Macrocyclic 14-Membered Ring Diketal Dilactams: Evaluation of their Divalent Cation Binding Properties

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Macrocyclic 14-Membered Ring Diketal Dilactams: Evaluation of their Divalent Cation Binding Properties

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The binding abilities of a new class of 14-membered ring ligands bearing diketal dilactam functions were explored by UV-visible spectrophotometry. Their formation constants, determined in THF solution, showed appreciable complexation with divalent cations (stability order: $Sr^{2+} \geq Ca^{2+} > Zn^{2+} \geq Mg^{2+} > Ba^{2+}$) whereas no association was observed with monovalent cations. The stoichiometry of the complexes formed was essentially 1:1 although sometimes a low percentage (<10%) of 1:2 (cation–ligand) species was detected. The corresponding formation constants determined by computation (STAR program) were in the range $1.5 < \log \beta_{11} < 4.8$ and $4.4 < \log \beta_{12} < 7.1$. They depend significantly on the nature of the substituents. In addition, solvent extractions carried out in a water–chloroform system showed the highest constants ($\log K_{ex}$) for the most substituted macrocycles 7b and 7c (norephedrine series) with a lipophilic skeleton.

Keywords: Macrocyclic diketal dilactams; Formation constants; Divalent cation complexation; UV-visible spectrophotometry

INTRODUCTION

Since the synthesis and cation complexing abilities of the crown ethers were reported [1], much effort has been exerted in macrocyclic chemistry to construct preorganized multidentate systems able to coordinate with specific substrates [2–4]. A great number of models with ranging ring size, substituents and types of donor atoms have been studied. Extensive reviews have been published in this field [5,6].

One approach for obtaining new macrocyclic systems is to use organic synthesis methods involving specific or novel reactions. In this connection, we recently reported the synthesis of achiral and chiral macrocyclic dilactams, variously substituted and bearing two ketal moieties [7,8]. They were generated in two steps from β-amino-alcohols *via* a novel transacetalisation reaction (Scheme 1), the mechanism of which was shown to depend on the stereochemistry of the intermediate hydroxyamidoketal [7].

The original structure of these new ligands, which contain secondary amides and infrequently encountered acetal functions, prompted us to investigate their cationic recognition properties. In addition, the presence in the molecules of two *cis* or *trans* methoxy substituents might modulate the stability of the cation–ligand interactions. Work on macrocyclic amides has already underlined the preferential selectivity of these compounds in favour of alkaline-earth cations [9–14]. The binding constants were increased in the case of *N*-substituted structures [12].

To explore quantitatively the properties of our hosts and evaluate the influence of the substituents, studies were undertaken by UV-visible spectrophotometry, which shows a high sensitivity without consuming too much material and is well-suited for the study of association constants ranging from 10^2 to $10^5 \, l \, mol^{-1}$ [15]. Measurements were carried out in solution and in a two-phase system. They consisted of: (i) determination of the complex stoichiometry and formation constants in THF solution, (ii) evaluation of the extractive properties by the liquid–liquid extraction technique.

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MeO / MeO — OMe / O
KCN, MeOH, Δ, 70 h

PTSA | CH$_2$Cl$_2$ or benzene*

aminoethanol   : R^1 = R^2 = R^3 = H   **1**

dimethylaminoethanol   : R^1 = R^2 = Me ; R^3 = H   **2** *

R-(-)-phenylglycinol   : R^1 = Ph ; R^2 = R^3 = H   **3**

S-(+)-alaninol   : R^2 = Me ; R^1 = R^3 = H   **4**

S-(+)-leucinol   : R^2 = iBu ; R^1 = R^3 = H   **5**

S-(-)-phenylalaninol   : R^2 = Bn ; R^1 = R^3 = H   **6**

1R,2S-(-)-norephedrine : R^1 = H ; R^2 = Me ; R^3 = Ph **7**

SCHEME 1

R = H   —   **1c**
R = Me   **2b**   **2c**

3b   **3a** : β-OMe   **3c** : α-OMe

4b :   R^2 = Me   **4a** : α-OMe   **4c** : β-OMe
5b :   R^2 = iBu   -   **5c** : β-OMe
6b :   R^2 = Bn   -   **6c** : β-OMe

7b   **7a** : α-OMe   **7c** : β-OMe

SCHEME 2

The study was performed on 14 previously synthesized macrocycles: **1c**, **2b**,**c**, **3a**,**b** (17:83), **3c**, **4a**,**b** (16:84), **4c**, **5b**,**c**, **6b**,**c**, **7a−c** (Scheme 2).

