Macrocyclic Polyether Tetralactams Part 3.† Spectroscopic Study and Molecular Modelling of their Complexes with Alkaline-earth Cations

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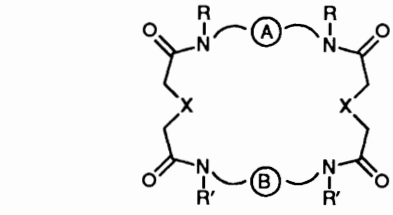
The formation of Ca^{2+}, Sr^{2+} and Ba^{2+} complexes with several 18-, 21- and 24-membered tetralactams has been investigated by UV, IR and NMR spectroscopy and molecular modelling techniques. These macrocycles form complexes with a 1:1 stoichiometry and the coordination of the metal ion is achieved by the four amide carbonyl groups, and the ether oxygen atoms of the ligand, and also by the anionic counterpart of the metal ion. On the other hand, unlike linear polyamides, it is found that a profound reorganization of these tetralactams occurs upon complexation as evidenced by ^{13}C and ^{19}F NMR spectroscopies. The existence of a single form having a mirror symmetry in the complex, with the carbonyl oxygen atoms oriented towards the cation, is postulated in solution. Molecular modelling of this complex supports this suggestion.

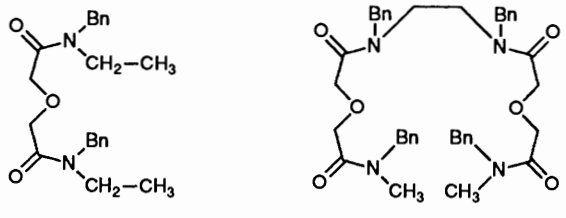
Neutral carriers for the calcium ion are attracting increasing interest as tools for biological applications as well as for the analysis and separation of this ion. In particular, considerable attention has been focused on non-cyclic and macrocyclic multidentate ligands bearing amide groups. Indeed, it is well established that the introduction of polar amide donors in a complexone plays an important role in the enhancement of the selectivity in cation binding in favour of cations of high charge density, and consequently leads to the preference for alkaline-earth cations over alkali metal ions of the same size. Thus acyclic oxa- or dioxa-diamide derivatives,[1] macrocyclic polyether–diamides,[2] bis(polyether–diamide) macrocycles,[3] and amide-armed polyaza macrocycles[4] show a high affinity for alkaline-earth metal ions. We are currently interested in macrocyclic polyether tetralactams[5] and we assumed that these structures, containing two ether diamide moieties in a macrocycle, might enhance the selectivity and the complexing properties through a 1:1 complex, unlike diamides[1a] and dilactams[2b] which mainly display a 1:2 (cation:ligand) stoichiometry in solution.

In a previous paper,[5e] we showed, by an extraction procedure with picrates, and by the determination of stability constants, that the 18-, 21- and 24-membered tetralactams depicted in Fig. 1 display a high selectivity for Ca^{2+}, Sr^{2+}, Ba^{2+} *versus* other ions like Na^+, K^+, Mg^{2+} and Zn^{2+}. In tetrahydrofuran solutions log K_s values as high as 6 were measured for these three ions.

We report here a structural study of the complexes between these macrocyclic polyether tetralactams and Ca^{2+}, Sr^{2+}, Ba^{2+} cations. It was impossible in our hands to obtain single crystals of these complexes, and therefore to use X-ray diffraction techniques, but valuable information was obtained from UV, IR and NMR spectroscopies, elemental analysis and molecular modelling. Thus, a reasonable structural representation of the complexes in solution may be proposed.



	A	B	X	R	R′
1	CH_2CH_2	CH_2CH_2	O	Bn	Bn
2	CH_2CH_2	CH_2CH_2	O	Bn	H
3	CH_2CH_2–N(Ph)–CH_2CH_2	CH_2CH_2	O	Bn	Bn
4	CH_2CH_2–N(Ph 4-F)–CH_2CH_2	CH_2CH_2	O	Bn	Bn
5	CH_2CH_2–N(Ph)–CH_2CH_2	CH_2CH_2	O	Bn	H
6	CH_2CH_2	CH_2CH_2	OCH_2CH_2O	Bn	Bn



7 **8**

Fig. 1 18-, 21-, 24-Membered tetralactams and open chain polyamides used in this study

Results and Discussion

Stoichiometry of the Complexes.—Analysis of the modification of the electronic spectra of THF solutions of metal picrates in the presence of increasing amounts of ligands gave information about the stoichiometry of ligand–cation complexes.[6] For tetralactams **1–6** the position of the absorption band of the picrate chromophore† indicated the existence of complexes either with tight ion pairs (ML, λ_{max} = 335–350 nm) or looser ones (ML_2, λ_{max} *ca.* 370 nm), but not entirely separated (a value near 377–380 nm is generally expected in this case).

On the other hand, the computational treatment of the equilibria showed that the main complex is ML for small ρ

† Part 2, see ref. 5e.

