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Synthesis and binding properties of calix[4]arenes with [2 + 2′] mixed ligating functional groups

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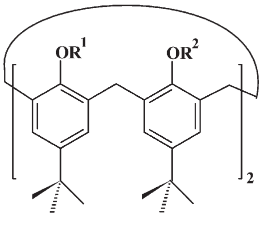
A series of mixed [2 + 2′] *p-tert*-butylcalix[4]arene have been synthesised by selective 1,3-dialkylation of phenolic groups using various alkylating agents such as benzyl bromide, methyl iodide, ethyl bromoacetate, and 2-methoxyethyl tosylate. The extraction and complexation properties of the synthesized calixarenes towards alkali and alkaline earth metal cations have been investigated in acetonitrile by means of UV spectrophotometry and ^{1}H NMR spectroscopy. The results show the formation of ML and/or ML_2 species depending on the ligand and the cation. The enthalpies and entropies of complexation of alkali metal cations by a tetraglycol, diglycol–dibenzyl and diglycol–diester derivatives have been obtained from calorimetric measurements. The results revealed that the formation of ML species is controlled by enthalpy while the formation of ML_2 from ML is entropy driven.

Introduction

Calixarenes, and particularly calix[4]arene derivatives, are an important family of synthetic host molecules.[1–3] Much work has been devoted to the synthesis and complexation studies of derivatives tetra-substituted at the lower rim with carbonyl-containing functional groups such as esters, ketones, amides, and carboxylic acids, which are effective ionophores for metal ions.[2–6] The ester and ketone derivatives display selectivity within the alkali cation series and amide derivatives within both alkali and alkaline earth cation series.[5,6] In order to design calixarene receptors with tunable and thus enhanced selectivities for specific cations, recent interest was taken in the synthesis of calix[4]arene derivatives with mixed functionalities.[4,7] Thus, substitutions with combinations of different groups containing heteroatoms such as oxygen, nitrogen, sulfur and other ligating atoms were examined. Contrary to the case of calix[4]arenes functionalised with four identical groups, only a few works have been reported for mixed derivatives. For example, ligands with [3 + 1] combinations of three ethyl esters with one methyl ester, one diethyl- or pyrrolidinylamide have been synthesized and showed improved extraction patterns for Li^+.[5] The complexation and extraction of alkali cations by [2 + 2′] calix[4]arene derivatives combining ethyl ester and methyl ketone, *tert*-butyl ester or diethylamide arms have also been reported.[5] With the [2 + 2′] mixed ethyl ester–methyl ketone derivative, the extraction percentage values were approximately the average of those of the tetraethyl ester and the tetramethyl ketone.[5] As part of a research project aimed at the removal of lanthanides and actinides from nuclear waste by extraction techniques, the [2 + 2′] mixed diphenylphosphine oxide–diethylamide calix[4]arene and the [2 + 2′] mixed diphenylphosphine oxide–di-*tert*-butyl ester calix[4]arene derivatives have been synthesized and their extraction and complexation properties investigated.[8–10] The synthesis of three [2 + 2′] calix[4]arene derivatives bearing two allyl groups and two methyl or two benzyl groups, and their use to extract thallium and silver cations have been also published.[11] Recently, we described the synthesis of several [2 + 2′] diethylmalonate calix[4]arene derivatives and the complexation of Li^+ and Na^+ by two of them has been investigated.[12]

We have previously reported the synthesis and crystal structures of 5,11,17,23-tetra-*tert*-butyl-25,27-di(phenylmethoxy)-26,28-di(2-methoxyethoxy)–calix[4]arene (**5**),[13,14] 5,11,17,23-tetra-*tert*-butyl-25,27-di(phenylmethoxy)-26,28-di(di-ethylacetamido)–calix[4]arene,[15] 5,11,17,23-tetra-*tert*-butyl-25,27-di(2-methoxyethoxy)-26,28-di(ethylacetate)–calix[4]arene (**7**)[16] and 5,11,17,23-tetra-*tert*-butyl-25,27-di(di-ethoxyphosphoryl)-26,28-di(ethylacetate)–calix[4]arene.[17] All these calixarenes adopted the *cone* conformation in the solid state which is probably retained in solution. A preliminary ^{1}H NMR study of the complexation of alkali metal cations in 50/50 $CDCl_3/CD_3CN$ indicated that ligand **5** strongly preferred the smaller alkali metal cations. However, the [2 + 2′] mixed diethoxyphosphoryl–ethylacetate derivative showed a preference for alkali cations in the order $Na^+ > K^+ > Rb^+ > Cs^+ > Li^+$.[17]

In this paper, we present the synthesis of ligands **2**, **3**, **4** and **6**, along with a complete study of the binding properties of **3**–**7** towards alkali and alkaline earth metal cations. We have determined the stoichiometry of the species formed in acetonitrile and the thermodynamical parameters of the complexation by ^{1}H NMR spectroscopy, UV spectrophotometry and calorimetry. For comparison, we also investigated calix[4]arenes **1** and **2** tetra-substituted at the lower rim, respectively by methoxy groups and glycol groups.



