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Macrocyclic Polyether Tetralactams II : A Study of their Binding Properties with Alkaline - Earth Cations

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Abstract *: Solvent extractions of alkali and alkaline-earth picrates were carried out in a water-chloroform system using newly synthesized tetralactams containing dimethyleneoxy moieties. These ligands display excellent extracting properties for* Ca^{2+}, Ba^{2+} *and* Sr^{2+} *cations. Some of the less lipophilic derivatives have greater preference for* Ba^{2+} *vs.* Na^{+} *and* Zn^{2+} *and, to a lesser extent,* K^{+}, Mg^{2+} *and* Ca^{2+}. *In addition, the stability constants were determined for the 1:1 and 1:2* M^{2+}*:tetralactam complexes by UV spectrophotometry in THF solution. In each series of tetralactams* $\log K_S$ *values as high as 6 were observed for* Ca^{2+}, Sr^{2+} *and* Ba^{2+} *ions. The 18-, 21- and 24- membered tetralactams complex preferentially* Sr^{2+}, Ca^{2+} *and* Ba^{2+} *cations respectively.*

In the preceding paper[1] we have reported the syntheses of some new macrocyclic tetralactams including two dimethyleneoxy moieties. As previously noticed[2] these compounds display interesting complexing properties with the alkaline - earth ions.

In order to obtain good alkaline-earth ion selectivities, we suggested that the incorporation of two ether diamide moieties into a macrocycle should be more efficient compared with open chain diamides or macrocyclic dilactams. Indeed, tetralactams were thought to form 1:1 complexes, while diamides and dilactams mainly displayed in solution a 1:2 (cation:ligand) stoichiometry.[3, 4]

A more extensive study has now been performed following two aims : first, to analyze the complexing properties of these new macrocycles (see figure 1), related to the ring size, the lipophilicity and the macrocyclic effect, and then to classify these compounds along with those existing in the literature, in particular the open chain diamides. Their cation binding abilities have been measured both from the liquid-liquid extraction technique[5] and the binding constant determinations in THF solutions by UV spectrophotometry.