First, we explored the complexation of compounds **3a−c** with alkaline and alkaline−earth cations, NH$_4^+$ and Zn^{2+}. These preliminary results, characterized by no appreciable complexation with monovalent metals in accordance with previous work on macrocyclic lactams [9−14], prompted us to focus our study on divalent cations which, in contrast, gave well defined complexes.
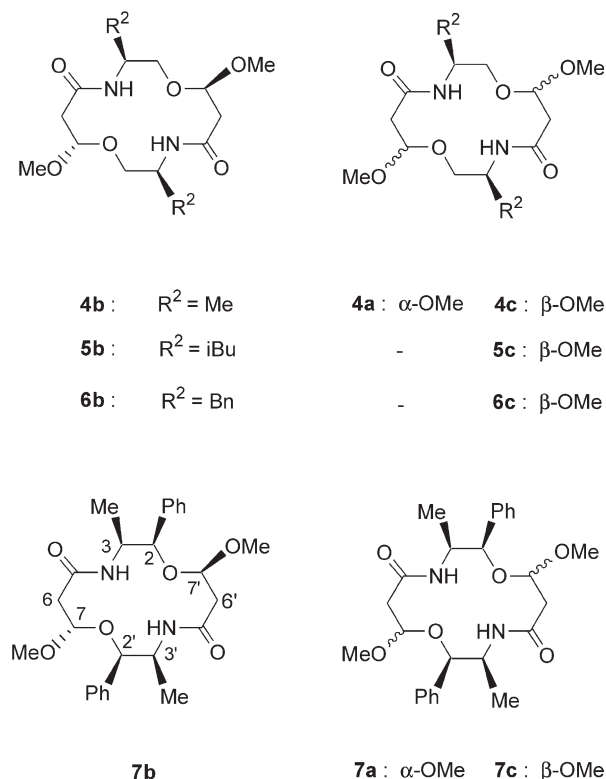
RESULTS AND DISCUSSION

Determination of Stoichiometries and Formation Constants of Complexes

The study involves the picrate ion absorbance in UV-visible spectrometry [16,17]. In a solvent of low polarity (THF), the cation complexation results in the conversion of a tight picrate ion pair into a loose ion pair. This change, due to an increase in the anion−cation interionic distance, induces a bathochromic shift of the UV absorption maximum.

The possible formation of three types of complexes was envisaged between the ligand L and the metal M, namely ML, ML$_2$ and M$_2$L, characterized,
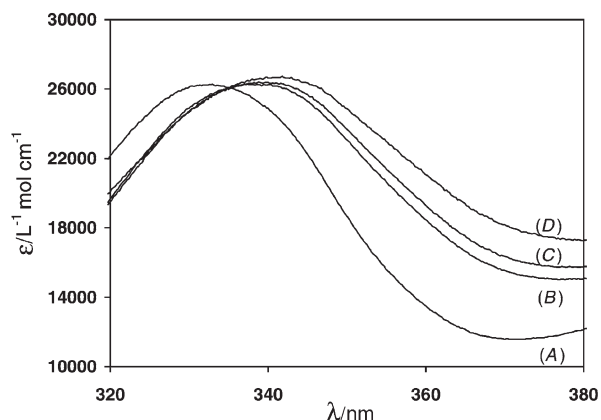
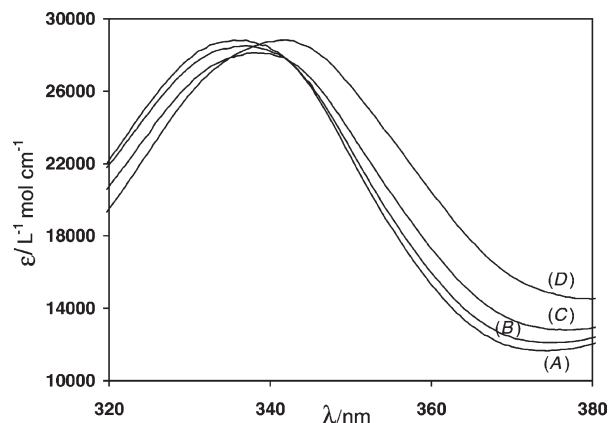FIGURE 1 UV absorption spectra of **7b**-CaPi$_2$ (A): $X = 0$; (B): $X = 1$; (C): $X = 23$; (D): $X = 75$.

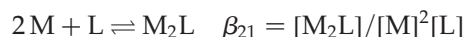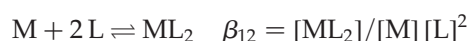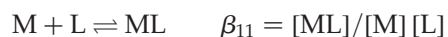FIGURE 2 UV absorption spectra of **5c**-SrPi$_2$, (A): $X = 0$; (B): $X = 1.6$; (C): $X = 6.6$; (D): $X = 25$.

respectively, by the following equilibria and formation constants: β_{11}, β_{12}, β_{21}.

$$M + L \rightleftharpoons ML \qquad \beta_{11} = [ML]/[M][L]$$

$$M + 2\,L \rightleftharpoons ML_2 \quad \beta_{12} = [ML_2]/[M][L]^2$$

$$2\,M + L \rightleftharpoons M_2L \quad \beta_{21} = [M_2L]/[M]^2[L]$$

The recorded spectra for each series of experiments, conducted with increasing X ratio ($X =$ [L]/[M]) could be divided into two categories: (i) curves characterized by the presence of one isosbestic point whatever the value of X; this corresponds to the exclusive 1:1 complex formation (Fig. 1), (ii) curves shifted for high X values and that no longer intersected the isosbestic point (Fig. 2); this can be explained by the appearance of a second complex of higher stoichiometry, which was identified as a 1:2 species.