1 $R^1 = R^2 = CH_3$
2 $R^1 = R^2 = CH_2CH_2OCH_3$
3 $R^1 = CH_2C_6H_5$ $R^2 = CH_3$
4 $R^1 = CH_2C_6H_5$ $R^2 = CH_2CO_2C_2H_5$
5 $R^1 = CH_2C_6H_5$ $R^2 = CH_2CH_2OCH_3$
6 $R^1 = CH_2CH_2OCH_3$ $R^2 = CH_3$
7 $R^1 = CH_2CH_2OCH_3$ $R^2 = CH_2CO_2C_2H_5$

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Experimental

Instrumentation

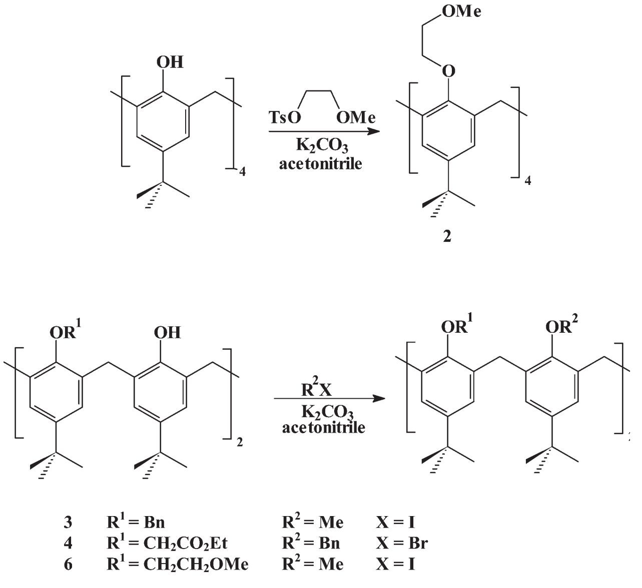
Uncorrected melting points (mps) were measured on Büchi 500 apparatus. ^{1}H NMR spectra were recorded on a Bruker SY200 spectrometer and FAB mass spectra on a VG-Analytical ZAB HF instrument. Elemental analyses were provided by the Microanalysis Service of the 'Institut de Chimie de Strasbourg'. Chromatography columns were prepared from Merck Kieselgel N° 11567. The UV spectra were recorded on a Perkin Elmer Lambda 11 spectrophotometer.

Materials

The solvents acetonitrile (SDS for HPLC, 0.03% water content) and dichloromethane (Fluka, purum) were used without further purification. The supporting electrolyte used in the stability constant determinations was Et_4NClO_4 (Acros). The metal salts chosen were perchlorates (Fluka, purum) except for caesium, where the salt used was $CsNO_3$ (Merck p.a.).The picrate salts employed in extraction were prepared by a literature method.[18] Tetramethoxy *p*-*tert*-butylcalix[4]arene **1** was prepared as previously described.[19]

Synthesis

The synthesis of [2 + 2′] substituted compounds **3**, **4** and **6** was performed in two steps: the synthesis of 1,3-di-substituted derivatives followed by the di-substitution of the two remaining phenolic hydrogens. The synthesis of compound **2** with four identical substituents required only one step (Scheme 1).



Scheme 1 Synthesis of ligands **2**, **3**, **4** and **6**.

5,11,17,23-tetra(tert-butyl)-25,26,27,28-tetra-methoxyethoxycalix[4]arene (2). A mixture of K_2CO_3 (40.0 g; 290 mmol) and *p*-*tert*-butylcalix[4]arene (12.97 g; 20.0 mmol) was stirred vigorously in CH_3CN (250 mL) for 3 h to promote intimate contact of the solids and to dissolve as much as possible. 2-Methoxyethyl tosylate (23.12 g; 100.0 mmol) was then added and the reaction mixture was refluxed for 5 days. After cooling, the excess of K_2CO_3 was filtered off before the solvents were removed under reduced pressure. A mixture of water and dichloromethane was added to the residue and the aqueous phase was acidified (pH ≈ 2). After complete dissolution, the organic layer was separated and dried over Na_2SO_4. After filtration and evaporation, **2** was obtained as a white solid by trituration with CH_3OH (85% yield). Mp 181–182 °C. ^{1}H NMR (300 MHz: $CDCl_3$), δ_H 6.78 (s, 8H, Ar**H**), 4.44 (d, 4H, *J* = 12.6, ArC**H$_2$**Ar), 4.09 (t, 8H, *J* = 6.0, ArOC**H$_2$**CH$_2$OCH$_3$), 3.91 (t, 8H, *J* = 6.0, ArOCH$_2$C**H$_2$**OCH$_3$) 3.46 (s, 12H, ArOCH$_2$CH$_2$OC**H$_3$**), 3.12 (d, 4H, *J* = 12.6, ArC**H$_2$**Ar), 1.06 (s, 36H, ArC(C**H$_3$**)$_3$). FAB(+) MS *m*/*z*: 880.7 [M]$^+$, 903.6 [M + Na]$^+$; Anal. Calcd. for $C_{56}H_{80}O_8$: C 76.33, H 9.15; found: C 76.21, H 9.00%.

5,11,17,23-tetra(tert-butyl)-25,27-dimethoxy-26,28-diphenylmethoxycalix[4]arene (3). K_2CO_3 (2.36 g; 17.0 mmol) was added to a solution of 1,3-di-benzyl *p*-*tert*-butylcalix[4]arene[17] (0.43 g; 0.50 mmol) and an excess of MeI in 25 mL of acetonitrile. The reaction mixture was refluxed for 24 h and then treated as for **2**. **3** was obtained as a white solid (82% yield). Mp 280–281 °C. ^{1}H NMR (300 MHz: $CDCl_3$), δ_H 7.43–6.45 (m, 18H, Ar**H** and ArOCH$_2$C$_6$**H$_5$**); 4.81–2.72 (m, 18H, ArC**H$_2$**Ar, ArOC**H$_2$**C$_6$H$_5$ and ArOC**H$_3$**), 1.52–0.82 (m, 36H, ArC(C**H$_3$**)$_3$), spectrum in coalescence. FAB(+) MS *m*/*z*: 856.7 [M]$^+$, 879.7 [M + Na]$^+$; Anal. Calcd. for $C_{60}H_{72}O_4$: C 84.07, H 8.47; found: C 84.27, H 8.45%.

