < \text{AN} \ll \text{PC}.$$

As shown for europium cryptates (Figure 4), the most stable complexes are generally formed with 221 in poor solvating solvents and with 211 in strongly solvating ones. It is clear that the results cannot be interpreted in terms of size effects only. They emphasize the role of the solvent, which is likely to interact with the highly charged cations. The role of the anion may also be important as it has been shown that Ln^{3+} can be complexed by ClO$_4^-$ in poor solvating media.[12] As the log β values reported are mostly determined in the presence of Et$_4$NClO$_4$ as supporting electrolyte, the results ought to be corrected for this effect. However, these corrections should remain small in comparison with the variation of stability between the different solvents, and should definitely not alter the trends observed.

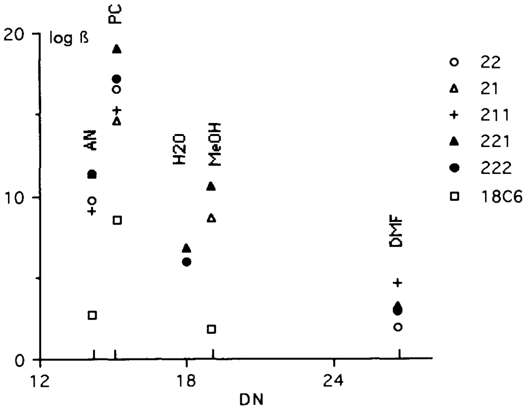

Figure 4 Variation of log β with the Gutmann's donor numbers of the solvents (DN) for trivalent europium cryptates.

In PC and in AN, lanthanide cryptates form two classes according to their degree of stabilization:[6,9,11,13] those stabilized by both favourable enthalpy and entropy, and those stabilized only by the enthalpic terms, the entropy contribution being negative and thus unfavourable. As the enthalpy terms are rather similar in PC and AN (Figure 5), the extra-stability of lanthanide cryptates in PC is due to favourable entropy changes originating from a more important release of solvent molecules. The variation of the entropy with the atomic number suggests an incomplete desolvation of the cation. On the basis of full

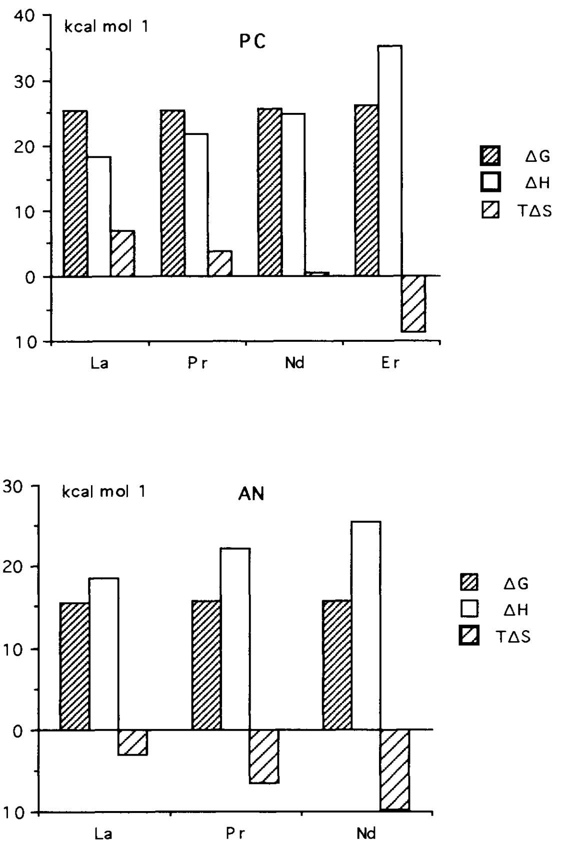

Figure 5 Energetic diagram for some lanthanide cryptates of 221 in propylene carbonate and acetonitrile