† In THF, the absorptions of alkaline-earth picrates were found at λ_{max} = 333.1 nm for $CaPic_2$, 336.7 nm for $SrPic_2$ and 341.4 nm for $BaPic_2$.

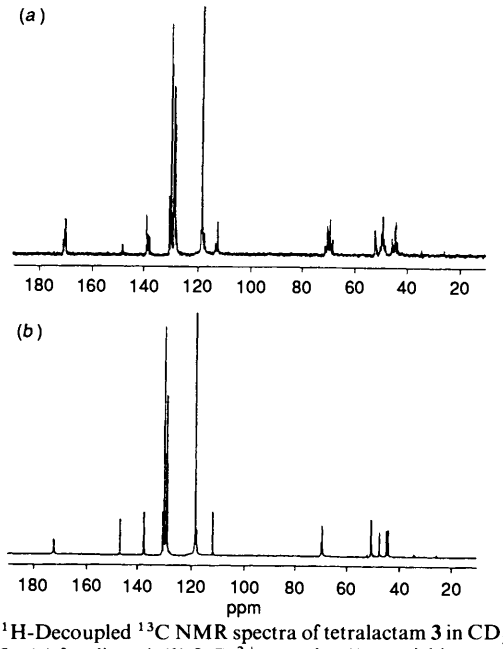


Fig. 2 ^{1}H-Decoupled ^{13}C NMR spectra of tetralactam **3** in CD_3CN at 62.9 MHz: (*a*) free ligand, (*b*) **3**-Ca^{2+} complex (1:1 stoichiometry)

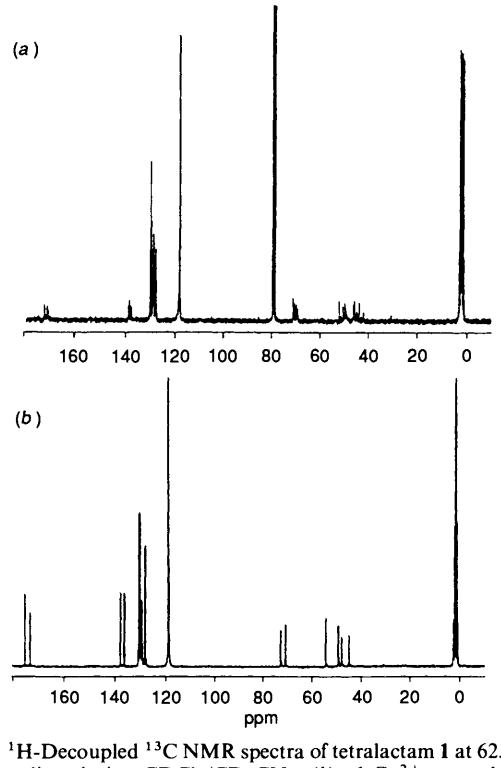


Fig. 3 ^{1}H-Decoupled ^{13}C NMR spectra of tetralactam **1** at 62.9 MHz: (*a*) free ligand in $CDCl_3/CD_3CN$, (*b*) **1**-Ca^{2+} complex (1:1 stoichiometry) in CD_3CN

values (*e.g.* 94% for $\rho = [\mathbf{3}]/[Ca^{2+}] = 1.1$ and 82% for $\rho = [\mathbf{2}]/[Ba^{2+}] = 4.6$) while the ML_2 complex is significantly involved only for the highest ρ values (respectively 88 and 25% for these two complexes and $\rho = 18$).

The main 1:1 stoichiometry found for small ρ values is confirmed by elemental analysis. The tetralactams–Ca^{2+}, Sr^{2+} or Ba^{2+} complexes were isolated in the solid state in ten cases (see Experimental section) and all present the 1:1 stoichiometry.

Reorganization of the Ligand by Complexation.—62.9 MHz ^{1}H-decoupled ^{13}C spectra of compounds **1**–**6** exhibited a high complexity for each type of carbon atom related to the phenomenon of hindered internal rotation around the carbon–nitrogen bond of the amide group.[7] Similar results were observed by Shanzer[8] for macrocyclic polymethylene tetralactams possessing a reflection symmetry. For instance we observed in CD_3CN up to six distinct benzyl carbon resonances for compound **1**, five for **2**, and four for **6**. A high multiplicity was also clearly seen for the other carbon resonances in CD_3CN as well as in $CDCl_3$ solutions as shown in Figs. 2(*a*) and 3(*a*). Thus, free macrocyclic polyether tetralactams **1**–**6** do not essentially exist in the highly symmetric conformation with all *trans* lactam bonds, even compound **6** despite its 24-membered ring.[8]

When an equimolar amount of calcium, strontium or barium perchlorate was added to acetonitrile solutions of the 18-, 21- or 24-membered tetralactams **2**, **3**, **5**, **6** significant changes in the spectrum occurred. A striking simplification was observed leading to only one signal per carbon [see Fig. 2(*b*) and Table 1].