5,11,17,23-tetra(tert-butyl)-25,27-diethoxycarbonylmethoxy-26,28-diphenylmethoxycalix[4]arene (4). K_2CO_3 (5.43 g; 39.2 mmol) was added to a solution of 1,3-diethoxycarbonylmethoxy-*p*-*tert*-butylcalix[4]arene[9] (3.21 g; 3.9 mmol) and an excess of benzyl bromide in CH_3CN (150 mL). The reaction mixture was refluxed for 48 h and treated as for **2**. The white solid has been obtained in 67% yield. Mp 148–149 °C. ^{1}H NMR (300 MHz: $CDCl_3$), δ_H 7.48–7.23 (m, 10H, ArOCH$_2$C$_6$**H$_5$**), 6.92 (s, 4H, Ar**H**) 6.60 (s, 4H, Ar**H**), 4.94 (s, 4H, ArOC**H$_2$**C$_6$H$_5$); 4.59 (s, 4H, ArOC**H$_2$**CO$_2$CH$_2$CH$_3$), 4.57 (d, 4H, *J* = 12.9, ArC**H$_2$**Ar), 4.01 (q, 4H, *J* = 7.1, ArOCH$_2$CO$_2$C**H$_2$**CH$_3$), 3.08 (d, 4H, *J* = 12.9, ArC**H$_2$**Ar), 1.18 (t, 6H, *J* = 7.1, ArOCH$_2$CO$_2$CH$_2$C**H$_3$**), 1.18 (s, 18H, ArC(C**H$_3$**)$_3$), 0.96 (s, 18H, ArC(C**H$_3$**)$_3$). FAB(+) MS *m*/*z*: 1000.8 [M]$^+$, 1023.6 [M + Na]$^+$; Anal. Calcd. for $C_{66}H_{80}O_8$: C 79.17, H 8.05; found: C 79.28, H 7.97%.

5,11,17,23-tetra(tert-butyl)-25,27-dimethoxy-26,28-dimethoxyethoxycalix[4]arene (6). K_2CO_3 (3.21 g; 23.2 mmol) was added to a solution of 1,3-di-methoxyethoxy *p*-*tert*-butylcalix[4]arene[13] (1.070 g; 1.4 mmol) and excess of MeI in CH_3CN (40 mL). The reaction mixture was heated at reflux for 24 h and then treated as for **2**. **6** was obtained as a white solid in 87% yield. Mp 166–167 °C. ^{1}H NMR (300 MHz: $CDCl_3$), δ_H 7.32–6.31 (m, 8H, Ar**H**), 4.33–3.11 (m, 28H, ArC**H$_2$**Ar, ArOC**H$_3$** and ArOC**H$_2$**C**H$_2$**OC**H$_3$**), 1.55–082 (m, 36H, ArC(C**H$_3$**)$_3$), spectrum in coalescence. FAB(+) MS *m*/*z*:792.6 [M]$^+$, 815.5 [M + Na]$^+$. Anal. Calcd. for $C_{52}H_{72}O_6$:C 78.75, H 9.15; found: C 78.94, H 8.95%.

Extraction studies

The extraction experiments of alkali metal picrates from water into dichloromethane were performed according to a procedure described in the literature.[20] Equal volumes (5 mL) of neutral aqueous solution of alkali metal picrate (2.5×10^{-3} mol L^{-1}) and CH_2Cl_2 solution (5 mL) of calixarene derivatives (2.5×10^{-3} mol L^{-1}) were mixed and magnetically shaken in a thermoregulated water bath at 20 °C for 30 min and then left standing for 2 to 6 h in order to obtain a complete separation of the two phases. The concentration of metal picrate remaining in the aqueous phase was determined from the absorbance *A* at 355 nm. The percentage extraction %*E* was derived from the following expression in which A_0 is the absorbance of the aqueous solution of a blank experiment without calixarene:

$$\%E = 100(A_0 - A)/A_0 \tag{1}$$

Stability constant measurements

The stability constants β_{xy} being the concentration ratios $[M_xL_y^{xn+}]/[M^{n+}]^x[L]^y$ and corresponding to the general equilibrium:

$$yL + xM^{n+} \rightleftarrows M_xL_y^{xn+} \tag{2}$$

(where M^{n+} = metal ion, L = ligand) were determined in acetonitrile by UV-absorption spectrophotometry at 25 °C. The ionic strength was been maintained at 0.01 mol L^{-1} using Et_4NClO_4. The spectra of ligand solutions of concentrations ranging between 10^{-4} and 2×10^{-4} mol L^{-1} and increasing concentration of metal ion, were recorded between 250 and 350 nm. Generally the metal to ligand ratio R at the end of the titration did not exceed 20 and the equilibria were quasi-instantaneous for all the systems. Addition of the metal ion to the ligand induced enough changes in the spectra to allow the analysis of the resulting data using the Letagrop program.[21] Best values for the formation constants β_{xy} of the various complex species and their molar absorptivity coefficients for various wavelengths are deduced from the best fit between the experimental and calculated UV spectra. The best fit is reflected by the lowest value of U (the sum of U values for all λ given) corresponding to the square sum of the differences between the experimental and calculated absorbances ($U = \Sigma\,(A_{cal} - A_{exp})^2$). As example the case of Na^+ complexation by ligand **7**, we report $U = 9.0810^{-2}$ when we consider the ML formation, $U = 1.1310^{-2}$ for ML_2 and $U = 4.33\ 10^{-3}$ for ML and ML_2 complexes, the best fit is obviously the one corresponding to the formation simultaneously of ML and ML_2 complexes. The β_{xy} values given in Table 1 correspond to the arithmetic means of at least three independent experiments.