desolvation, an entropy gain should be expected on going from La^{3+} to Nd^{3+}, since the smaller the cation the greater its solvation The opposite trend is observed and shows that the cation retains part of its solvation shell in the complexes, suggesting interactions between complexed lanthanide and the medium The single ion enthalpies of transfer from PC to AN of 221 and 222 cryptates determined using a thermodynamic cycle between the two solvents, or the direct measurements of the enthalpies of solution of the lanthanide salts, are independent of the ligands but vary with the cation [13] In fact they are equal to the enthalpies of transfer of the cations, indicating a cation recognition by the solvent despite the presence of the ligand Therefore the 'cryptate' extrathermodynamic convention, which implies the complete shielding of the cation by the cryptand in the cryptate, is not valid for trivalent lanthanides

2.4 Stabilization of Unusual Oxidation States of Lanthanides

Stabilization of divalent samarium, europium, and ytterbium can be achieved by complexation with cryptands or even coronands In H_2O,[6] DMF,[10] and MeOH,[6] the reduction of trivalent lanthanide cryptates and coronates always occurs at higher potentials than the reduction of the uncomplexed cations, indicating a stabilization of the divalent complexes, but in PC[14] and AN,[11] no systematic stabilization is observed When these reductions are reversible and without any charge in the stoichiometries of the complexes, the stability constants of the divalent complexes can be calculated from the difference in the reduction potential of the complexed and uncomplexed cations and the stability of their trivalent homologues The variation of log β thus obtained with the Gutmann's donor numbers (DN) of the solvents (illustrated in Figure 6 in the case of the europium complexes) shows that (i) the stability of a given complex is quite independent of the solvent, (ii) 222 forms the most stable complexes in agreement with size considerations in all solvents, and (iii) a very strong macrobicyclic effect is observed, the difference in stability between 222 and 22 complexes being 7 5 and 10 log units in AN and DMF, respectively These results show that, in contrast to trivalent lanthanides, the stability of divalent lanthanide cryptates is controlled by size rather than by solvent effects

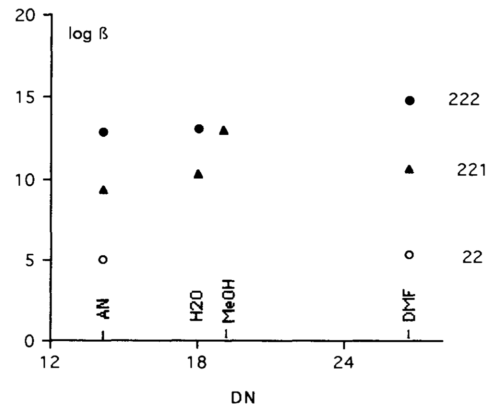

Figure 6 Variation of log β with the donor numbers of the solvent for divalent europium cryptates

3 Lanthanide Complexes with Ionizable Macrocycles

Another class of macrocyclic ligands with pendant ionizable functions has been and still is being widely explored with lanthanide cations The presence of carboxylic acids, the ionizable groups most frequently met with in these macrocycles, imparts two characteristics on these ligands (i) the formation of strong complexes owing to the establishment of electrostatic interactions, and consequently the selective complexation of lanthanides over alkali and alkaline-earth cations, (ii) the solubility in water of the ligands and their complexes These properties are essential for the application of these ligands to the analysis of biological material *in vivo* [5] The stability of such complexes should also depend on different factors such as the ligand flexibility, the number and the nature of the donor sites, and the steric requirements of both the macrocyclic framework and the carboxylate groups Therefore, in order to discover the best lanthanide selective agents, a great variety of compounds of different sizes (from 9- to 18-membered rings) with different types of donor atoms have been synthesized and tested for complexation of lanthanides In some compounds the carboxylic acids have been replaced by phosphorous-containing acid functions Some of the most representative structures are shown in Figure 7