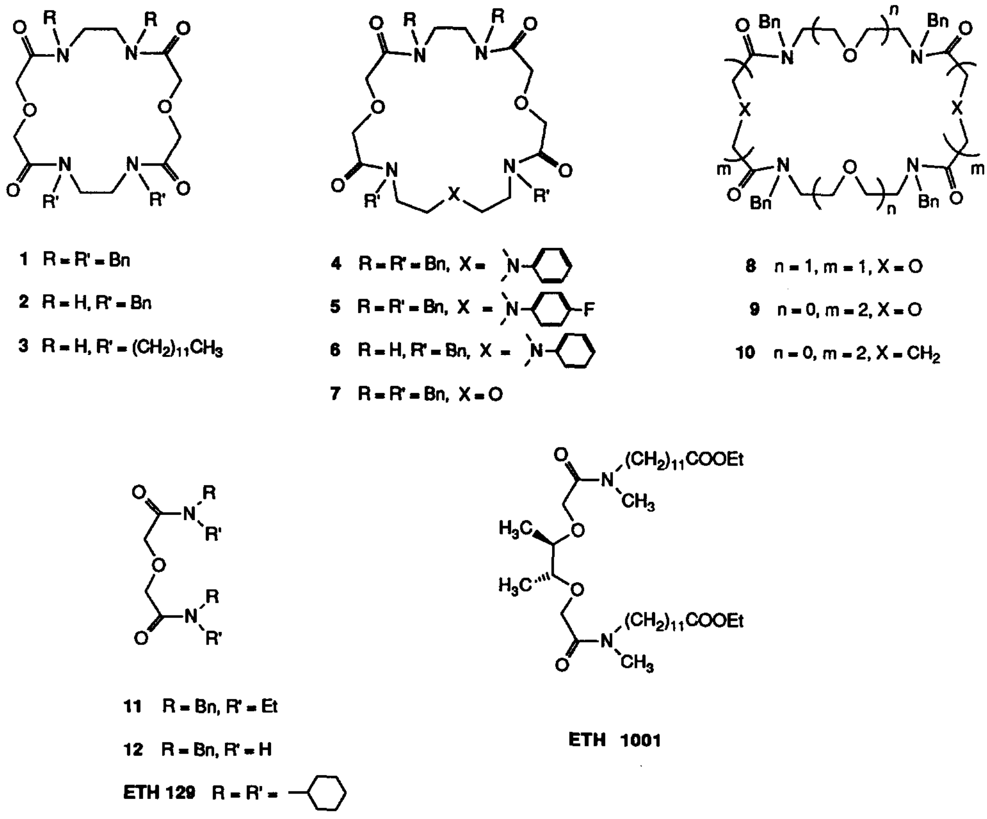

Figure 1 : 18-, 21-, 24-membered Tetralactams and Open Chain Diamides used in this study

RESULTS AND DISCUSSION

Complexation studies by liquid-liquid extraction

Picrates salts of the alkali (Na^+, K^+), alkaline-earth (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and zinc cations were extracted from an aqueous phase to a chloroformic one by complex formation with the ligand ; the decrease in absorbance of the picrate ion in the aqueous phase was monitored by UV-Vis spectroscopy. The percent limits of extraction and the lipophilicities, as log P,[6] are indicated in table 1 along with literature data for ETH 1001 [3] and 18-C-6.[7]

The 1:1 stoichiometry of the complexes in solution was assigned by complexation studies in aprotic solvent (vide infra) and was verified by elemental analysis of the picrates or perchlorates complexes.[2]

Table 1 : Extraction Ratio (E %) of Alkali, Alkaline-Earth and Zn^{2+} Picrates by Ligands **1-12** a)

Picrate salt compound	Na^+	K^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Zn^{2+}	log P b
1	5.8	6.5	4.5	77.5	$\boxed{87.5}$	$\boxed{89.2}$	1.0	3.8
2	0	2.7	2.8	4.0	22.0	$\boxed{76.6}$	0	1.9
3	2.6	1.2	c	4.7	c	22.1	c	8.7
4	0.5	0.9	2.5	$\boxed{88.2}$	$\boxed{90.1}$	68.3	3.9	5.2
5	2.4	2.5	1.6	$\boxed{90.0}$	$\boxed{85.1}$	72.9	2.4	5.2
6	0	0	1.2	17.9	15.5	$\boxed{58.9}$	0	2.2
7	1.0	0.9	3.2	68.9	$\boxed{88.2}$	$\boxed{82.1}$	16.2	3.8
8	49.2	54.9	32.2	63.1	c	64.4	46.1	3.8
9	3.0	7.1	0	58.9	52.6	$\boxed{67.7}$	1.8	3.8
10	0	c	13.6	15.2	c	c	15.0	5.1
11	0.5	0	0	37.4	c	47.5	0	2.5
12	0	0	c	2.4	c	0	c	< 1.9
ETH 129 d)	0	1	8.4	76.0	81.8	79.5	58.0	6.7
ETH 1001 e)	c	c	3.0	38.0	15.0	18.0	c	6.2
18-C-6 f)	6.3	69.0	2.5	26.2	69.0	75.8	c	0

a) Extraction conditions : temperature 25.0 ± 0.2 °C ; aqueous phase (0.25 mL) : [picrate] = 1.5×10^{-2} M ; organic phase ($HCCl_3$, 0.25 mL) : [ligand] = 1.5×10^{-2} M ; b) lipophilicity measured by RPTLC technique ; c) not determined ; d) $[\text{ligand}]_{HCCl_3} = 2[\text{picrate}]_{aq} = 3 \times 10^{-2}$ M ; e) $[\text{picrate}]_{aq} = 6.5 \times 10^{-4}$ M ; $[\text{ligand}]_{CH_2Cl_2} = 1.5 \times 10^{-3}$ M according to [6] ; f) $[\text{picrate}]_{aq} = [\text{ligand}]_{CH_2Cl_2} = 3 \times 10^{-3}$ M according to [7].