The processing of the experimental data involved computational methods (STAR and STAR-FA programs) [18]. All the results obtained with alkaline-earth and zinc picrates are grouped in Table I which also contains, for comparison, the formation constants, determined under the same conditions, of previously described complexes: metal picrates–18-membered ring tetralactams **I** and **II** [12] (Scheme 3).

Computational processing of the results clearly pointed to the formation of either a single type of complex ML or two complex species ML and ML$_2$. Both stoichiometries proved satisfactory and suggested that formation of M$_2$L complexes could be ruled out.

When the experiments were consistent with the additional formation of the ML$_2$ complex alongside the preponderant formation of the ML complex, the calculations showed that the ML$_2$/ML ratio remained low ($<10\%$), even for high X values.

In these cases, the constants log β_{12} ranged from 4.45 (**2b**-Sr^{2+}) to 7.08 (**7c**-Zn^{2+}), the mean value being near 5. This corresponds to an equilibrium ML + L = ML$_2$ with low stability constants K_{12} (1.23–2.14).

For all the compounds, the 1:1 complex was the more stable species. The concentration plots are of the same type as for compound **5c** (Fig. 3).

The log β_{11} values ranged from 1.51 to 4.80 with a mean value close to 3, which indicated moderate interactions. The most stable associations were observed for Ca^{2+} and Sr^{2+}, the ionic radii of which are close to 1Å. The least complexed cation was Ba^{2+} for which, moreover, no ML$_2$ formation was observed.

The ionic selectivity can be ordered as follows: Ca^{2+} ≈ Sr^{2+} > Zn^{2+} ≈ Mg^{2+} > Ba^{2+} with the corresponding ligand orders for Ca^{2+} : **7c** > **1c** > **7b** > **5b** > **7a** ≈ **4c** > **6c** > **5c** > **3a, b** > **3c** > **6b** > **4a, b** > **2c** > **2b** and Sr^{2+} : **7b** ≈ **1c** > **5b** > **7c** > **3c** > **5c** > **4c** > **2b** ≈ **2c** > **6c** > **4a, b** > **3a, b** > **7a** > **6b**. These rankings show that the best binding abilities correspond to the macrocycles substituted at the 2 and 3 positions (compounds **7**). For 3-monosubstituted ligands **3–6**, the ranking iBu > Me > Bn > Ph for Ca^{2+} and iBu > Ph > Me > Bn for Sr^{2+} indicates that the complexation: (i) was a function of the substituent bulkiness in the presence of alkyl groups, (ii) might be modified by the "picrate effect" with aryl substituents as a result of π–π interactions between picrate ion and the aromatic unit of the ligand [19]. The lowest constants were observed for 3,3-dimethyl compounds **2**, probably because of the steric hindrance induced by the two methyl groups on C-3 preventing approach of the cation to both faces of the ligand. Finally, the unsubstituted macrocycle **1c** held an unexpected place in the above order.

Considering now the stereochemistry of the OMe group, the *cis* compounds **4c** and **6c** exhibited higher constants than their *trans* homologues **4b** and **6b** for

TABLE I Formation constants (log β_{ii}) and standard deviation $\sigma(\log \beta_{ii})$ (molar scale) for complexes: metal picrates–ligands 1c–7c