The generally high stability constants of the fully deprotonated complexes of polyamino polycarboxylate ligands have often been determined by carrying out competitive experiments using a precipitation agent[15] or an auxiliary ligand, either Arsenazo-III[16] or EDTA (ethylenediaminetetraacetic acid) [17] The ligand DACDA,[6] derived from the diazatetraoxamonocycle 22, by substitution of the two secondary amine functions with methylene carboxylic acids, forms less stable complexes than EDTA as $10\ 8 \leq \log \beta \leq 12\ 2$ instead of $15\ 5 \leq \log \beta \leq 19\ 8$ The log β values are approximately constant for the lighter cations and decrease for the heavier ones This behaviour is in contrast with that of EDTA complexes, the stability of which increases regularly along the series However, there is a good selectivity for Ln^{3+} with respect to the other cations, contrary to EDTA which is not able to discriminate between alkalis, alkaline-earths, and lanthanides The related 15-membered DAPDA[6] forms complexes of similar stability ($10\ 1 \leq \log \beta \leq 11\ 9$) and exhibits a small selectivity for Eu^{3+} The octadentate ligand DOTA[15] complexes lanthanide cations very strongly ($28\ 2 \leq \log \beta \leq 29\ 2$), approximately 10 times more than EDTA However, it is less selective TETA[15] complexes have comparable stabilities to those of EDTA ($14\ 5 \leq \log \beta \leq 16\ 5$, at 80 °C)

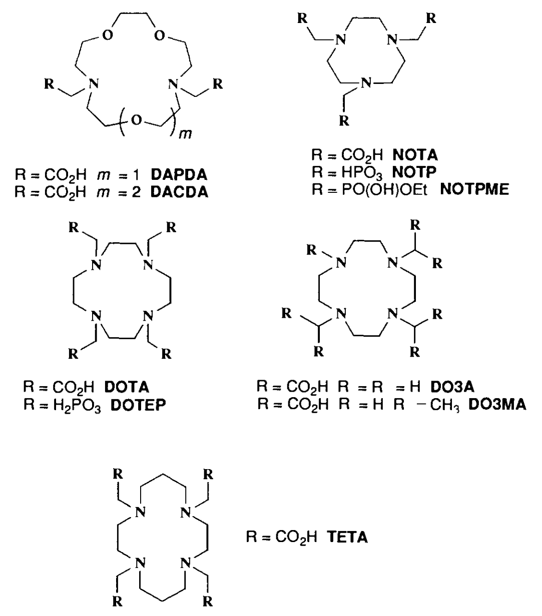

Figure 7 Chemical structures of some ionizable macrocycles

Both DOTA and TETA behave as classical non-cyclic ligands as the stability of their complexes increases along the series with the increase of the charge density. The predominance of the electrostatic factor is further supported by the observation that log β values for the Gd complexes of DOTA and its 12-membered triazatriacetate homologue, the hexadentate NOTA, lie on the linear plot of the stability constants *vs* $\sum pK_a$ for a variety of polyaminopolycarboxylate open ligands, all forming 5-membered O–Ln–N rings.[16]

Most of the more recent papers deal with the complexation of the highly paramagnetic Gd^{3+} cations, which is the best suited for contrast agents, by tricarboxylic acids able to form non-ionic complexes.[17–20] The carboxylic arms can be substituted in various ways in order to increase the rigidity and/or the number of donor sites. For instance, DO3MA, in which the three propionic acid arms are α-methylated, forms the most stable heptadentate gadolinium complex with log $\beta = 25.3$.[18] It is nearly as stable as its DOTA homologue (log $\beta = 25.8$) despite the lower donor site number of the ligand, but in agreement with the relative basicity of the two ligands. Recently, Martell *et al.* studied a series a triazamacrocyclic ligands with three pendant acetate donor groups and increasing number of ether oxygen atoms.[17] The general trend is a decrease of the stability of the complexes with the increase of the cavity size. However, the Gd complex of the large flexible 18-membered ring, which enables a good adjustment of the cation to all the donor atoms in agreement with the structure of the solid complex, is slightly more stable than its 15-membered homologue. The more rigid 12-membered ligand is the best complexing agent as it favours a cage structure. A series of macrocyclic bis-amide derivatives of EDTA and DTPA (diethylenetriamine pentaacetic acid) have also been tested with Gd^{3+}, one of them displaying the highest Gd^{3+}/Zn^{2+} selectivity ever found with polyaminopolycarboxylate ligands.[19]