Calorimetric measurements

The calorimetric determinations were made in acetonitrile at 25 °C, using a precision Isoperibol titration calorimeter (Tronac 450, Orem, Utah). The experimental procedure has been reported in detail elsewhere.[22] The metallic salts ($C_M = 10^{-1}$ mol L^{-1}) were titrated into a 50 mL solution of calixarene ($C_L = 10^{-3}$ mol L^{-1}). Heat-of-dilution corrections were made by the titration of metal salt solution into the solvent. $\Delta_c H°_{xy}$ values were refined from calorimetric data using the SIRKO program.[23] β_{xy} values determined by UV spectrophotometry being taken as fixed, since the refinement simultaneously of β_{xy} and $\Delta_c H°_{xy}$, when the complexes are not too strong, lead to a comparable β_{xy} values. When the complexes are enough strong, stability constants can not be determined by calorimetry, then β_{xy} values have to be fixed to calculate $\Delta_c H°_{xy}$. In all cases, the goodness of the fit is appreciated considering the R factor total and/or R_limit parameters. Finally $T\Delta_c S°_{xy}$ values were derived from the expression: $\Delta_c G°_{xy} = \Delta_c H°_{xy} - T\Delta_c S°_{xy}$, knowing $\Delta_c G°_{xy} = -RT\ln\beta_{xy}$

Results and discussion

Calixarene derivatives **2**, **4**, **5** and **7** were synthesized in their cone conformation by treating the appropriate calixarene precursor with an alkylating agent in the presence of potassium carbonate in acetonitrile. The coalescence of the ^1H NMR spectra of the tetramethoxy **1** and the di-methoxycalixarene derivatives **3** and **6** indicated that these ligands are not in the cone conformation due to the possible rotation of the methoxy groups through the calixarene annulus.

Extraction of metal picrates

Extraction percentages (%E) of alkali and alkaline earth metal picrates by compounds **1** to **7** are given in Table 2. They provide a first estimation of the binding abilities of these ligands towards the two series of metal cations.

Alkali cations. Comparing to some good extractants, as tetraamide or tetraester calix[4]arene, and under the same conditions, the values obtained with compounds **1**–**7** are generally very low. The highest value (%E = 34.5) is found for the extraction of sodium picrate by the [2 + 2′] glycol-ester derivative **7**.

Ligand **1**, particularly, is a very poor extractant since only Li^+ and Na^+ are slightly extracted, with %E of 4.1 and 6.2, respectively. These results are globally consistent with extraction percentages, obtained by Chang and Cho[19] from a basic aqueous phase.

Table 1 Stability constants ($\log\beta_{xy} \pm \sigma_{N-1}$) for their alkali and alkaline earth metal ion complexes of ligands **1**–**7** in acetonitrile at 25 °C ($I = 10^{-2}$ M)

				$\log\beta_{xy}$								
Compounds	R^1	R^2	M : L	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
1	CH_3	CH_3	1 : 1	5.10 ± 0.01	3.71 ± 0.10	[a]	[a]	[a]	3.03 ± 0.20	3.29 ± 0.10	3.21 ± 0.20	3.28 ± 0.20
2	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$	1 : 1			4.51 ± 0.02	3.32 ± 0.02	[a]	3.27 ± 0.01	3.91 ± 0.02	3.01 ± 0.02	5.09 ± 0.10
			1 : 2	9.23 ± 0.05	9.64 ± 0.01							
3	$CH_2C_6H_5$	CH_3	1 : 1	3.54 ± 0.01	3.42 ± 0.01	[a]	[a]	[a]	[a]	[a]	[a]	[a]
4	$CH_2C_6H_5$	$CH_2CO_2C_2H_5$	1 : 1	4.30 ± 0.05	4.84 ± 0.05	2.90 ± 0.05	2.97 ± 0.10	[a]	[a]	3.78 ± .05	2.47 ± 0.15	2.74 ± 0.15
5	$CH_2C_6H_5$	$CH_2CH_2OCH_3$	1 : 1	3.76 ± 0.05	3.80 ± 0.10	2.69 ± 0.05	[a]	[a]	[a]	3.00 ± 0.10	3.37 ± 0.05	3.11 ± 0.05
			1 : 2	7.88 ± 0.10								
6	$CH_2CH_2OCH_3$	CH_3	1 : 1	5.41 ± 0.10	4.67 ± 0.01	3.36 ± 0.02	3.25 ± 0.05	[a]	[a]	3.22 ± 0.10	3.27 ± 0.10	[a]
7	$CH_2CH_2OCH_3$	$CH_2CO_2C_2H_5$	1 : 1	5.99 ± 0.10	5.37 ± 0.20	5.06 ± 0.06	2.92 ± 0.07	3.19 ± 0.01	3.01 ± 0.10	4.63 ± 0.01		
			1 : 2	10.72 ± 0.10	9.16 ± 0.10					8.07 ± 0.03	3.39 ± 0.10	4.94 ± 0.05

[a] Small spectral variations.

Table 2 Extraction percentages (%*E*)[a] of alkali and alkaline earth metal picrates from water into dichloromethane, at 20 °C

	%*E*								
Compounds	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
1	4.1	6.2	<1	<1	<1	6.3	4.1	<1	3.9
2	2.5	14.9	4.7	3.4	1.7	6.0	6.6	1.8	3.0
3	4.7	4.0	6.3	2.0	2.3	5.1	3.9	2.2	4.9
4	2.7	15.9	12.3	2.8	4.3	2.4	2.1	<1	<1
5	9.4	4.1	2.0	5.4	2.5	2.3	1.0	<1	1.3
6	6.1	4.4	5.5	2.0	2.4	6.8	3.3	<1	3.9
7	7.1	34.5	7.6	4.6	1.6	9.8	7.9	4.3	8.8

[a] standard deviation σ_{N-1} of the mean of *n* experiments: 0.05–0.1.

The substitution of two opposite methyl residues of **1** by two benzyl or two glycol groups does not lead to substantial changes in the extraction profiles, except for a slight increase in the extraction of the larger cations from K^+–Cs^+ without introducing any significant selectivity.

The glycol tetra-substituted derivative **2** shows a preference for Na^+ over the other alkali metal cations with selectivity $S_{Na/K}$, = 3.2, expressed as the ratio of the extraction percentages of the two cations.