18-membered tetralactams. For tetralactams **1-3**, a selectivity trend for the extraction of alkaline-earth cations ($Mg^{2+} < Ca^{2+} < Sr^{2+} < Ba^{2+}$) is noticed. Among these three macrocycles **1** exhibits the higher extraction abilities for Ca^{2+}, Sr^{2+} and Ba^{2+} picrates and a high selectivity for these three cations with respect to the other experimented cations. Compared with **1**, compound **2** has two secondary amide groups and thus a weaker lipophilicity. As a consequence it is less efficient for extracting all metal picrates ; the difference being most noticeable with the calcium (4.0%) and strontium (22.0%) salts. However, as can be seen, **2** shows an excellent selectivity for Ba^{2+} extraction. In an attempt to enhance the lipophilicity of **2**, compound **3** was examined. Although Ba^{2+} is the best extracted cation, the selectivity is much poorer than that observed for the analogous compound **2**.

The selectivity order $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$ observed may not be explained simply in terms of "lock and key" concept. As a matter of fact, examination of CPK space-filling models of the tetralactams studied in this paper reveals that the coordination sites of these macrocycles are not oriented inside the cavity. In the more favourable conformation, with respect to complexation, the four amide carbonyls rather display a cone structure. This is also supported by the ^{13}C NMR studies of the complexes.[2b] On the other hand, these tetralactams afford 1:1 complexes and with six complexation sites may not ensure the stripping of the ion's entire solvation shell (Ca^{2+}, Sr^{2+}, Ba^{2+} requiring a higher coordination number). In this case, interaction of the metal ion trapped by the tetralactam, with water molecules is still possible. At last the distribution of the alkaline-earth picrates into the chloroform phase decreases in the order of their free energies of hydration, and thus in an inverse relationship with their ionic radius[8]. So the selectivity of extraction of the alkaline-earth cations by **1-3** is probably ascribable to the difficulty for the highly hydrated complex to be extracted in the organic phase.

For **1**, the Ca^{2+}, Sr^{2+}, Ba^{2+} complexes are better isolated from the aqueous phase due to the lipophilic effect of the four benzyl groups, whereas for **2** the reduced lipophilicity (two benzyl groups) allows only a good extraction of the Ba^{2+} ion having the lowest hydration energy. In the case of **3**, the drop in selectivity for Ba^{2+} must reflect a less lipophilic complex compared to **2**. This is expected from the greater length and flexibility of the saturated sidearms in **3**, giving it more accessible to the aqueous solvent than **2** where stacking interactions dues to the benzyl groups can undergo.

In tetralactams **1-3** the preference of alkaline-earth over alkaline cations confirms the importance of the basic system featuring high polarity coordination sites (carbonyl amide), the presence of more polar donors favouring more charged cations.[9] The replacement of CH_2O moieties in crown ethers by amide functions modify considerably the properties of the host. Thus tetralactams **1**, **2** and 18-crown-6 which have the same ring size and the same number of coordination sites, exhibit very different extraction abilities with respect to K^+ which has a size identical to that of Ba^{2+}. The Ba^{2+}/K^+ selectivity coefficient increases from 1.1 for 18-crown-6 to 14 for **1** and 28 for **2**.

The spatial arrangement of the coordination sites in these tetralactams may be also invoked to explain the easier extraction of Ca^{2+}, Sr^{2+} and Ba^{2+} cations. As a matter of fact the complexes of these cations with a coordination number ≥ 8 show quite irregular geometries while for the other cations poorly extracted (Na^+, K^+, Mg^{2+}, Zn^{2+}) the coordination number is generally equal to 6, leading to well-defined octahedral complexes.

21-membered tetralactams. Tetralactams **4**, **5** display the same general trend for the extraction properties than the 18-membered tetralactam **1**. However the poorer extraction of Ba^{2+} and the Ca^{2+}, $Sr^{2+} > Ba^{2+}$ selectivity sequence show that the hydration energy of the cation extracted is not the only factor implied in this case. For **6**, except Ca^{2+}, metal loadings are lower than for the analogous compound **2**, but the selectivity Ba^{2+}/M^+ and Ba^{2+}/M^{2+} is preserved.