All these ligands, especially DOTA and DO3MA, are amongst the best sequestering agents for lanthanides. However, the accurate determination of large stability constants is difficult and several values have been reported for the GdDOTA⁻ complex in the range 28.0 to 23.60 log units, according to the method and the background electrolyte. Recently, Desreux *et al.* found a lower value of log $\beta = 22.1$ from kinetics measurements.[21] Thus the GdDOTA⁻ complex would not be more stable than its DTPA homologue. However the correlation between log β of polyaminopolycarboxylate complexes and $\sum pK_a$ of the ligands still includes this new value and the stability of the DOTA complexes and related complexes depends on the electrostatic nature of the bonds with the metal ion, rather than on steric factors. However the presence of the macrocyclic structure leads to very rigid complexes in which the cation is well encapsulated. They are thus prevented from dissociation in aqueous solution, even in acidic conditions, as compared with their open homologues. In that respect, $GdDOTA^-$ dissociates much more slowly than $GdDTPA^{2-}$ even in acidic medium (half-life of 85 days at pH 2 and > 200 days at pH 5). Moreover the high stability and kinetic inertness of macrocyclic polycarboxylic complexes improve their tolerance and prevent any competition with endogenous cations such as Zn^{2+}, Ca^{2+}, or Cu^{2+}. Thus they are very good candidates for water-soluble shift reagents and some of them are already used as contrast agents for NMR imaging (MRI).[5]

Compounds featuring phosphorus-containing ionizable groups, like phosphonic acids (NOTP)[22] and phosphinic acid (DOTEP),[23] have been designed to monitor intracellular cation concentrations by ${}^{31}P$-NMR spectroscopy (Figure 7). As the phosphinate RPO_2^- group is more electron-withdrawing than CO_2^- and PO_3^{2-}, the oxygen donor basicity falling in the same order, all the donor atoms of DOTEP are less basic than those of DOTA or DOTP. This results in a decrease of the metal–ligand interactions and in lower stability constants. The fact that the stability of these complexes is still controlled by electrostatic interactions rather than by steric factors is further illustrated by the agreement between the experimental log β value for the Gd complex and the value predicted from the linear relationship between log β and the sum of the ligand's pK_a (see above). However, at physiological pH (7.4), the difference in stability between DOTEP and DOTA complexes is reduced because of the decreased competition between protons and Ln^{3+} for binding DOTEP at this pH. The LnDOTEP complexes are slow to form but dissociate slowly, giving these systems similar kinetic advantages for *in vivo* uses as LnDOTA. On the other hand, the methylenephosphonate monoethylester NOTPME[22] forms considerably less stable complexes than either NOTP or NOTA.

4 Lanthanide Complexes with Calixarenes

Calixarenes are a new class of macrocyclic receptors formed by *para*-substituted phenolic units linked *ortho* by methylene groups.[4] The binding abilities of calixarenes towards metal ions were thought to be due to the existence of a template effect during some syntheses, but were first demonstrated by transport experiments by Izatt *et al.*[24] These molecules transport alkali and alkaline-earth picrates from an aqueous source phase to an aqueous receiving phase through a bulk haloformic membrane, provided that the source phase is basic enough to ensure partial deprotonation of the ligands and formation of neutral complexes. Because of their great insolubility in most usual solvents, the study of the complexing power of calixarenes in solution has been limited. However, further substitution of the phenolic hydrogens of calixarenes by various types of ligating groups led to more soluble compounds, the structures of which seemed to be better pre-organized for hosting a metallic cation.[4] For instance, the cone conformation preferentially adopted by the tetrameric oligomers defines a hydrophilic cavity, as an extension of the lipophilic one formed by the aromatic rings, where a cation can be encaged. In the past few years, the complexing power towards alkalis and alkaline-earths of a great variety of calixaryl derivatives featuring ester, amide, ketone, and carboxylic acid functions has been established on the basis of extraction and transport experiments as well as stability constant determinations.[4,25] High complexation and extraction selectivities have been demonstrated which were based mainly on the fit between the cation and the cavity sizes. Parent phenolic calixarenes and their chemically modified derivatives are also expected to bind lanthanide cations. This was confirmed, for the first time, by Harrowfield *et al.* through the isolation from DMF of a binuclear complex of europium with the *p*-t-butylcalix[8]arene.[26] Its *X*-ray structure shows that the complexed ligand is