Ligand	log	Mg²⁺ (r = 0.65 Å)		Ca²⁺ (r = 0.99 Å)		Sr²⁺ (r = 1.10 Å)		Ba²⁺ (r = 1.29 Å)		Zn²⁺ (r = 0.74 Å)	
1c	β_{11}	3.83	0.01	3.87	0.01	4.80	0.03	2.10	0.10	3.50	0.02
	β_{12}	5.95	0.02	4.77	0.19	6.40	0.02	–	–	5.80	0.05
2b	β_{11}	2.78	0.01	1.63	0.03	3.27	0.03	1.90	0.20	2.03	0.07
	β_{12}	–	–	–	–	4.45	0.01	–	–	–	–
2c	β_{11}	1.51	0.05	1.83	0.01	3.27	0.03	ND	ND	2.39	0.18
	β_{12}	–	–	–	–	4.46	0.01	ND	ND	4.87	0.12
3a,b (17:83)	β_{11}	3.00	0.01	3.29	0.01	2.92	0.01	2.42	0.02	3.13	0.01
	β_{12}	–	–	–	–	–	–	–	–	5.75	0.08
3c	β_{11}	2.90	0.01	3.10	0.01	3.67	0.01	2.12	0.06	3.20	0.01
	β_{12}	–	–	–	–	–	–	–	–	–	–
4a,b (16:84)	β_{11}	2.45	0.01	2.85	0.04	3.14	0.03	2.37	0.02	2.75	0.01
	β_{12}	–	–	4.76	0.04	5.37	0.12	–	–	5.81	0.01
4c	β_{11}	2.15	0.03	3.69	0.04	3.38	0.01	2.87	0.01	2.55	0.02
	β_{12}	–	–	5.59	0.20	–	–	–	–	–	–
5b	β_{11}	2.09	0.01	3.77	0.01	4.10	0.03	1.78	0.03	2.27	0.30
	β_{12}	–	–	–	–	6.95	0.03	–	–	–	–
5c	β_{11}	3.74	0.01	3.31	0.01	3.61	0.03	2.53	0.01	3.33	0.01
	β_{12}	5.78	0.13	–	–	5.85	0.12	–	–	–	–
6b	β_{11}	2.65	0.01	2.91	0.02	2.25	0.03	2.00	0.46	2.77	0.01
	β_{12}	5.40	0.01	–	–	–	–	–	–	–	–
6c	β_{11}	2.78	0.08	3.62	0.04	3.17	0.01	2.58	0.02	2.52	0.01
	β_{12}	5.00	0.25	5.17	0.14	–	–	–	–	5.40	0.05
7a	β_{11}	3.49	0.07	3.69	0.03	2.59	0.02	2.67	0.02	3.21	0.02
	β_{12}	5.24	0.32	5.47	0.21	–	–	–	–	–	–
7b	β_{11}	3.01	0.01	3.83	0.01	4.80	0.03	3.26	0.01	UC	UC
	β_{12}	–	–	–	–	6.40	0.20	–	–	UC	UC
7c	β_{11}	3.19	0.01	3.92	0.03	3.82	0.01	2.75	0.04	4.55	0.01
	β_{12}	–	–	5.14	0.36	–	–	–	–	7.08	0.01
I*	β_{11}	UC	UC	3.96	X	4.87	X	3.36	X	–	–
	β_{12}	UC	UC	6.00	Y	7.47	Y	5.53	Y	–	–
II*	β_{11}	5.48	Y	5.57	Y	6.50	Y	4.88	X	–	–
	β_{12}	7.48	Y	7.96	Y	9.50	Y	7.83	Y	–	–

* Ref. [12]. ND, not determined; UC, uncomputable. X = 0.05–0.10 and Y ≈ 0.20.
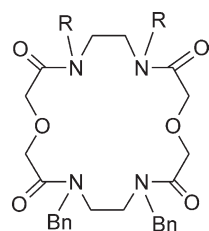
I : R = H

II : R = Bn

SCHEME 3
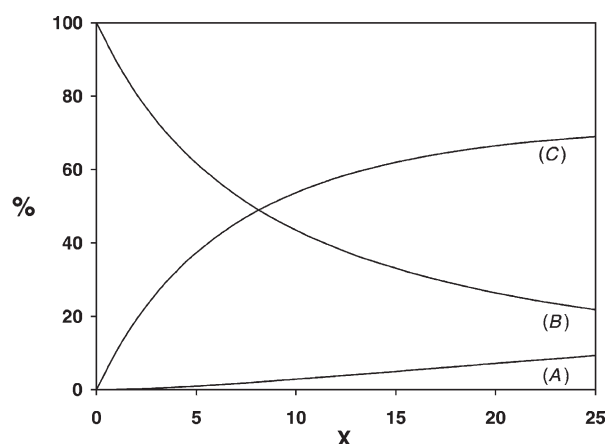
FIGURE 3 Concentration profile of **5c**-SrPi$_2$, (A): ML$_2$; (B): M; (C): ML.

TABLE II Extraction constant (log K_{ex}) and lipophilicity (log P) of the ligands

| Ligand | log K_{ex} | | | log P* |
	Ca^{2+}	Sr^{2+}	Zn^{2+}	
1c	1.62	2.30	–	0.5
3a,b	2.55	–	–	1.6
3c	1.99	3.49	2.86	1.6
4c	2.42	3.77	–	0.6
5b	3.56	3.86	–	2.3
6c	3.44	3.50	–	2.4
7b	3.71	4.25	2.29	2.6
7c	3.82	4.05	3.69	2.6
I[†]	3.97[‡]	5.07[‡]	0[‡]	1.9

*Lipophilicity measured by RPTLC technique. [†]Ref. [12]. [‡]Values calculated from the extraction ratio (E%) given in Ref. [12].