On the other hand, the 282.4 MHz ^{1}H-decoupled ^{19}F NMR spectrum of the tetralactam **4** exhibited eight resonances which are reduced to one by adding calcium perchlorate.[5c] This simplification is less significant with other ions: two signals with Zn^{2+}, three with Mg^{2+} and no modification for Na^+.

A similar simplification was observed in ^{13}C NMR spectra for the two complexes **1**–$Ca(ClO_4)_2$ and **1**–$Sr(ClO_4)_2$ in CD_3CN solution [see Fig. 3(*b*)]. However for this 18-membered tetralactam, two ^{13}C signals of equal intensity were observed for each type of carbon in the complex, probably related to a conformer with two *trans* and two *cis* benzyl bonds. As a matter of fact, further addition of perchlorate salt (three equivalents) did not cause any significant shift or additional spectral simplification.

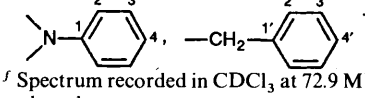
These results contrast sharply with the structural behaviour of the two open chain polyamides **7** and **8** and their Ca^{2+} or Ba^{2+} complexes. Thus, the free ligand **7** showed two sets of signals, indicating the presence of the *trans* and of the *cis* form. Relying on the chemical shift of the diagnostic benzyl carbon,[8] the isomer with NCH_2Ph *cis* to the carbonyl oxygen is favoured over the *trans* isomer. The relative intensity of the peaks corresponding to the two isomers was not affected by the complexation of **7** with $Ca(ClO_4)_2$ or $Ba(ClO_4)_2$, though shifts in their positions were noticed. A similar trend was observed for the tetramide **8** for which several sets of signals are observed upon complexation (see Fig. 4). It is noteworthy that **8** and **3** have the same Ca^{2+} stability constant in THF solution (log K_s *ca.* 6).

Obviously, the alkaline-earth cations do not affect the conformation of the amidic group in acyclic polyamides, while, for macrocyclic tetralactams, the metal ion induces large structural changes in the host, related to their strong interactions. This conformational reorganization agrees with our previous conclusions suggesting that tetralactam–cation complexation is not a passive fitting of lock and key.[5e]

Complexation Sites.—Sites of complexation were located by IR spectroscopy in the solid state and by ^{13}C NMR spectroscopy in solution. Table 2 summarizes the IR spectral data of the carbonyl group for the complex formation of alkaline-earth salts with **1**–**6**. These data were obtained by recording IR spectra of the ligand and isolated complexes (see Experimental section) in KBr pellets. Complexation with tetrabenzylated macrocycles was accompanied by a shift to lower frequency of the carbonyl stretching frequency (17–26 cm^{-1}) whatever the cation and counter-anion. These results may be related to the decrease of the double bond character of the C=O bond by coordination of the oxygen atom donor. A variation of the same magnitude has been observed by Simon[9] for alkaline-earth

Table 1 ^{13}C NMR shifts (δ) of ligands in their free form and in their Ca^{2+}, Sr^{2+}, Ba^{2+} complexes[a] in CD_3CN at 62.9 MHz. The multiplicity of signals is given in parentheses.