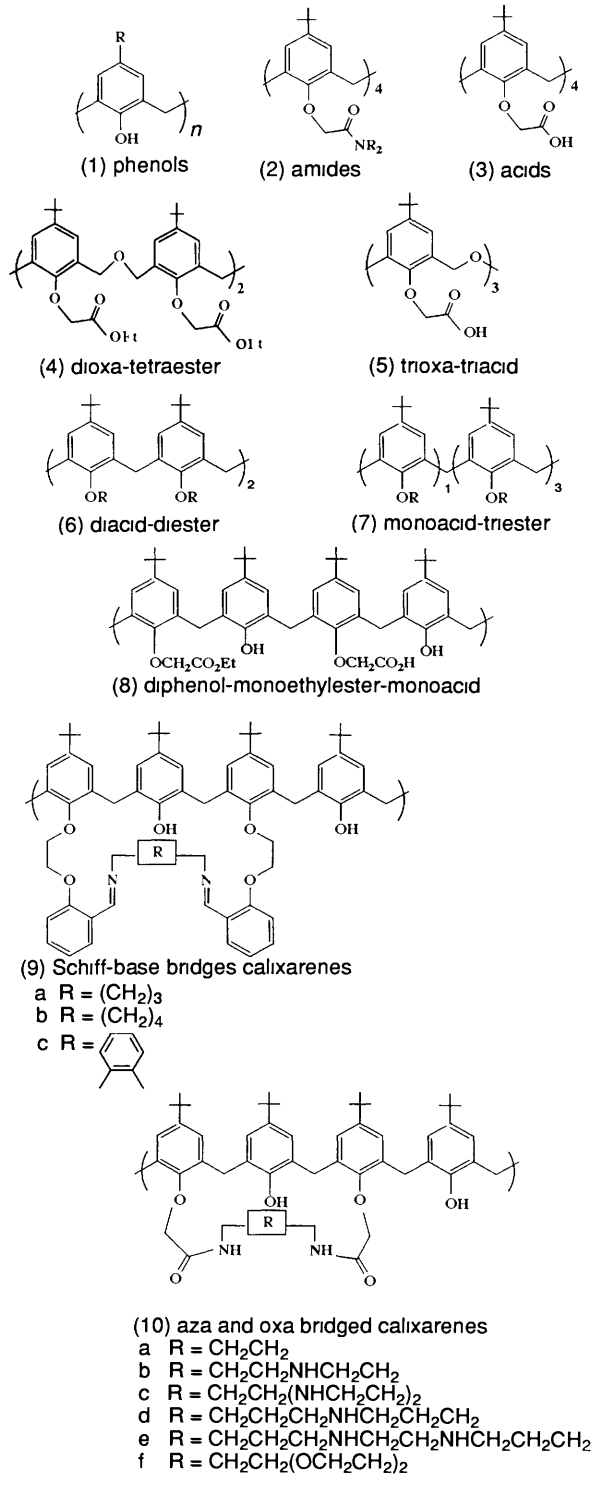

Figure 8 Chemical structures of some calixarenes and their chemically modified derivatives

hexadeprotonated and can be considered as a ditopic receptor Each europium is coordinated to two solvent molecules and three phenolic groups, in addition, both cations are bridged by two phenoxide oxygen donor atoms of the macrocycle and by one molecule of DMF Complexes with other lanthanides and other oligomers were further obtained and characterized by *X*-ray crystallography [4,27] As the study of the complexation of lanthanides by calixarenes in solution has only just started, we have tried in the following sections to report exhaustively on this topic The basic structures of calixarenes which have been studied in this frame are represented in Figure 8