On the other hand the expansion of the ring size by a dimethyleneoxy moiety (compound **7**) produces an increase of the Zn^{2+} extraction.

24-membered tetralactams. With same lipophilicity, but for a higher number of coordination sites (2 ether oxygen atoms more), the more flexible 24-membered tetralactam **9** extracts the alkaline-earth cations to a lesser extent than the 18-membered homolog **1**. Among all the studied tetralactams, **9** has the best selectivity Ca^{2+}/Mg^{2+}.

Ether oxygen atom effect. In the solvent extraction of alkaline-earth cations by tetralactams, the extractability and cation selectivity cannot be explained only by the lipophilicity effect and the presence of amide group in the extractants. The insertion and arrangement of ether oxygen atoms play an important role. Thus, the insertion of ether oxygen atoms improves appreciably the extractability of Ca^{2+} and the selectivity Ca^{2+}/Mg^{2+} (**9** in comparison with **10**).

A more interesting result is that, in spite of comparable size, lipophilicity and same number of donor oxygen atoms, **8** and **9** display an extraction selectivity behaviour in deep contrast. Thus, **8** exhibits same extractability of Ca^{2+} and Ba^{2+} than **9**, but much poorer selectivity with respect to Na^+, K^+, Mg^{2+} and Zn^{2+}. The extractability of Zn^{2+} has been already noticed for the 21-membered tetralactam **7** including too a $O(CH_2CH_2N)_2$ moiety in the ring.

Macrocyclic effect. The macrocyclic effect observed for macrocycle **9** vs. ETH 1001 is evidenced by an increased selectivity for Ca^{2+}, Sr^{2+} and Ba^{2+} with respect to Mg^{2+}. The same effect, to a lesser extent however, exists between **1**, **4**, **5** and ETH 129. The enhanced selectivity Ca^{2+}/Zn^{2+} observed for tetralactams (excepted **7** and **8**) vs. ETH 129 may result from higher rigidity of macrocycles. However diamide **11** displays better selectivities Ca^{2+}/Mg^{2+} and Ca^{2+}/Zn^{2+} than tetralactams with a dimethyleneoxy moiety, but with a poorer metal loading. A macrocyclic effect may be also noticed when compounds **12** and **2** or **6** are compared. Under the same experimental conditions, the open chain compound **12** gives very low extraction. This result suggests no significative contribution of more lipophilic 1:2 sandwich complexes in the solvent extraction by **12**.

Stability constants

The stability constants were measured in tetrahydrofuran solutions by UV spectrophotometry for tetralactams/metallic picrates complexes. This technique is particularly suitable for the measurement of the stability constants ranging between 10^2 and 10^5 $l.mol^{-1}$.[10] Furthermore, in a solvent of low polarity (THF), absorptions of the metallic picrates show a bathochromic shift in the presence of ligand resulting from the change of a tight ion pair to a looser ion pair.[11, 12]

The stability constants were calculated by taking into account the formation of the two ML and ML_2 complexes as suggested by the existence of two isosbestic points. Thus, for instance, addition of **6** to calcium picrate produces a tight ion pair complex ML with $\lambda_{max} = 340.6$ nm. When a large excess of ligand **6** is added a change in the maximum is observed; the initially formed ML complex is converted into a ML_2 separated ion pair with $\lambda_{max} = 356.9$ nm. Isosbestic points appear at 338.9 and 343.1 nm (see figure 2).

The alkaline and magnesium ions being extracted to a lesser extent by the studied macrocycles, it will be expected that these ions would lead to weak stability constants difficult to measure. Such a behaviour was verified for the macrocycle **4** and the Na^+ cation and also for **6** and magnesium (no spectral variation up to ρ = [ligand] / [metal] = 30). Nevertheless it was not a general rule.

The calculated constants and the complexation selectivities are respectively gathered in tables 2 and 3. K_1 stability constants as high as 10^6 $l.mol^{-1}$ were observed for each macrocyclic family but three distinct behaviours were noticed.