Compound	—CH_3	$-CH_2-N(-C=O)-$	$-CH_2-Ph$ + $Ar-N(-CH_2-)-$	$-CH_2O-$	$>N-Ar$ + $-CH_2-Ar$ [b]	$>C=O$
1		43.91–46.25 (≥6)	49.60–52.22 (≥6)	68.97–71.21 (≥5)	C-1′: 137.54–138.51 (≥4); C-2′,3′,4′: 127.48–130.00 (≥9)	170.30–171.77 (≥6)
1–Ca^{2+}		44.63, 47.86	48.89, 54.11	70.52, 72.45	C-1′: 136.24, 137.59; C-2′,3′,4′: 127.73–130.21 (6)	172.69, 175.00
1–Sr^{2+}		45.00, 47.53	48.96, 53.59	70.50, 72.51	C-1′: 135.92, 137.48; C-2′,3′,4′: 128.07–130.17 (6)	172.41, 174.82
2		39.04–46.39 (≥7)	49.66–51.38 (≥5)	70.63–74.12 (≥6)	C-1′: 137.20–138.75 (≥4); C-2′,3′,4′: 128.15–129.94 (≥6)	170.82–172.65 (≥4)
2–Ba^{2+}		40.18,[c] 44.10	50.95	70.83	C-1′: 136.77; C-2′,3′,4′: 127.95, 128.95, 130.07	173.03, 173.39
3		43.61–46.17 (≥11)	48.19–52.16 (≥14)	68.48–71.66 (≥10)	C-1: 148.04–148.27 (≥2); C-2: 112.21–113.36 (≥4); C-4: 117.22[d] (≥1); C-1′: 137.77–138.93 (≥6); C-3,2′,3′,4′: 127.89–130.53 (≥9)	169.93–170.97 (≥5)
3–Ca^{2+}		44.22, 44.93	47.47,[e] 50.64, 50.97	69.82	C-1: 146.74; C-2: 111.84; C-4: 117.78; C-1′: 137.42, 137.67; C-3,2′,3′,4′: 128.96–130.60 (≥5)	172.21, 172.47
3–Sr^{2+}		44.20, 45.05	47.36,[e] 50.80, 51.31	68.97	C-1: 146.58; C-2: 111.84; C-4: 117.86; C-1′: 136.71, 136.94; C-3,2′,3′,4′: 128.69–130.59 (≥6)	172.25, 172.52
3–Ba^{2+}		44.11, 44.65	48.02,[e] 50.41	70.02	C-1: 146.76; C-2: 112.02; C-4: 117.90; C-1′: 137.43, 137.72; C-3,2′,3′,4′: 128.85–130.60 (≥5)	171.84, 172.06
4[f]		40.51–44.84 (≥10)	47.87–51.86 (≥11)	68.05–71.21 (≥9)	C-1: 143.26–143.51 (≥2); C-2: 111.86–112.33 (≥4); C-3: 115.68–116.06 (≥4); C-4: 153.0–157.0 (≥4); C-1′: 135.47–137.21 (≥9); C-2′,3′,4′: 126.28–129.23 (≥22)	168.90–170.61 (≥8)
5		39.35–45.17 (≥6)	48.88–52.23 (≥7)	70.62–72.95 (≥7)	C-1: 148.15–148.20 (≥2); C-2: 112.53–113.38 (≥3); C-4: 117.17[d] (≥2); C-1′: 137.62–138.86 (≥4); C-3,2′,3′,4′: 128.27–130.67 (≥11)	170.37–171.47 (≥7)
5–Ca^{2+}		40.13,[c] 46.53	48.50,[e] 53.08	70.06, 70.55	C-1: 148.90; C-2: 112.55; C-4: 117.64; C-1′: 136.12; C-3,2′,3′,4′: 128.86–130.32 (4)	172.55, 173.57
6		43.12–46.21 (≥4)	48.88–51.92 (≥4)	70.04–71.28 (≥6)	C-1′: 138.53–139.04 (≥3); C-2′,3′,4′: 127.97–129.84 (≥7)	170.42–170.87 (≥2)
6–Ca^{2+}		44.27	51.60	70.26, 70.56	C-1′: 136.01; C-2′,3′,4′: 128.45, 129.32, 130.22	173.41
6–Ba^{2+}		44.39	51.59	70.62, 71.00	C-1′: 136.50; C-2′,3′,4′: 128.32, 129.21,130.08	173.37
7[g]	12.89, *14.17*	41.37, *41.95*	*48.41*, 50.42	*70.05*, 70.59	C-1′: 138.70, *139.34*; C-2′,3′,4′: 128.05–129.72	169.42, *169.61*
7–Ca^{2+}	12.60, *13.44*	*42.15*, 42.57	*49.12*, 50.51	*69.60*, 69.86	C-1′: 136.55, *137.79*; C-2′,3′,4′: 128.05–130.01	171.65
7–Ba^{2+}	12.68, *13.56*	*42.02*, 42.42	*48.93*, 50.49	*70.19*, 70.41	C-1′: 136.97, *138.08*; C-2′,3′,4′: 127.95–129.96	171.31, 171.37
8	33.80, 34.34	43.82–45.97 (4)	49.18–52.90 (6)	69.99–70.92 (6)	C-1′: 138.28–139.01 (3); C-2′,3′,4′: 127.97–129.84 (8)	169.96, 170.42
8–Ca^{2+}	34.29, 34.46	43.99–45.19 (3)	50.46–52.75 (6)	69.69	C-1′: 135.98–137.37 (3); C-2′,3′,4′: 128.11–130.19 (9)	171.80–172.87 (4)

[a] Conditions: ligand (0.05 mmol), $M(ClO_4)_2$ (0.05 mmol), CD_3CN (0.5 cm^3). [b] Numbers of carbons indicate their assignments as follows:  . [c] Assigned to $-CH_2-NH-C(=O)-$. [d] Signals occluded by solvent at 118.4 ppm. [e] Assigned to $-CH_2-N(-Ar)-$. [f] Spectrum recorded in $CDCl_3$ at 72.9 MHz. [g] Values in italic correspond to a configuration of the first amide moiety with the benzylic group *cis* to the carbonyl oxygen.

complexes with linear amides. This variation drops down to 10–15 cm^{-1} for the dibenzylated compounds and was assumed to be related to the existence of pre-formed H-bonds in the free ligand. At the opposite, a high wavenumber shift was noticed for the amide II band *e.g.* 33 cm^{-1} for [Ca(**6**)$(ClO_4)_2$] complex; the ν(NH) band variation was not observed owing to the presence of water in the complexes. The ν(C–O) stretching band is difficult to locate, ranging in the same wavenumber area as the bands of perchlorate anion. However a 10–15 cm^{-1} shift to higher frequency of the C–O stretching band was noticed for the complex formation of calcium thiocyanate or picrate with **1**, **3** and **4**. A similar shift band was noticed for the [Ca(**9**)$(SCN)_2$] complex (Ca^{2+} ionophore ETH 129)[1d] where the metal is coordinated to the ether oxygen atom as evidenced by the crystal structure determination of the complex.[10]

The addition of perchlorate salts of alkaline-earth cations to our ligands induced ^1H and ^{13}C NMR spectral shifts. The comparative analysis of ^{13}C NMR spectra for free and bound tetralactams (see Table 1), which present a more simplified picture than ^1H NMR spectra, is informative in several respects.