The replacement of two glycol functions of **2** by two benzyl groups shifted the selectivity to the smaller cation Li^+ (%*E* = 9.4). Whereas the replacement of two glycol functions by two ethyl ester functions, **7**, increases the extraction levels in particular for Na^+, %*E* = 34.5, with a significant selectivity for Na^+ over Cs^+ about 20. The latter ligand was found to be better extractant comparing to the *p*-*tert*-butylcalix[4]arene tetraethyl ester with an extraction percentage around 29 and $S_{Na/Cs} = 4.8$.[24]

Compound **4**, which combines two benzyl groups and two ester functions, show a low extraction level %*E* < 16, with a near 'plateau' selectivity for Na^+ and K^+.

Alkaline earth metal cations. Extraction percentages of the alkaline earth metal picrates by ligand **1**–**7** are even lower than those of the alkali picrates (%*E* < 10) and no selectivity is noticeable in this series. The best extraction levels are obtained with the [2 + 2′] ethyl ester-glycol derivative **7** with extraction percentages varying from 4.3% for Sr^{2+} to 9.8% for Mg^{2+}. These results are in perfect agreement with those of Arnaud-Neu *et al.*[25] who estimated that ester derivatives were poor extractants of alkaline earth metal picrates.

Stability constants in acetonitrile

Complexation data for alkali and alkaline earth metal cations are given in Table 1.

Alkali metal cations. In the series of alkali cations, the tetramethoxy **1** complexed only the small cations Li^+ and Na^+, the Li^+ complex being 25 times more stable than the Na^+ complex. These results are consistent with those found by Shinkai *et al.*[26] based on ^1H NMR experiments in a 4 : 1 (v/v) $CDC1_3/CD_3OD$ mixture. They showed that the rapidly inverting free ligand was frozen in the cone conformation by the addition of Li^+ and Na^+ cations, which interact strongly with four methoxy oxygens. However, with K^+, Shinkai *et al.*[26] suggested that the cation is bound to the upper rim of a partial cone or a 1,3-alternate conformation of **1**, through one or two oxygens and two benzene rings. This kind of interaction is too weak to be detected in the UV domain. Therefore, we assume that in case of **1** the complexation and conformational isomerism are controlled by the cation size. On the other hand, the stronger stability of $[Li\ \mathbf{1}]^+$ as compared to $[Na\ \mathbf{1}]^+$ may also be related to the solvation of these cations in acetonitrile.

As ligand **3** forms complexes only with Li^+ and Na^+, the introduction of benzyl groups in **1** does not change its binding affinity. However, the 1 : 1 complexes formed with Li^+ and Na^+ have approximately the same stability.

Ligand **6** bearing two glycol and two methoxy units forms 1 : 1 species with all alkali cations except Cs^+. Comparing to **1**, **6** complexes more efficiently alkali cations probably because of a greater number of donor sites (*e.g.* log $\beta_{11}[Na\ \mathbf{6}]^+ = 4.67$ and log $\beta_{11}[Na\ \mathbf{1}]^+ = 3.71$). However, similarly to **1**, its affinity is still in favour of the smaller cations.

The tetraglycol derivative **2** complexes all alkali cations, except Cs^+. The smaller cations (Li^+ and Na^+) form with **2** an ML_2 complex of similar stability. This stoichiometry was confirmed in the case of Na^+ by ^1H NMR titration in 1 : 1 CD_3CN/CD_3Cl which showed invariance of the spectra from the 1 : 2 (M : L) ratio (Fig.1). By the way, since the first addition of sodium perchlorate to **2**, the ^1H NMR spectra showed new signals corresponding to the complex, which appeared simultaneously with those of free ligand suggesting a slow ligand-cation exchange at NMR scale.

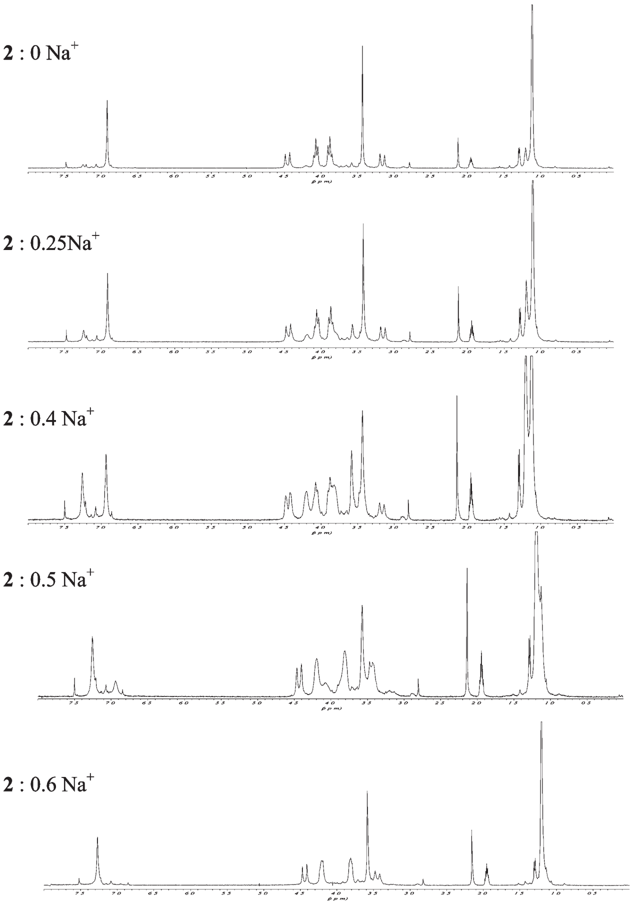


Fig. 1 ^1H NMR titration of **2** by $NaClO_4$ in $CD_3CN/CDCl_3$ (1 : 1).

The larger cations K^+ and Rb^+ form exclusively 1 : 1 complexes with **2**, $[K\ \mathbf{2}]^+$ being 10 times more stable than $[Rb\ \mathbf{2}]^+$.