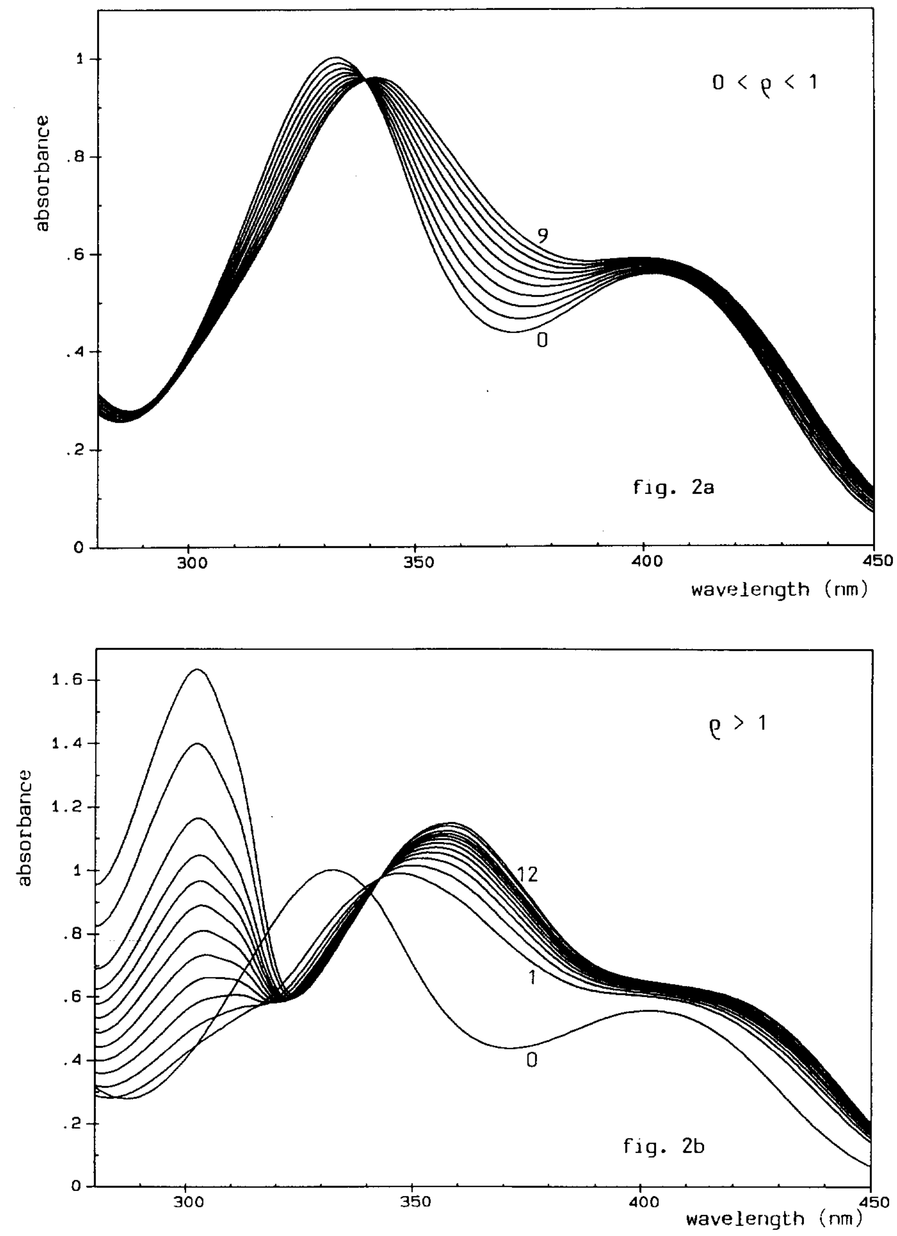

Figure 2 : Ultraviolet spectra of a $3.37x10^{-5}$ M THF solution of calcium picrate in the presence of varying amounts of tetralactam **6** at 25°C. Molar ratio (ρ) of ligand to picrate salt concentrations is varied as follows
fig. 2a : 0, 0.00 ; 1, 0.10 ; 2, 0.21 ; 3, 0.31 ; 4, 0.42 ; 5, 0.52 ; 6, 0.63 ; 7, 0.73 ; 8, 0.83 ; 9, 0.94.
fig. 2b : 0, 0.00 ; 1, 2.08 ; 2, 3.11 ; 3, 4.15 ; 4, 5.19 ; 5, 6.23 ; 6, 7.27 ; 7, 8.30 ; 8, 9.34 ; 9, 10.38 ; 10, 11.86 ; 11, 14.83 ; 12, 17.80