Table 2 IR spectral (KBr) data of C=O for the complexes of metal perchlorates, thiocyanates or picrates salts with **1–6**

Free ligand	ν(C=O)/cm^{-1}	Complex	ν(C=O)/cm^{-1}	$\Delta\nu$/cm^{-1} [a]
1	1652	[Ca(**1**)$(ClO_4)_2$]	1627	25
		[Ca(**1**)$(Pic)_2$]	1635	17
		[Sr(**1**)$(ClO_4)_2$]	1630	22
		[Ba(**1**)$(Pic)_2$]	1635	17
2	1652	[Ba(**2**)$(ClO_4)_2$]	1642	10
		[Ba(**2**)$(SCN)_2$]	1637 [b]	15
		[Ba(**2**)$(Pic)_2$]	1638	14
3	1656	[Ca(**3**)$(ClO_4)_2$]	1635	21
		[Ca(**3**)$(SCN)_2$]	1637	19
		[Sr(**3**)$(ClO_4)_2$]	1630	26
		[Ba(**3**)$(ClO_4)_2$]	1639	17
4	1654	[Ca(**4**)$(ClO_4)_2$]	1636	18
		[Ca(**4**)$(Pic)_2$]	1635	19
5	1656	[Ca(**5**)$(ClO_4)_2$]	1643	13
		[Ca(**5**)$(SCN)_2$]	1643	13
6	1650	[Ca(**6**)$(ClO_4)_2$]	1633	17
		[Ca(**6**)$(SCN)_2$]	1632	18
		[Ba(**6**)$(ClO_4)_2$]	1625	25

[a] $\Delta\nu$ = ν(C=O) (free ligand) − ν(C=O) (complex). [b] A second band is observed at 1665 cm^{-1}.

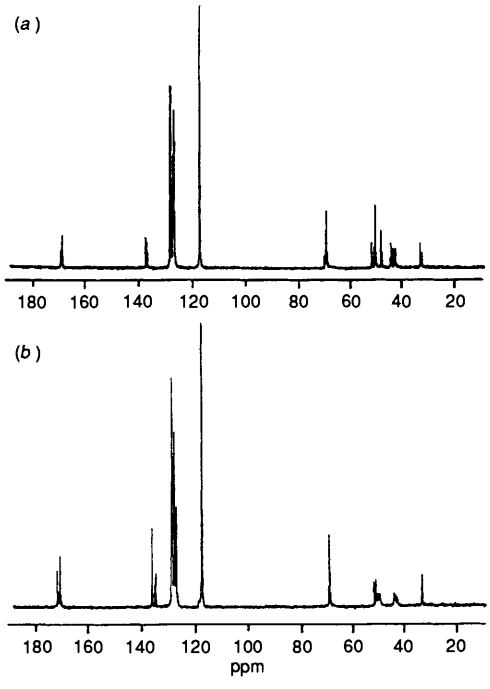


Fig. 4 ^{1}H-Decoupled ^{13}C NMR spectra of tetramide **8** in CD_3CN at 62.9 MHz: (*a*) free ligand, (*b*) **8**–Ca^{2+} complex (1:1 stoichiometry)

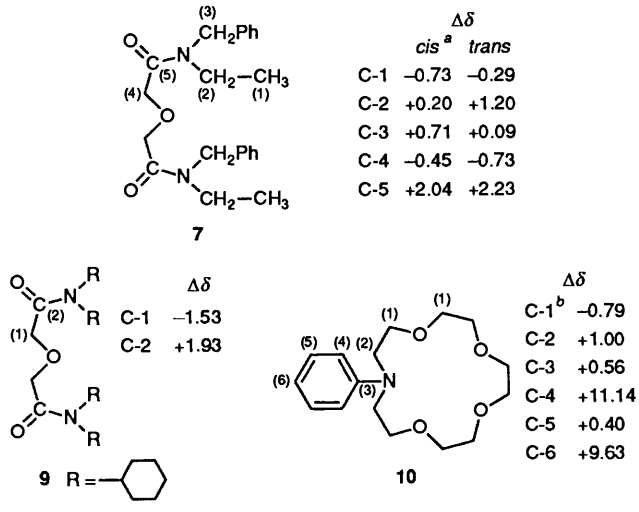


Fig. 5 Ca^{2+}-Induced changes in ^{13}C NMR chemical shift of model compounds. Conditions: ligand (0.05 mmol), $Ca(ClO_4)_2$, $6H_2O$ (0.05 mmol), CD_3CN (0.5 cm^3). $\Delta\delta = \delta_{complex} - \delta_{free\ ligand}$. (*a*) *cis* Corresponds to a configuration of the first amide moiety with the benzyl group *cis* to the carbonyl oxygen. (*b*) Calculated from the averaged values of four signals.