The presence of two benzyl groups with two glycol groups in **5**, led to the formation of 1 : 1 complexes with Li^+, Na^+ and K^+ and an additional 1 : 2 species with Li^+. The mononuclear

Table 3 Enthalpy and entropy of complexation of alkali metal cations (with perchlorate counterion) by calix[4]arenes **2**, **5** and **7**, in acetonitrile at 25 °C : $-\Delta_c G^\circ_{xy}$, $-\Delta_c H^\circ_{xy}$, $T\Delta_c S^\circ_{xy}$ (kJ mol^{-1}) and $\Delta_c S^\circ_{xy}$ (J K^{-1} mol^{-1})

Compounds		Li^+	Na^+	K^+	Rb^+	Cs^+
2	$\log \beta_{11}$	-	-	4.51 ± 0.10	3.32 ± 0.10	-
	$-\Delta_c G^\circ_{11}$	-	-	25.7 ± 0.6	18.9 ± .1	-
	$-\Delta_c H^\circ_{11}$	-	-	28.3 ± 0.6	24.8 ± 0.5	-
	$T\Delta_c S^\circ_{11}$	-	-	−2.6 ± 0.6	−5.8 ± 0.6	-
	$\Delta_c S^\circ_{11}$	-	-	−8.7 ± 2.1	−19.6 ± 2.0	-
	$\log \beta_{12}$	9.23 ± 0.05	9.64 ± 0.05	-	-	-
	$-\Delta_c G^\circ_{12}$	52.6 ± 0.3	54.9 ± 0.3	-	-	-
	$-\Delta_c H^\circ_{12}$	28.3 ± 0.6	46.4 ± 1.1	-	-	-
	$T\Delta_c S^\circ_{12}$	24.3 ± 0.9	8.5 ± 1.4	-	-	-
	$\Delta_c S^\circ_{12}$	81.7 ± 3.1	28.5 ± 4.7	-	-	-
5	$\log \beta_{11}$	3.76 ± 0.05	3.80 ± 0.10	2.69 ± 0.05	-	-
	$-\Delta_c G^\circ_{11}$	21.4 ± 0.3	21.6 ± 0.6	15.3 ± 0.3	-	-
	$-\Delta_c H^\circ_{11}$	30.5 ± 0.5	32.1 ± 1.0	8.4 ± 1.4	-	-
	$T\Delta_c S^\circ_{11}$	−9.1 ± 0.8	−10.5 ± 1.6	6.9 ± 1.7	-	-
	$\Delta_c S^\circ_{11}$	−30.6 ± 2.7	−35.1 ± 5.4	23.1 ± 5.7	-	-
	$\log \beta_{12}$	7.88 ± 0.10	-	-	-	-
	$-\Delta_c G^\circ_{12}$	44.9 ± 0.6	-	-	-	-
	$-\Delta_c H^\circ_{12}$	20.0 ± 0.6	-	-	-	-
	$T\Delta_c S^\circ_{12}$	24.9 ± 1.2	-	-	-	-
	$\Delta_c S^\circ_{12}$	83.6 ± 4.0	-	-	-	-
7	$\log \beta_{11}$	5.99 ± 0.10	5.37 ± 0.20	5.06 ± 0.06	2.92 ± 0.07	3.19 ± 0.01
	$-\Delta_c G^\circ_{11}$	34.1 ± 0.6	30.6 ± 1.2	28.9 ± 0.4	16.6 ± 0.4	18.2 ± 0.1
	$-\Delta_c H^\circ_{11}$	33.8 ± 0.7	63.7 ± 0.2	44.5 ± 0.2	17.9 ± 0.4	6.7 ± 1.3
	$T\Delta_c S^\circ_{11}$	0.3 ± 1.3	−33.1 ± 1.4	−15.6 ± 0.6	−1.2 ± 0.8	11.4 ± 1.4
	$\Delta_c S^\circ_{11}$	1.0 ± 4.4	−111.0 ± 4.7	−52.3 ± 2.0	−4.2 ± 2.7	38.4 ± 4.7
	$\log \beta_{12}$	10.72 ± 0.10	9.1 ± 0.1	-	-	-
	$-\Delta_c G^\circ_{12}$	61.3 ± 0.6	52.1 ± 0.6	-	-	-
	$-\Delta_c H^\circ_{12}$	19.0 ± 2.8	65.4 ± 3.4	-	-	-
	$T\Delta_c S^\circ_{12}$	42.3 ± 3.2	−13.3 ± 4.0	-	-	-
	$\Delta_c S^\circ_{12}$	141.1 ± 10.7	−44.6 ± 13.0	-	-	-

complexes formed with **5** are more stable than with **3** (the dibenzyl dimethyl derivative), the K^+ complex, not detected with **3**, is now of measurable stability ($\log \beta_{11}[K\ \mathbf{5}]^+ = 2.69$). Like ligand **3**, **5** seems less adapted to the inclusion of lithium compared to **1** and **6**. On the other hand, the 1 : 2 complex is more stable ($\log K_{12}[Li\ \mathbf{5}_2] = 4.12$) than the ML complex ($\log K_{11}[Li\ \mathbf{5}]^+ = 3.76$), thus showing a positive cooperative effect.

Ligand **7**, which combines two ester and two glycol functions in distal position, behaves differently to **2**. Unlike **2**, ligand **7** forms stable 1 : 1 complexes with all alkali metal cations, accompanied in the case of Li^+ and Na^+ by 1 : 2 complexes. The selectivity profile is also similar, as the stability of the 1 : 1 complexes decreases from Li^+ to Rb^+ and increases for Cs^+. The stability constants of the mononuclear complexes are the highest for all the ligands studied (*e.g.* $\log \beta_{11}[Li\ \mathbf{7}]^+ = 5.99$). The 1 : 2 species are also more stable with Li^+ than with Na^+: $\log K_{12}[Na\ \mathbf{7}_2]^+ = 3.89$ and $\log K_{12}[Li\ \mathbf{7}_2]^+ = 4.73$, with a selectivity $S_{Li/Na} = 10$. It can also be noted that the formation of the 1 : 2 species is less favoured than the formation of 1 : 1 species, as the $[Li\mathbf{7}_2]^+$ complex seems to be about 18 times less stable than $[Li\ \mathbf{7}]^+$.