TABLE III Selectivity of ligands **1c–7c** for Sr^{2+} compared with Ca^{2+} and Zn^{2+}

Ligand	K_{ex} (Sr)$^{2+}$/K_{ex} (Ca)$^{2+}$	K_{ex} (Sr)$^{2+}$/K_{ex} (Zn)$^{2+}$
1c	4.8	–
3c	31.6	4.3
4c	22.6	–
5b	2.0	–
6c	1.1	–
7b	3.4	90.5
7c	1.7	2.3

both cations Ca^{2+} and Sr^{2+}, while this phenomenon was reversed for isomers **5b** and **5c** owing probably to the bulkiness of the iBu substituent. In contrast, for the 2- or 3-phenyl compounds **7** and **3**, the stereoisomers **b** and **c** showed different selectivities towards Ca^{2+} (**7c** > **7b**; **3a**, **b** > **3c**) and Sr^{2+} (**7b** > **7c**; **3c** > **3a**, **b**).

On the whole, for 1:1 complex formation, which was the dominant process, the selectivity range observed for a given ligand could be explained by the high flexibility of the 14-membered ring structures. The results are quite comparable to those obtained by Cazaux *et al.* [12] for the *N*-diunsubstituted tetralactam **I** while the corresponding *N*-tetrabenzyl compound **II** shows higher constants (Table I).

These first results, obtained in homogeneous medium for a new family of ligands, had to be completed by examination of their behaviour in a biphasic system, which is more representative of a transport situation, one of the main present targets for macrocyclic compounds [20]. This aspect was accordingly examined in a second study.

Liquid–Liquid Extraction

The method was based on the extraction of a metal picrate from an aqueous into a chloroform phase

containing the ligand [21,22]. At the analytical equilibria, the picrate concentration in the organic phase (C_{exp}) was determined by measuring the absorption of the anion by UV-visible spectrophotometry.

The measurements were carried out for macrocycles that presented the best binding abilities in a homogeneous system, namely **1c**, **3a–c**, **4c**, **5b**, **6c**, **7b** and **7c** with Ca^{2+}, Sr^{2+} and Zn^{2+}. Table II gives the extraction constants (log K_{ex}) and the lipophilicity (log P) of the ligands.

The best extracting properties were observed for macrocycles **7b** and **7c** with Sr^{2+}, the *trans* **7b** configuration of the methoxy groups being more favourable to the association. Furthermore, whatever the ligand, Sr^{2+} was the most easily extracted cation. The following order: Sr^{2+} > Ca^{2+} > Zn^{2+} is a function of the size and hydration energy of the cation [23,24]. The corresponding selectivities vs. Ca^{2+} and Zn^{2+} are presented in Table III. The best ratios are observed for Sr^{2+}/Ca$^{2+} \approx 32$ (**3c**) and Sr^{2+}/Zn$^{2+} \approx 90$ (**7b**). The extraction constants are in the range of that calculated for the 18-membered ring tetralactam **I** with Ca^{2+} [12] (Table II).

Comparison of Monophasic and Biphasic Systems

Comparing both systems, important similarities could be seen with regard to the three cations

studied. Firstly, 2,3-disubstituted compounds **7** were the best performing ligands. Secondly, in the 3-monosubstituted series **4–6**, the bulky iBu substituent (macrocycles **5**) gave the highest constants. Finally, the stereochemistry of the OMe group led to the same order of selectivity for compounds **7** and **3** (*vide supra*), exclusive series in which isomers **b** and **c** were studied in both cases. In contrast, the most striking difference concerned the unsubstituted macrocycle **1c**, which showed a poor extracting capability, whereas it displayed, with Sr^{2+} in homogeneous system, a complexing constant identical to that of **7b**. The explanation of this discrepancy may lie in the very different lipophilicity of the skeletons as shown in Table II.

MATERIALS AND METHODS

Spectrophotometric grade THF was used rapidly to prevent peroxidation. Spectrophotometric grade chloroform was washed three times with water to eliminate traces of ethanol. Acetonitrile was used without further purification. Water was distilled three times on quartz (resistivity $> 10^6$ ohm cm^{-1}).

Recording Absorption Spectra

UV-visible spectra were run on a double-beam Kontron Uvikon 941 spectrophotometer, driven with Uvikon 900 software from Bio-Tek Instrument (scan speed: 200 nm min^{-1}; bandwidth: 2 nm; absorption accuracy: 0.001) using 1 cm thick cells. They were recorded from 200 to 500 nm in 0.5 nm steps. The experimental absorbance range was from 0.2 to 2.

General Procedure for the Preparation of Compounds

The 14-membered ring diketal dilactams were synthesized and recrystallized as previously described [7,8]. Metal picrates were prepared by the method of Silberrad and Phillips [25], i.e. from the corresponding metal carbonate and picric acid.

Determination of Stoichiometry and Stability Constants

An approximately 5×10^{-5} molar (C_M^0) solution of the relevant metal picrate was prepared in THF, 1 ml of which was placed in the spectrometer cell. More of this solution was used to prepare a 10^{-3} M (C_L^0) solution of ligand. Using a microsyringe, amounts of this solution were incrementally added to the cell through a silicone septum inserted in its Teflon tap. In these conditions, the metal picrate concentration was kept constant at molarity C_M^0, the ligand analytical concentration C_L being variable.