(i) The significant downfield shift observed for the amide carbonyl resonance (1.5–2.8 ppm) with the whole set of cations examined suggested a simultaneous coordination of all four amide oxygens. Similar shifts for the carbonyl carbon atom occurred with linear diamides **7** or **9** used as model compounds after addition of one equivalent of $Ca(ClO_4)_2$ in CD_3CN (see Fig. 5).

(ii) The participation of the ether oxygen atoms in the complexation could not be established soundly from the NMR data of several complexes owing to the structural heterogeneity of the uncomplexed ligands, arising from the rotational isomerism around the C–N bonds of the amide groups: the signals of CH_2O nuclei in the 1:1 complex appear in the same chemical shift range as the multiple resonance systems in the uncomplexed ligands. So, a high field shift, as expected in the case of an oxygen binding,[11] could not be determined clearly. However the binding of barium, strontium and calcium to **2**, **3** and **5** respectively, reveals that these CH_2O carbon resonances were shifted to higher field by 1.1–1.5 ppm from the multiplet centre of the free ligand. These values can be compared to the high field shift observed for the same carbons in the model compounds after adding calcium perchlorate, especially with ETH 129 ($\Delta\delta$ = −1.5 ppm). Like the ether oxygens of the ETH 129 those of the tetralactams are thus able to participate in the complexation. For **1** the CH_2O signals shift to lower field with added Ca^{2+} or Sr^{2+}. In this case, the magnetic effect caused by the adjacent cationic centre should play a minor role as opposed to the conformational contribution.

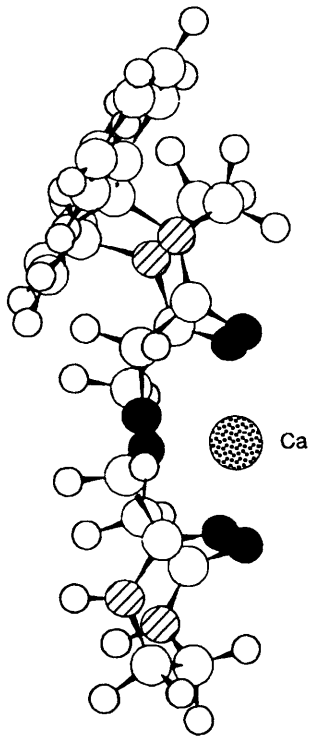


Fig. 6 3D Representation of the tetralactam **2**–Ca^{2+} complex (oxygen donor atoms are drawn in black)

(iii) The aromatic carbons in the *ortho* and *para* positions of the *N*-phenyl group of the macrocycles **3** and **5** underwent only weak shifts (<2 ppm). This behaviour precludes the contribution of the nitrogen atom in the complexation. As a comparison, in the case of *N*-phenylaza-15-crown-5 (**10**) where the nitrogen is involved as a coordination site,[12] a large downfield shift for the *ortho* and *para* carbon atoms (respectively 11.14 and 9.63 ppm) was observed in the ^{13}C NMR spectrum recorded in the presence of one equivalent of calcium perchlorate in the same conditions of concentration and solvent (see Fig. 5). A similar phenomenon was observed by ^{1}H NMR spectroscopy. After complexation by Ca^{2+}, Sr^{2+} or Ba^{2+} the protons located in the *ortho* position of the *N*-phenyl group are weakly affected (0.1 ppm upfield shift). On the contrary, in the *N*-phenylazacrown **10** these protons undergo a downfield shift of 0.4–0.55 ppm upon complexation with alkaline-earth cations.[12] Moreover, in the spectrum of the fully protonated tetralactam **3** (obtained after addition of deuteriated trifluoroacetic acid to a solution of free compound) this signal is deshielded by 1.2 ppm.

For the fluorinated compound **4**, the ^{19}F chemical shift variations induced by the cations remained relatively weak (<1 ppm) and were independent of the strength of complexation.* On the other hand, Metcalfe[13] has observed with fluoro-BAPTA compounds important variations of the ^{19}F chemical shift related to the complexation, the induced chemical shifts paralleling the stability constants of the complexes. In the present case, the simplifications in multiplicity noticed on the spectra could be better described as conformational modifications occurring during the complexation.