[2 + 2′] ethyl ester-benzyl derivative **4** formed only 1 : 1 species from Li^+ to Rb^+. The stabilities are lower than that of the corresponding complexes with **7**, Cs^+ being even not complexed. The absence of 1 : 2 complexes can also be noticed, and contrary to ligand **7** which prefers Li^+, **4** is selective for Na^+.

In conclusion, the presence of ester groups adjacent to glycol ones, improve the complexation of lithium, sodium and potassium by a factor of 10 with respect to the methoxy groups. Methoxy groups improve, at their turn, the complexation of these alkali cations by a factor of 10 to 100 with respect to benzyl groups. Generally, benzyl groups weaken the efficiency of calixarene derivatives as already observed for **4** and **7**.

Alkaline earth metal cations. The comparison of the results obtained within **1**, **3** and **6** showed that, in the presence of four methoxy groups (as in **1**), all alkaline earth cations are similarly complexed ($\log \beta_{11}$ around 3). Mg^{2+} and Ca^{2+} are weakly complexed compared to Li^+ and Na^+, of, respectively, the same radii. On the contrary, the larger cations Sr^{2+} and Ba^{2+} are strongly complexed whereas Rb^+ and Cs^+ are not. When two methoxy groups are replaced by glycolic chains (as in **6**), only Ca^{2+} and Sr^{2+} are complexed, forming mononuclear species with comparable stabilities (3.2 log units). However, the substitution of two methoxy by two benzyl groups (as in **3**) leads to a ligand unable to complex these cations.

Ligand **2** forms 1 : 1 species with a particular affinity for Ba^{2+} ($\log \beta_{11} = 5.09$). Both ligands **5** and **6**, where two glycol groups have been replaced by benzyl and methyl groups, respectively, complex Ca^{2+} and Sr^{2+}, forming 1 : 1 species. A 1 : 1 species is also formed with **5** and Ba^{2+} ($\log \beta_{11} = 3.11$). The presence of ester and glycol groups in **7** gives rise to the formation of 1 : 1 complexes with all the cations of the series and of an additional 1 : 2 species with Ca^{2+}. As **2**, ligand **7** is selective for Ba^{2+}.

The formation of 1 : 2 species with **7** and Ca^{2+} is not surprising, as this type of complex has already been observed for the same ligand with Li^+ and Na^+. This complex is 10 times less stable than the corresponding ML species: $\log K_{11}[Ca\ \mathbf{7}]^{2+} = 4.63$ and $\log K_{12}[Ca\ \mathbf{7}_2]^{2+}) = 3.44$. The stability constants of the mononuclear complex with ligand **4** show a selectivity about 10 for Ca^{2+} with respect to Sr^{2+} and Ba^{2+}.

Thermodynamic parameters of the complexation of alkali cations with ligands 2, 5 and 7

Overall enthalpy and entropy of complexation of alkali cations with ligands **2**, **5** and **7** are grouped in Table 3. The corresponding energy diagrams are presented in Fig. 2–4.

The stability of the 1 : 1 complexes of K^+ and Rb^+ with ligand **2** is enthalpy controlled since $-\Delta_c H^\circ_{11} > T\Delta_c S_{11}$ (Fig.2). The enthalpy and entropy terms corresponding to both complexes are comparable. The formation of 1 : 2 complex with Na^+ is characterized by a very negative and favourable enthalpy term overcoming a much smaller though still favourable entropy term. With Li^+, the enthalpy is still favourable but lower than with Na^+ and compensated by a larger entropy term.

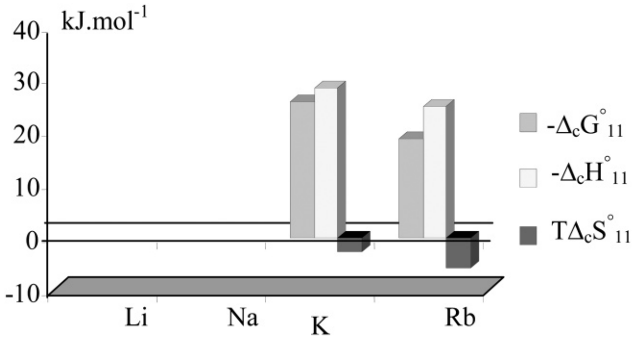


Fig. 2 Energy diagrams for the 1 : 1 complexes of alkali metal cations with ligand **2** in acetonitrile.

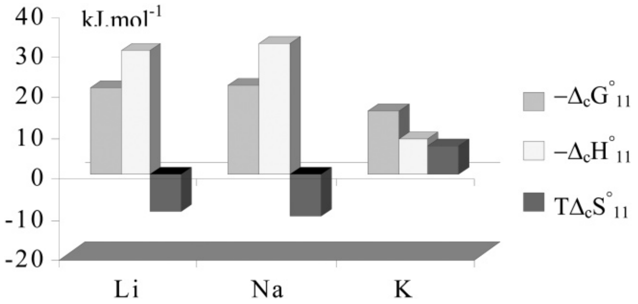


Fig. 3 Energy diagrams for the 1 : 1 complexes of alkali metal cations with ligand **5** in acetonitrile.

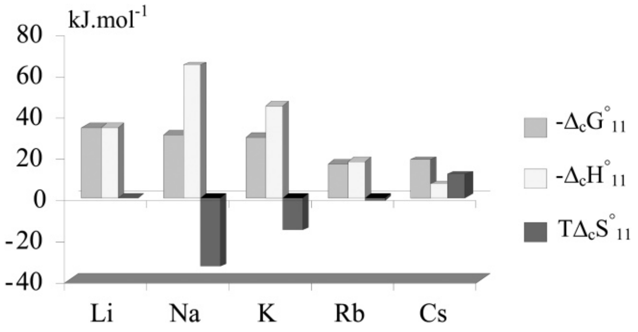


Fig. 4 Energy diagrams for the 1 : 1 complexes of alkali metal cations with ligand **7** in acetonitrile.