4.1 Phenolic Calixarenes

The complexing abilities of the *p*-t-butylcalix[8]arene (1, $n = 8$) in solution were also established by Harrowfield [4,26] This study was carried out in *N*,*N*-dimethylformamide by UV-visible absorption spectrophotometry after deprotonation of the ligands using Et_3N in excess and it showed the simultaneous formation of a binuclear and a mononuclear complex of europium for which the stability constants were 4 $10^5 M^{-1}$ and $\approx 10^3 M^{-1}$, respectively Two other oligomers (R = iso-propyl, n = 4,8) were later tested towards Pr^{3+}, Eu^{3+}, and Yb^{3+} in the same conditions [28] The results confirmed the presence of the dinuclear and mononuclear complexes with the octamer, whereas the only 1 1 species was found with the tetramer It must be noted that the degree of deprotonation of the ligands is unknown in either study and may be different in the free and complexed forms The complexes with the octamer are slightly more stable than their homologues with the tetramer With a given ligand, there is no significant variation of stability on going from Pr^{3+} to Eu^{3+} and Yb^{3+}, and hence no selectivity of either the octamer or the tetramer within the lanthanides, as far as the cations studied are representative of the whole series

Sulfonation in the *para* position of the phenolic calixarenes (1, $R = SO_3^-$) leads to water-soluble compounds The binding properties of such a tetramer were studied with all the lanthanides in water by pHmetric measurements [29] This ligand behaves as a di-acid (LH_2 if the electric charges of the sulfonate groups are omitted) as the dissociation of the third and the fourth phenols could not be achieved The overall stability constants of the LnL_2OH^{2-} species formed are very high – around 20 log units – and increase slightly along the series The results also indicate that this ligand is a useful colorimetric reagent for cerium(III) in the presence of other rare-earth cations

4.2 Chemically Modified Calixarenes

The introduction of functions containing 'hard' heteroatoms, like esters or amides, should lead to better complexing agents for lanthanides A 1 1 complex of the *p*-t-butylcalix[4]arene tetradiethylamide (2, $n = 4$, R = Et) has been prepared with $EuCl_3$ [30] This complex is water-soluble, in contrast to the ligand which is sparingly soluble in methanol By analysing its luminescence spectrum, it was established that only one molecule of water was coordinated to the complexed cation This indicates an almost complete shielding of the cation from the solvent This contrasts with the europium cryptate of 222 in which three water molecules still interact with the complexed cation [31] The high level of complexation of lanthanides by two *p*-t-butylcalix[4]arene tetraamides ($n = 4$, R = Et, and R_2 = pyrrolidinyl) has been confirmed by stability constant determinations (Table 1) [32] These compounds are looser and less selective binders than cryptand 221 [6] Although they should provide a greater number of donor sites, the corresponding hexaamides ($n = 6$, R = Et, and R_2 = pyrrolidinyl) form less stable complexes with log $\beta \approx 4$—5 However the results of extraction of lanthanide picrates from water to dichloromethane by these calixarene amides do not exactly reflect the trends observed in complexation because (i) Eu^{3+} is better extracted than Pr^{3+} and Yb^{3+} by both tetramers, and (ii) Eu^{3+} is better extracted by the hexamers than by the tetramers [32] It can also be seen that substituent variation in the amide podands of calix[4]-, calix[5]-, and calix[6]arenes has significant effects on the extraction of europium picrate, as seen in Figure 9, which gives %E, the percentage cation extracted They can influence the biphasic transfer of the cation according to their electronic, steric, and lipophilic characters For instance, alkyl groups contribute to rather high extraction levels but the effect of an increasing number of carbons in the substituent (from ethyl to pentyl) is different for the pentamers and the hexamers Whereas a regular increase is observed with the pentamers, the opposite variation takes place with the hexamers The presence of substituents with multiple bonds like allyl or propargyl, or with a rather bulky and rigid cyclic