The C_L/C_M^0 ratio was progressively increased first in 0.1 unit steps, then beyond 1 in 1 unit steps and beyond 10 in 10 unit steps first up to a value of 80 (compounds **3a–c** and **7b**) and then to a value of 40 (all other compounds). The pure solvent was used in the reference cell. Experiments were performed at 25°C.

For each solution, the Beer's law relationship for the absorbance is written:

$$A(\lambda) = l[\varepsilon_M(\lambda)C_M + \varepsilon_{ML}(\lambda)C_{ML} + \varepsilon_{ML2}(\lambda)C_{ML2} + \ldots]$$

where l is the optical path length in cm; ϵ: the molar absorption coefficient and C_i the concentration of the species present in the solution (the concentrations of these neutral pairs being very low, it could be assumed that concentrations and activities were identical).

The absorbance data obtained at the different metal–ligand ratios were processed by using the STAR program [18], which simulates the equilibria involved and refines the binding constants by minimizing the least-square function corresponding to each model. For each cation–ligand pair, the stability constants were calculated taking into account first the formation of a single complex ML and second the formation of both ML and ML$_2$ complexes as suggested by the absorbance variations. The program gives several statistical characteristic parameters to test the chosen chemical model, among which σ_r, the standard deviation of the absorbance that may be compared to the instrumental error of the spectrometer (<0.005) and $\langle r_{i,j} \rangle$, the residual mean. The choice of model was also guided by use of the STAR-FA program [18], which suggests the number of absorbing species in solution by factor analysis of the absorbance data matrix (≈ 45 wavelengths and 24 solutions). The formation of ML$_2$ was considered when the standard deviation σ (log β_{12}) was less than 0.40. Table IV groups together the formation constants (log β_{ii}) and the statistical tests given by STAR for the Ca^{2+}-ligand complexes **1c–7c**.

In addition, Table V gives, as an example, the information obtained with STAR and STAR-FA for the complexes corresponding to the studied macrocycles and the Ca^{2+} ion. It comprises: (i) the number of complexes, (ii) the UV characteristics (λ_{max}, ε_{max}), (iii) the bathochromic shift.

Extractions

The first measurements yielded low extraction values. Consequently, it was necessary to set a well-defined experimental protocol to obtain good reproducibility and reliability. For this purpose, the solvents (CHCl$_3$ and H$_2$O) were first saturated with each other to prevent volume changes of either phase

TABLE IV Formation constants (log β_{ii}) and statistical tests given by STAR for complexes **1c–7c** with Ca^{2+}

Ligand		log β_{ii}	σ (log β_{ii})	σ_r	$\langle r_{i,j} \rangle$
1c	β_{11}	3.87	0.01	2.9	2.0
	β_{12}	4.77	0.19		
2b	β_{11}	1.63	0.03	4.5	3.7
	β_{12}	–	–		
2c	β_{11}	1.83	0.01	3.3	2.7
	β_{12}	–	–		
3a,b (17:83)	β_{11}	3.29	0.01	4.3	1.5
	β_{12}	–	–		
3c	β_{11}	3.10	0.01	2.6	1.9
	β_{12}	–	–		
4a,b (16:84)	β_{11}	2.85	0.04	2.8	2.1
	β_{12}	4.76	0.04		
4c	β_{11}	3.69	0.04	1.9	1.3
	β_{12}	5.59	0.20		
5b	β_{11}	3.77	0.01	6.6	5.1
	β_{12}	–	–		
5c	β_{11}	3.31	0.01	4.0	3.1
	β_{12}	–	–		
6b	β_{11}	2.91	0.02	3.5	2.8
	β_{12}	–	–		
6c	β_{11}	3.62	0.04	2.5	1.9
	β_{12}	5.17	0.14		
7a	β_{11}	3.69	0.03	5.3	3.4
	β_{12}	5.47	0.21		
7b	β_{11}	3.83	0.01	5.2	4.04
	β_{12}	–	–		
7c	β_{11}	3.92	0.03	3.6	2.5
	β_{12}	5.14	0.36		

occurring during the extractions; the cores of each phase were then used exclusively. The experiments were carried out by adding a chloroform solution of ligand ($C_L^0 \approx 10^{-2}$ M, 1 ml) to an aqueous solution of metal picrate ($C_M^0 \approx 10^{-2}$ M, 1 ml) in cone-shaped tubes, which were shaken for 15 min at 25°C on a vortex mixer, and then centrifuged for 15 min at 4000 rpm to promote complete phase separation. All the solutions were prepared by weighing. The densities of these solutions were considered equal to those of the equilibrated solvents, i.e. $d_w = 1.000$ g cm^{-3} for the aqueous solution and $d_o = 1.454$ g cm^{-3} for the

chloroform solution. Three to five samples ($V_P \approx$ 100–200 µl) of the chloroform phase were diluted in CH$_3$CN ($\approx$ 2 ml). The corresponding spectra were recorded with CH$_3$CN in the reference cell.