Participation of the Anion in Complex Formation.—Picrates. It was already observed (see stoichiometry of the complexes) from the UV λ_{max} values that the picrate anion always remains bound to the cation either tightly or, sometimes, loosely. Owing to the fact that the 18-, 21- and 24-membered tetralactams contain six or eight chelating sites and that the alkaline-earth cations use 8 to 11 coordination sites, it can be expected that the coordination shell of the cation will be completed by the picrate anion and, if necessary, either by a solvent molecule (water or tetrahydrofuran) or by the participation of one nitro group of the anion as was evidenced by X-ray diffraction in the dibenzo-24 crown-8–$Ba(Pic)_2$ complex.[14]

Perchlorates. The 'isolated' perchlorate anion has a T_d symmetry and shows a ν(Cl–O) (ν_3) single band[15] at 1100 cm^{-1}. When the perchlorate anion is bound to a cation, a two- or three-fold band appears, related to the loss of tetrahedral symmetry. In the isolated perchlorate complexes we observed the same multiple pattern for the ν_3 band. Thus, the perchlorate anion remains bound to the alkaline-earth cation in all the complexes.

Thiocyanates. The ν(C–N) bands of the complexes remain compatible with two equivalent anions bound to the metal at the nitrogen atom.[16] Namely, the tetralactams–thiocyanate complexes show single bands at 2058 ([Ba(**2**)$(SCN)_2$] and [Ca(**6**)$(SCN)_2$]), 2057 ([Ca(**3**)$(SCN)_2$]) and 2038 cm^{-1} ([Ca(**5**)$(SCN)_2$]).

Structures of the Complexes.—As discussed previously, the binding of Ca^{2+}, Sr^{2+} and Ba^{2+} to tetralactams **1**–**6** follows a 1:1 stoichiometry, the four carbonyl groups and the ether atoms being coordinated to the metal. The simplification of the ^{13}C NMR spectra after complexation is similar whatever the cation and suggests the stabilization of one rotamer possessing a mirror symmetry. Among these symmetric isomers only the form where the four carbonyl groups are directed in the same direction seems able to give a strong 1:1 complex. On the other hand, the inspection of CPK space filling models suggests that the coordination sites of these macrocycles are not oriented inside the cavity. The convergent arrangement of the four amide carbonyl groups rather displays a cone structure. This is supported by the fact that ring size is not the main factor playing a role in the complexation process for these tetralactams.[5e]

In order to achieve a better understanding of the conformational behaviour of these complexes, molecular modelling was performed on the representative compound **2** with the DISCOVER program.†

In a first attempt the Ca^{2+} parameters in the CVFF force field were checked with the diacetamide–$Ca(ClO_4)_2$ complex, its RX structure being known.[17] All distances and angles fit very well with the experimental data after molecular mechanics calculations (minimization with the conjugate gradient algorithm) starting from the 2D representation of its 4:1 diacetamide:Ca^{2+} complex. Using a similar method and a rough conformational search by dynamic simulation at 1000 K over 1 ps the Ca^{2+}-chelated form depicted in Fig. 6 appeared the most stable‡ for a possible octacoordinated complex. This structure presents the following features: the four carbonyl groups are nearly coplanar and oriented towards the calcium ion (distances Ca···O are 2.36–2.40 Å). The participation in the complex of the ether oxygen atoms (*d* Ca···O = 2.50 Å) and of the two anions gives eight coordination sites for Ca^{2+}. Since Ca^{2+} generally accepts a coordination number of 8–9, its coordination shell is either full, or could be completed with one molecule of solvent (H_2O, THF).

* In ^{19}F NMR spectra the chemical shift variations (in CD_3CN) are $\Delta\delta$ = +0.17 and +0.62 ppm for **4**–Ca^{2+} and **4**–Mg^{2+} complexes respectively ($\Delta\delta = \delta_{complex} - \delta_{free\ ligand}$) and the stability constants measured in tetrahydrofuran solutions by UV spectrophotometry for **4**-metallic picrates are: log K_s = 6.2 (Ca^{2+}) and 5.0 (Mg^{2+}).

† DISCOVER is a program from BIOSYM, San Diego, California.

‡ No significant changes were observed during a MD simulation at 300 K over 100 ps.

Table 3 Elemental analyses of complexes[a]

Complex	C (%)		H (%)		N (%)	
	Calc.	Found	Calc.	Found	Calc.	Found
$[Ca(\mathbf{1})(Pic)_2]\cdot 2H_2O$	51.66	51.66	4.33	3.94	11.58	11.85
$[Ba(\mathbf{1})(Pic)_2]\cdot H_2O$	48.48	48.72	3.91	3.72	10.87	11.06
$[Ba(\mathbf{2})(Pic)_2]$	41.87	41.65	3.33	3.28	12.85	12.84
$[Ba(\mathbf{2})(SCN)_2]\cdot H_2O$	43.79	43.89	4.46	4.58	10.94	10.85
$[Ca(\mathbf{3})(ClO_4)_2]\cdot 2H_2O$	53.83	53.92	5.36	5.24	6.54	6.47
$[Ca(\mathbf{4})(Pic)_2]$	55.00	54.86	4.31	4.19	11.76	11.91
$[Ca(\mathbf{4})(ClO_4)_2]$	54.75	54.98	4.98	5.20	6.65	6.59
$[Ca(\mathbf{5})(ClO_4)_2]\cdot 6H_2O$	42.42	42.14	5.55	5.37	7.27	7.12
$[Ca(\mathbf{6})(ClO_4)_2]\cdot H_2O$	51.72	51.63	5.33	5.25	5.48	5.47
$[Ca(\mathbf{6})(SCN)_2]\cdot H_2O$	58.83	58.95	5.80	5.62	8.95	8.86

[a] All these complexes have a 1:1 stoichiometry.