Table 1 Lanthanide cation binding with chemically modified calixarenes

Structure No	n	R	R′	Log β (MeOH)		
				Pr^{3+}	Eu^{3+}	Yb^{3+}
2	4	Et		8 5	8 7	8 1
	4	pyrrol[a]		8 1	8 0	8 2
	6	Et			4 4	
	6	pyrrol[a]			5 2	
3[b]	4			20 7	25 0	24 8
6[c]		$CH_2CO_2Bu^t$	CH_2CO_2H	13 5	13 4	14 4
7		CH_2CO_2H	CH_2CO_2Et	8 3	8 3	9 3
		CH_2CO_2H	$CH_2CO_2Bu^t$	8 8	8 5	9 4
5[b]				17 0	15 9	18 0
8[b]				22 9	23 2	24 8
9		$(CH_2)_3$			4 8	
9		$(CH_2)_4$			4 1	
9		Ph			3 7	
				log β (AN)		
4				5 1	4 6	3 4

$R_2 = (CH_2)_4$ (pyrrolidinyl) [b] simultaneous formation of 1 1 1 and 1 1 2 complexes simultaneous formation of 1 1 1 complexes

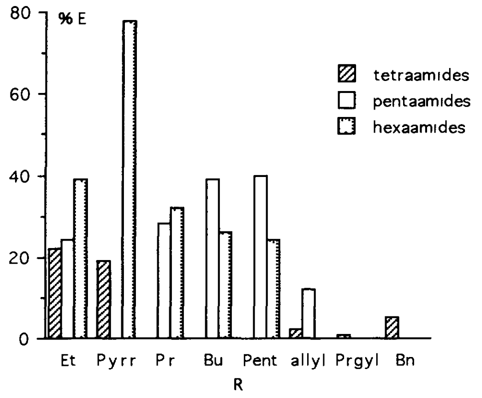

Figure 9 Influence of the substituent variation on the percentage extraction of europium picrate by calix[4]-, calix[5]-, and calix[6]arene amides

structure like benzyl, reduces drastically the %E values The steric constraints of the latter and the electron withdrawing of the former could be responsible for these low extraction levels The highest extraction by far is obtained with the hexa-pyrrolidinylamide derivative

With a dioxa tetraester ($R' = CH_2CO_2Et$) bearing two $O{-}CH_2$ units next to two opposite bridging methylene (4), the stability of the complexes in acetonitrile decreases from Pr^{3+} to Eu^{3+} and Yb^{3+} (Table 1) [32] It is known from its *X*-ray structure that this ligand adopts the 1,2-alternate conformation and defines a larger cavity than would a simple tetramer in the cone conformation [25] The size of the cavity becomes less and less likely to be compatible with the cations along the series, thus resulting in a drop in log β from Eu^{3+} to Yb^{3+}

The *p*-t-butylcalix[4]arene tetracarboxylic acid (3, $n = 4$) has also been investigated, as well as some related tetramers with mixed functionalities [(6), (7), and (8)] [32] The trioxa-triacid (5), a trimer possessing three additional oxygen atoms in the macrocyclic framework, was also tested for its ability to form neutral complexes with trivalent cations With all ligands, very stable mononuclear unprotected complexes are formed (Table 1) However, they are predominent or alone at higher pH only, as the corresponding protonated species are present at lower pH The best complexing agents are, in decreasing order, the tetraacid, the mixed diphenol-monoethylester-monoacid, and the trioxa-triacid In all cases, log β values increase from Pr^{3+} to Yb^{3+} However these variations do not exceed 1 log unit except with the diphenol-monoethylester-monoacid and the tetraacid for which Δlog $\beta = 1$ 9 and 4 1, respectively Apart from the trioxa-triacid and the triethylester-monoacid, the Eu^{3+} complexes are at least as stable as their Pr^{3+} homologues Lanthanide complexes with calixarene-acids are much stronger than those of alkali and alkaline-earth cations for instance Δlog $\beta \approx 15$ between the unprotonated complexes of europium and sodium,[25] with the tetraacid a result consistent with the electrostatic stabilization of the complexes which prevails with anionic ligands In most cases log β values are higher than those found with the amide derivatives However, although the tetraacid is, for instance, formally a stronger binder than the *p*-t-butylcalix[4]arene tetradiethylamide, it would be less effective if used in acidic conditions, as its complexation power is pH dependent