Table 2 : Stability Constants (log K_s) in THF for 1:1 and 1:2 (in brackets) Complexation of Alkaline-Earth Metal Picrates with Macrocycles **1-9** (K_1 in $l.mol^{-1}$ at 25°C ± 0.2 and K_2 in $l^2.mol^{-2}$)

compound \ cation	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
1	5.48 (2.00)	5.57 (2.39)	6.50 (3.00)	4.88 (2.95)
2	UC	3.96 (2.04)	4.87 (2.60)	3.36 (2.17)
3	ND	ND	ND	4.11 (2.50)
4	4.98 (5.05)	6.20 (4.00)	6.40 (3.80)	6.20 (3.60)
5	ND	6.20 (3.90)	ND	ND
6	NV	5.53 (3.88)	5.38 (3.60)	4.87 (3.41)
7	UC	6.60 (4.60)	6.30 (4.10)	6.20 (3.85)
9	ND	4.64 (4.34)	ND	6.60 (3.00)

ND = not determined ; UC = uncomputable ; NV = none variation in the UV spectrum

18-membered rings : di and tetrabenzylated compounds **2** and **1** show a good selectivity for strontium vs. magnesium (complex 10 times more stable), calcium (~ 8 times) or moreover barium (30 to 40 times). The log K_S differences between metallic cations are almost equal in the two di- and tetrabenzylated series. The global result is a decrease in the stability constants for the dibenzylated species of about 1.6 logarithmic unit. The maximal log K_1 is 6.5 for the **1**/Sr^{2+} complex.

21-membered rings : the prominent fact is the lack of selectivity between alkaline-earth cations excepted for Ca^{2+}, Sr^{2+} and Ba^{2+} vs. Mg^{2+} (~ 20 times more stable complexes). The dibenzylated compound is differentiated from the tetrabenzylated ones by the decrease in their stability constants of 1 ± 0.3 logarithmic unit. In this series all the tetrabenzylated compounds show log $K_1 > 6$.

24-membered rings : the two realized experiments indicate a high selectivity for Barium. The **9**/Ba^{2+} complex is 91 times more stable than the **9**/Ca^{2+} one and exhibit the most important stability constant (log K_1 = 6.6) observed for a tetralactam.

Table 3 : Selectivity of Alkaline-Earth Cation Complexation

Compound	Cation Selectivities a)					
	Ca^{2+} / Mg^{2+}	Sr^{2+} / Mg^{2+}	Sr^{2+} / Ca^{2+}	Sr^{2+} / Ba^{2+}	Ba^{2+} / Mg^{2+}	Ba^{2+} / Ca^{2+}
1	1.2	$\boxed{10.2}$	$\boxed{8.3}$	$\boxed{41}$	0.25	0.2
2	-	-	$\boxed{8.1}$	$\boxed{32}$	-	0.25
4	$\boxed{16.6}$	$\boxed{26.3}$	~ 1	~ 1	$\boxed{16.6}$	~ 1
6	-	-	0.7	3.2	-	0.22
7	-	-	~ 1	~ 1	-	~ 1
9	-	-	-	-	-	$\boxed{91}$

a) Selectivities are expressed as ratios of stability constants

The lower stability constants for the dibenzylated compounds **2** and **6** can be explained by the existence of two secondary amide functions with less electron donating carbonyl groups and also by the destabilization of the complex relative to the free ligand due, in the latter case,to the establishment of a NH...O binding interaction either intramolecular or with the solvent (tetrahydrofuran). A poorer binding of lariats containing a secondary amide vs. a tertiary amide in the sidearms was also observed recently by Gokel.[13]

In all the cases ML_2 complexes were found to be less stable than the ML ones, with log K_1/K_2 values ranging from 1.7 to 3.6 excepted for **4**/Mg^{2+} and **9**/Ca^{2+} complexes. If the ML_2 complexes were sandwich-like, it could be expected in these two latter cases an unfavourable geometry of the 1:1 complex due to the necessary balance between geometrical constraints (dictated by the hexacoordination of the Mg^{2+} cation for instance), the number and the nature of the coordination sites (belonging or not to the ligand).