Calibration curves enabled us to determine the concentration of cations (C_{mes}) in the CH$_3$CN solutions. The spectra obtained in acetonitrile were not modified by the addition of CHCl$_3$ aliquots. Thus, for each metal picrate (Ca^{2+}, Sr^{2+} and Zn^{2+}), the curves $A(\lambda) = f(C_{MPi2})$ of twelve CH$_3$CN solutions ($c \approx 10^{-5}$–10^{-4} M) were plotted. These curves were not always straight lines owing to the formation of the MPi$^+$ pair in acetonitrile. They were run for $\lambda = 370$ nm near the maximum of the main optical absorption band of the free anion picrate ($\lambda \approx 380$ nm). A polynomial development (least square) fitted the curves from 0 to 10^{-3} M. It was linear for Sr^{2+} and quadratic for Ca^{2+} and Zn^{2+}. The densities of the CHCl$_3$–CH$_3$CN mixtures were measured using the following experimental relation:
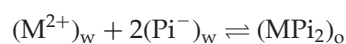
$$d = 0.777 + \left(\frac{0.305 \times m_{CHCl_3}}{m_{CH_3CN}} \right)$$

where m_{CHCl_3}, mass of the sample; m_{CH_3CN}, mass of acetonitrile (2 ml).

The concentration of the cation in the chloroform phase was then:

$$C_{exp} = [M^{2+}]_o = C_{mes} \left(\frac{1 + m_{CHCl_3}}{m_{CH_3CN}} \right) \left(\frac{d_{CHCl_3}}{d} \right)$$

The picrate partition ratio K_P between the two layers was calculated by differential UV-visible spectrophotometry using an analogue procedure.

$$(M^{2+})_w + 2(Pi^-)_w \rightleftharpoons (MPi_2)_o$$

$$K_p = \frac{[MPi_2]_o}{[M^{2+}]_w [Pi^-]_w^2} = \frac{[MPi_2]_o}{[M^{2+}]_w^3}$$

TABLE V UV characteristics of species in equilibrium for the complexes Ca^{2+} ligands **1c–7c**

| Ligand	STAR/FA		STAR			
	Complex number	λ_1*	$\lambda_1 - \lambda_{Ca}$*	ε_1[†]	λ_2*	ε_2[†]
1c	2	334	1	24715	355	[‡]
2b	1	353	20	[‡]	–	–
2c	1	354	21	[‡]	–	–
3a,b (17:83)	1	342	9	26703	–	–
3c	1	342	9	27068	–	–
4a,b (16:84)	2	338	5	23832	348	25700
4c	2	335	2	22330	357	39190
5b	1	341	8	25600	–	–
5c	1	343	10	26100	–	–
6b	1	344	11	26460	–	–
6c	2	338	11	23831	354	[‡]
7a	2	339	6	23825	360	54862
7b	1	342	9	27174	–	–
7c	2	339	6	24600	361	[‡]

*in nm. [†]in l mol^{-1} cm^{-1}. [‡]Inaccurate value. λ_1: absorption wave length of the ML complexes; λ_2: absorption wave length of the ML$_2$ complexes.

where M^{2+} is the bivalent cation; Pi^- the picrate anion; L the ligand; w the aqueous phase and o the organic phase.

The organic phase picrate concentration $[MPi_2]_o$ was found to be $\approx 10^{-7} M$.

Following Cram [22], the selected model was characterized by equilibria I and II:

$$(M^{2+})_w + 2(Pi^-)_w \rightleftharpoons (MPi_2)_o \qquad (I)$$

$$(M^{2+})_w + 2(Pi^-)_w + (L)_o \rightleftharpoons (MLPi_2)_o \qquad (II)$$
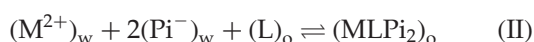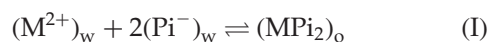
For divalent cations, the extraction constant K_{ex} was expressed by the following relation:

$$K_{ex} = \frac{[MLPi_2]_o}{4[M^{2+}]_w^3 [L]_o}$$

The conservation of mass gave four relations that enabled us to calculate successively $[M^{2+}]_w$, $[MPi_2]_o$, $[MLPi_2]_o$, $[L]_o$ and K_{ex} from C_M^0, C_L^0, C_{exp} and K_p:

$$S \begin{cases} C_{exp} = [MPi_2]_o + [MLPi_2]_o \\ C_M^0 = [M^{2+}]_w + Q_v \times C_{exp} \\ [MPi_2]_o = 4 K_p [M^{2+}]_w^3 \\ C_L^0 = [L]_o + [MLPi_2]_o \end{cases}$$

where Q_v (experimental ratio): V_{CHCl_3}/V_{H_2O}.

For each couple studied, the data necessary for the calculation of the extraction constants are reported in Table VI.