The ability of *p*-t-butylcalix[4]arene tetracarboxylic acid to bind lanthanides has also been established by extraction experiments, from water to toluene or chloroform [33] The extraction constants of the 1 2 metal ligand complexes for the water–toluene system follow the order Eu > Nd > Yb > Er > La, which is consistent with the trends found with this ligand in complexation, and in the same order found for stability constants of 1 1 complexes with simple carboxylic acids Upon addition of excess Na^+, both extractibility and selectivity increase Lanthanides are better extracted from water to chloroform by the *p*-t-butylcalix[6]arene hexaacid, according to the same cation exchange mechanism as 1 2 metal ligand complexes The order of extractibility is Nd, Eu > La > Er > Yb In the presence of excess Na^+ in the aqueous phase, this order did not change, although the extractibility decreased and the lanthanides were extracted as 1 1 complexes Recent results concerning extraction and transport experiments through bulk liquid membranes of a dimethoxy-diacid calix[4]arene show a great influence of the cation of the background electrolyte [34] In the presence of a quaternary ammonium cation no cation transfer is observed, whereas in the presence of $M^+ = Na^+$ or K^+, Ln^{3+} are co-extracted with the alkali ions as $LnML_2$ complexes This stoichiometry has been confirmed by fast-atom bombardment mass spectrometry (FAB-MS) The weak selectivity observed follows the order $La < Y \leq Er$

Some bridged calixarenes in the cone conformation, in which two opposite phenolic oxygen atoms are connected *via* bridges containing different kinds of donor sites, should contribute to the high coordination numbers required by lanthanides, better than the simple *p*-t-butylcalix[4]arene Existence of 1 1 complexes of europium in methanol with three Schiff-base bridged calixarenes (9a—c) was detected Their stability decreases for the longer bridged (9b) and also for the more rigid aromatic ligand (9c) [35]

Other bridged calixarenes, containing poly(oxyethylene) and poly(azaethylene) links (10), form weak complexes with Gd^{3+} and the rare-earths Y^{3+} and Sc^{3+}, as demonstrated by a FAB-MS study [36] The aza-derivative (10a) is the best complexing agent for Sc^{3+}, whereas the oxygen bridged calix[4]arene (10f) is the best for Gd^{3+} and Y^{3+} The effect of methylation of the free OH groups leads to weaker complexes For trivalent cations, no clear relationships between the ion radius and the size of the cavity is observed, as the achievement of high coordination numbers is also an additional important factor

5 Conclusion

In this survey, we have tried to point out the more important factors of the complexation of lanthanide cations by macrocyclic receptors by selecting some examples from amongst the numerous studies involving cryptands and neutral or ionizable coronands These macrocycles display many features (large number of donor sites, presence of oxygen and nitrogen atoms or a combination of both types of heteroatoms) favourable to a strong binding of lanthanide cations, which may find numerous applications However, in contrast to alkali and alkaline-earth cations, high complexation selectivity amongst lanthanide cations is difficult to achieve, as the variation of the stability constants along the series results from an interplay of often antagonistic factors (size, solvation, and charge effects, ligand flexibility) Data on the complexation of lanthanides by calixarenes are still scarce but a great number of derivatives have not yet been tested with these cations The few results obtained so far indicate a generally high stability for lanthanide complexes of calixarenes, which, associated with their recently reported strong fluorescence,[37] should make them useful, for instance, as luminescent probes and tags for the analysis of biological materials

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