As a result of this study, the calcium ion fits better with a 21-membered tetralactam like **4** or **7**, the strontium ion with a 18-membered ring like **1** and the barium ion with a 24-membered ring like **9**. Thus, the ring size is not the main factor playing a role in the complexation process.

Comparison with extraction experiments

An apparent discrepancy, serious in the case of tetralactams **2** and **6**, is found between the two-phases extraction data and the homogeneous stability constants. On the one hand **2** and **6** extract poorly Ca^{2+}, Sr^{2+} and nicely Ba^{2+}. On the other hand the stability constants of the complexes of **2** and **6** with Ca^{2+} or Sr^{2+} are larger than with Ba^{2+}. These results are interpreted in terms of lipophilicity of the complexes which plays a minor role in homogeneous cation binding but a major one in liquid-liquid extraction.[5,14]

These findings confirm that if the extraction of aqueous metallic picrates is not favoured by the heavy hydration of the cation, a high energy of hydration may assist stronger ion-dipole interaction with the donor oxygens of ligand in the homogeneous phase complexation.[7]

CONCLUSION

The results described in this paper reveal that polyether tetralactams with 18-24 ring atoms show varying binding properties according to their ring size and the nature of substituents on nitrogen atoms. A high selectivity for Ca^{2+}, Sr^{2+} and Ba^{2+} versus other ions like Na^+, K^+, Mg^{2+} and Zn^{2+} is found by liquid-liquid extraction technique, and by stability constants determination in tetrahydrofuran solution. In the last case, the 18-, 21-, 24-membered tetralactams complex preferentially Sr^{2+}, Ca^{2+} and Ba^{2+} cations, respectively, and log K_s values as high as 6 were observed for these three ions.

Although other membrane ingredients may affect electrode selectivity, there is a general correlation between solvent extraction data and electrode selectivities.[15] On the other hand, log K_s (M^{2+}) found are close to that observed for neutral carrier based ion-selective electrodes, like ETH 129.[16] These findings lead to possible applications, being studied now, for these tetralactams as components of selective electrode membranes.

EXPERIMENTAL SECTION

UV-vis spectra were monitored on a Perkin-Elmer Lambda 17 spectrophotometer.
The synthesis of compounds **1-10** is reported in preceeding papers.[1, 17] Compound **12** and ETH 129 were prepared as described.[18, 19] Metal picrates were prepared from picric acid and the corresponding metal hydroxyde or metal carbonate as reported.[20] Tetrahydrofuran (THF) was dried over sodium. THF and chloroform were purified by distillation just before use.

Compound **11** was prepared from diglycolic acid dichloride and N-benzylethylamine. 94% yield ; oil ; IR ($HCCl_3$), 1650 cm^{-1} (C=O) ; ^1H NMR ($CDCl_3$, 80 MHz), δ 1.10 (t, 6H, CH_3), 3.26 (q, 4H, $\underline{CH_2}CH_3$), 4.40 (s, 4H, CH_2O), 4.63 (s, 4H, $\underline{CH_2}Ph$), 7.27 (s, 10H, Ph) ; Anal. Calcd. for. $C_{22}H_{28}N_2O_3$: C, 71.71 ; H, 7.66 ; N, 7.60. Found : C, 71.64 ; H, 7.58 ; N, 7.60.