Lipophilicity Determination

Lipophilicities of the ligands were determined by their TLC retention R_F according to Ellgehausen [26]. The TLC system was calibrated with a set of reference compounds of known lipophilicities [27] (acetophenone: $\log P = 1.58$; nitrobenzene: $\log P = 1.85$; *p*-chloronitrobenzene: $\log P = 2.39$; naphthalene: $\log P = 3.37$). TLC was performed with 0.25 mm thick glass-backed $RP-18F_{254}S$ reversed-phase plates using methanol–water (80:20) as solvent.

CONCLUSIONS

We have explored the binding abilities of a new class of 14-membered ring ligands bearing two secondary amide and acetal functions. Two studies were performed by UV-visible spectrophotometry: determination of the formation constants in tetrahydrofuran solution and evaluation of their extractive properties in a biphasic system.

The results obtained reveal that with divalent cations, the best complexations were with Sr^{2+} and Ca^{2+}, the ionic radii of which are close to 1 Å. In contrast, no association was detected with monovalent cations. This preference for more highly charged cations is probably due to the presence of high polarity coordination sites (CO amide), as already reported [12,28]. The complexes formed were essentially of the ML type; they were sometimes accompanied by a small percentage of ML_2. Also, the number of skeletons examined showed that the complexation and recognition properties depend on the nature of the 2 and 3-substituents and enabled us to make a first selection from among the different structures. The highest formation and extraction constants were observed for the highly substituted 2,2′-phenyl-3,3′-methyl macrocycles **7b** and **7c**. The $\log \beta_{11}$ values obtained for the Ca^{2+} and Sr^{2+} cations are in the same range as those determined in the same conditions for the 18-membered ring

TABLE VI   Extraction results

Complex	C_M^0 $(10^{-3} M)$	C_L^0 $(10^{-3} M)$	Q_v	K_p	C_{exp} $(10^{-6} M)$	$[M^{2+}]_w$ $(10^{-3} M)$	$[L]_o$ $(10^{-3} M)$	$[MLPi_2]_o$ $(10^{-6} M)$	K_{ex}
1c-Ca^{2+}	7.084	13.281	1.64	1.43	2.83	7.079	13.280	0.80	42
1c-Sr^{2+}	5.492	11.812	1.37	0.18	1.70	5.489	11.810	1.58	202
3a,b-Ca^{2+}	9.203	10.362	1.00	1.43	15.87	9.187	10.350	11.44	356
3c-Ca^{2+}	9.278	9.770	1.00	1.43	7.64	9.270	9.767	3.08	99
3c-Sr^{2+}	5.765	3.332	2.22	0.18	8.03	5.747	3.324	7.89	3126
3c-Zn^{2+}	8.238	26.123	0.92	0.15	41.68	8.199	26.082	41.34	719
4c-Ca^{2+}	7.123	11.871	1.04	1.43	6.55	7.116	11.867	4.49	263
4c-Sr^{2+}	4.672	11.830	1.62	0.18	27.85	4.627	11.802	27.77	5940
5b-Ca^{2+}	3.912	8.112	0.81	1.43	7.32	3.906	8.105	69.82	3614
5b-Sr^{2+}	3.146	9.860	0.70	0.18	8.86	3.140	9.852	8.84	7242
6c-Ca^{2+}	5.756	13.784	1.36	1.43	29.36	5.716	13.755	28.29	2753
6c-Sr^{2+}	5.456	12.458	1.41	0.18	25.36	5.421	12.433	25.24	3187
7b-Ca^{2+}	8.142	14.768	1.07	1.43	155.94	7.975	14.615	153.00	5160
7b-Sr^{2+}	4.168	11.045	1.06	0.18	54.49	4.110	10.991	54.44	17828
7b-Zn^{2+}	10.446	9.254	1.08	0.15	9.00	10.436	9.246	8.30	197
7c-Ca^{2+}	6.311	6.634	1.53	1.43	44.07	6.243	6.591	42.70	6651
7c-Sr^{2+}	5.248	6.952	1.28	0.18	43.20	5.193	6.909	43.10	11136
7c-Zn^{2+}	6.748	7.758	0.94	0.15	45.71	6.705	7.713	45.50	4895

tetralactam **I** including two secondary and two tertiary amide functions [12]. They should be improved by substituting both *N*-amide groups with lipophilic chains.

Based on the above information concerning our ligands, it is now possible to envisage an extension of this work by NMR studies in order (i) to identify the coordination sites, (ii) to determine the importance, in the complexation, of the ketal functions infrequently encountered in macrocyclic structures, (iii) finally to emphasize the differences of conformations between the flexible free ligands and their cationic complexes. This work will be the object of a following paper.

Thus, after the discovery of new macrocyclic compounds generated by an original methodology [7,8], we can now design a new class of ligands offering an interesting selectivity towards Sr^{2+} and Ca^{2+}, the binding properties of which should be improved.

Acknowledgements

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