The proposed structure compares well with those determined by X-ray diffraction for octacoordinated 18-crown-6/$Ca(SCN)_2$[18] (*d* Ca···O = 2.56–2.74 Å) and diacetamide–$Ca(ClO_4)_2$[17] (*d* Ca···O = 2.38–2.45 Å). A particular agreement is noticed with the nonacoordinated ETH 129–$Ca(SCN)_2$ complex[10] (*d* Ca···O amide = 2.39 and 2.47 Å, *d* Ca···O ether = 2.55 Å).

A pattern similar to that of **2**–Ca^{2+} can be proposed for the complexes of the 21-membered macrocycles. As previously seen in these complexes the nitrogen atom bearing the phenyl group is not involved in the complexation.

Finally, for the 24-membered tetralactam **6**, the eight intracyclic chelating sites (4 carbonyl oxygens and 4 ether oxygens) plus the counterions exactly agree with the optimum coordination number for barium (10 *vs.* 8–9 for calcium). Such a feature could explain the greater affinity[5e] of compound **6** for Ba^{2+} *vs.* Ca^{2+} in a similar arrangement of the complex.

Experimental

General.—UV–VIS absorption spectra were monitored on a Perkin-Elmer Lambda 17 spectrophotometer. ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AC 250 (62.9 MHz) and on a Bruker AC 300 (282.4 MHz) respectively. The deuterium signals of the solvents served as internal locks and Me_4Si or CF_3CO_2H as external references. Infrared spectra were recorded on a Perkin-Elmer 883 spectrometer in potassium bromide discs. Elemental analyses were carried out by the *Service Commun de Microanalyse Elementaire UPS-INP* in Toulouse.

Materials.—Metal picrates were prepared as previously reported.[19] $Ca(SCN)_2\cdot 4H_2O$, $Ca(ClO_4)_2\cdot 6H_2O$, $Sr(ClO_4)_2\cdot 6H_2O$, $Ba(SCN)_2\cdot 2H_2O$, $Ba(ClO_4)_2\cdot 3H_2O$, $Zn(ClO_4)_2\cdot 6H_2O$ were purchased from Strem and $Mg(ClO_4)_2$, $NaClO_4$ from Aldrich. These salts were used as received. Deuteriated solvent CD_3CN (99.6% D) was purchased from CEA. THF was purified by distillation over sodium just before use.

Syntheses of Ligands.—The following compounds were prepared as described in the literature: tetralactams **1**–**5**,[5d] tetralactam **6**,[5a] diamide **7**,[5e] ETH 129 **9**.[1b] Tetramide **8** was prepared by the procedure described for **1**–**5**. Column chromatography (silica gel, 95:5 dichloromethane:ethanol) gave **8** as a colourless oil (72% yield); $\nu_{max}(CHCl_3)/cm^{-1}$ 1657 (C=O amide); δ(80 MHz, CD_3CN) 2.86 (6 H, s, CH_3), 3.36–3.56 (4 H, m, CH_2N), 4.35–4.55 (16 H, m, CH_2O and CH_2Ph), 7.25 (20 H, s, Ph) (Found: C, 70.65; H, 6.9; N, 8.2. $C_{40}H_{46}N_4O_6$ requires C, 70.77; H, 6.83; N, 8.25%).

Syntheses of Complexes.—The calcium, strontium and barium tetralactam complexes were prepared by mixing 10^{-2} mol dm^{-3} equimolar solutions of the tetralactam and salt of the studied cation in methanol (picrates or perchlorates) or diethyl ether or acetone (thiocyanates). The resulting crystals were collected, washed with diethyl ether or acetone and dried under vacuum. Elemental analyses of the complexes are given in Table 3.

^{13}C and ^{19}F NMR Experiments.—Samples were prepared by mixing 0.05 mmol of the perchlorate salt with 0.05 mmol of the ligand, followed by the addition of 0.5 cm^3 of CD_3CN. The mixture was then stirred until dissolution occurred and NMR spectra were recorded. ^{19}F NMR data for compound **4** (δ, CD_3CN): free ligand −53.77, −53.84, −53.92, −54.73, −54.88, −55.02, −55.36, −55.46; upon addition of perchlorate salt $Ca(ClO_4)_2$, −54.45; $Mg(ClO_4)_2$, −53.58, −53.94, −54.42; $Zn(ClO_4)_2$, −53.44, −54.24.

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