Picrate extraction procedure : The method was essentially that of Frensdorff[21] and Cram.[22] Solutions of picrates salts in distilled water (0.015 M) and solutions of ligands in chloroform (0.015 M) were used. Equal volumes of the two solutions (0.25 ml) in stoppered centrifuge tubes were mixed with a small bar (5 mm) on a magnetic stirrer for 15 hrs. The extractions were conducted at 25 ± 0.2°C. The centrifugation was carried out to obtain complete phase separation. The percent of a picrate salt extracted (E%) was calculated from the difference between the original and final aqueous picrate concentrations. The reported values of the E% (table 1) were the average of three independent experiments. The aqueous (1.45×10^4 cm^{-1} M^{-1} for M^+ Pic^- and 2.9×10^4 cm^{-1} M^{-1} for M^{2+} Pic_2^- at $\lambda_{max} = 354$ nm) extinction coefficients were used.
In control experiments, no detectable amount of any ligand was present in the aqueous phase.

Lipophilicity determination : Lipophilicities of the ligands were determined by their TLC retention R_F according to [23]. The TLC system is calibrated with a set of reference compounds of known lipophilicities.[6] TLC was performed with Whatman KC18 reversed-phase plates and the solvent system used consisted of methanol-water (8-2 by volume). The compounds tested were detected on the fluorescence indicator impregnated plates under ultraviolet light at 254nm.

Stability constants : The stability constants for ion-ligand complexes were determined by UV spectrophotometry in tetrahydrofuran solution following Smid.[11]
In THF the maxima of the main optical absorption band of alkaline-earth picrates are found at $\lambda_m = 322.5$ nm ($\varepsilon_m = 24\ 700$ cm^{-1} M^{-1}) for $MgPic_2$, 333.1 nm ($\varepsilon_m = 29\ 700$ cm^{-1} M^{-1}) for $CaPic_2$, 336.7 nm ($\varepsilon_m = 31\ 000$ cm^{-1} M^{-1}) for $SrPic_2$ and 341.4 nm ($\varepsilon_m = 34\ 000$ cm^{-1} M^{-1}) for $BaPic_2$.
The cells of the spectrophotometer were equipped with Teflon stoppers that allowed the introduction of the tetralactam solution via a syringe. The tetralactam solution aliquots (10^{-2} or 10^{-3} M in THF) were added to a 3.3×10^{-5} M solution of metallic picrate in THF. The resulting O.D. variations were monitored between 280

and 450 nm for each value of the ratio ρ = [ligand] / [metal] (20-30 runs) and analyzed using the UV STAB program.

The equilibria occurring during the complexation process can be reduced to the following set :

$$M + L \overset{K_1}{\rightleftharpoons} ML \qquad \text{with} \quad K_1 = x / (l_o - x - 2y)(m_o - x - y)$$

$$ML + L \overset{K_2}{\rightleftharpoons} ML_2 \qquad \text{with} \quad K_2 = y / x\,(l_o - x - 2y)$$

where x and y are the respective molar concentrations for the ML and ML_2 complexes at the equilibrium, l_o and m_o the starting concentrations for the ligand and the metallic salt.

If the path length of the cell is 1 cm, the OD at the equilibrium for each ρ value is given by $OD = x\,\varepsilon_{ML} + y\,\varepsilon_{ML_2} + (l_o - x - 2y)\varepsilon_L + (m_o - x - y)\varepsilon_M$ where ε is the molar extinction coefficient of the different species.

The UVSTAB program was adapted from a literature program[24] used in the lanthanide-induced shift calculations. For each K_1 and K_2 value varying between two fixed limits, x and y as well as ε_{ML} and ε_{ML_2} are obtained by a bilinear regression and minimization of the quantity $Q = \Sigma(OD_{exp.} - OD_{calcd.})^2$. The reliability coefficient $R_e = (Q/\Sigma OD^2_{exp})^{1/2}$ measures the relative error between the calculated and the experimental values.

Two experimental series were performed : one for $0 < \rho < 1$ and the other for $1 < \rho < 100$. Each was characterized by an isosbestic point and is thus correlated to a given equilibrium.

The stability constants were calculated following this method with an uncertainty of ± 0.2 when $\log K_s > 6$ and 0.05-0.1 for $\log K_s \leq 5$.

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