The formation of 1 : 1 complexes with **5** gives rise to highly positive $-\Delta_cH^\circ_{11}$ terms of 30.5 and 32.1 kJ mol^{-1}, respectively for Li$^+$ and Na$^+$ (Fig. 3). The corresponding entropy terms, $T\Delta_cS^\circ_{11}$, are negative indicating a purely enthalpy controlled stabilization of these complexes. For K$^+$, the $-\Delta_cH^\circ_{11}$ value is only 8.4 kJ mol^{-1} and even if the entropy term becomes positive the enthalpy still governs the stabilization. Regarding the 1 : 2 complex of Li$^+$, its formation is entirely due to a favourable entropy term ($T\Delta_cS^\circ_2$ = 34 kJ mol^{-1}), the stepwise value of the enthalpy being positive and unfavourable ($-\Delta_cH^\circ_2 = -10.5$ kJ mol^{-1}).

Apart from Cs$^+$, the stability of the 1 : 1 complexes formed with alkali cations and the [2 + 2′] mixed glycol–ethyl ester **7** is purely enthalpy driven with very favourable values of $-\Delta_cH^\circ_{11}$ (Fig. 4). $T\Delta_cS^\circ_{11}$ values are negative or close to 0 ($0 \leq T\Delta_cS^\circ_{11} \leq -33$ kJ mol^{-1}), and hence unfavorable. With Cs$^+$, both enthalpy and entropy terms are small but favourable (−6.7 and 11.4 kJ mol^{-1}, respectively). It is interesting to note that the enthalpy changes increase from Li$^+$ to Na$^+$ and then decreases from Na$^+$ to Cs$^+$, whereas the entropy term varies in the opposite, showing good compensation between both terms. The comparison between 1 : 2 species of Li$^+$ and Na$^+$ shows that their stability is entropy controlled, the enthalpy term being either unfavourable or very low ($-\Delta_cH^\circ_2 = -14.8$ and 1.7 kJ mol^{-1}, respectively). The higher stability of [Li $\mathbf{7}_2$]$^+$ compared to [Na $\mathbf{7}_2$]$^+$ is due to a more favourable entropy term (40 instead of 20 kJ mol^{-1}).

We will attempt to discuss the origin of enthalpy and entropy complexation in term of solvation effects, cation nature and ligand binding sites properties, with reference to previous work.[27,28]

Positive and hence favourable $-\Delta_cH^\circ$ contributions are observed in most of the systems involving **2**, **5** and **7**. They result from strong interactions between the donor sites present on these ligands (ether, benzyl, ester groups) and the cations and by the low solvation of these groups in acetonitrile. The variations of these terms in the alkali metal cation series indicate a decrease from Li$^+$ to Na$^+$ and then an increase, resulting from the simultaneous operation of different antagonistic effects, *i.e.* the variation of the cation size, solvation and electronic density in the series. Solvation effects govern the complexation of the smaller cations, whereas the electronic density is mostly responsible for the stabilization of the larger cation complexes.

The entropy changes, negative in most cases, are less favourable. This can be related to the combined effects of the solvation of the different entities (cation, ligand and complex) and the loss of conformational freedom of the ligand upon complexation.

For ligands **5** and **7** their trend of entropy changes in the series is a decrease from Li$^+$ to Na$^+$ followed by an increase from Na$^+$. These variations may result from the antagonistic factors. Firstly, the cation may not be sufficiently shielded by the ligand as its size increases, and thus would still be in interaction with some solvent molecules, contributing to a decrease of the entropy terms. As the size of the cation increases it may also be that the complexes are in equilibrium with many conformers as suggested by previous modelling studies,[28] thus contributing to an increase of freedom of the system, leading to an increase of the $T\Delta_cS^\circ_{11}$ values.

With ligand **2**, the entropy terms decrease as the size of the cation increases ($\Delta_cS^\circ_{11} = -8.7$ J K^{-1} mol^{-1} and $\Delta_cS^\circ_{11} = -19.6$ J K^{-1} mol^{-1} for K$^+$ and Rb$^+$, respectively) suggesting the predominance of the solvation factor. Considering this latter suggestion and the proximity of the $-\Delta_cH^\circ_{11}$ values, the decrease of the stability of these complexes, along the series, can be related to solvation effects.

Regarding the formation of the 1 : 2 complexes from the 1 : 1 complexes with Li$^+$ and the two ligands **5** and **7**, the entropy changes are much more favourable than the enthalpy ones ($-\Delta_cH^\circ_2 = -10.5$ and -14.8 kJ mol^{-1}, respectively, and $T\Delta_cS^\circ_2$ = 34 and 42 kJ mol^{-1}, respectively). The same observation is made with Na$^+$ and **7**. These results indicate that the second ligand is interacting less with the metal ion than the first one certainly for steric reasons. However, it is expected that the species involved in the complexation process have to be desolvated more strongly to allow higher coordination numbers to be reached.

The replacement of two glycol units of **2** by two ethyl esters (ligand **7**), leads to higher $-\Delta_cH^\circ_{11}$ and to lower $T\Delta_cS^\circ_{11}$ values in the case of the K$^+$ complex, and a reverse situation in the Rb$^+$ case. Similarly the replacement of two benzyl units of **5** by two ethyl esters shows a more favorable enthalpy terms for **7** with Li$^+$, Na$^+$ and K$^+$ and more negative entropy terms for **7** than for **5** except for Li$^+$. From this observation we can conclude that the high binding energy of Li$^+$, Na$^+$ and K$^+$ with ethyl esters (basic character) is responsible of highest stability of complexes formed with ligand **7**.

Conclusion

The complexation of alkali and alkaline earth metal ions by calixarenes **1**–**7** has been followed by UV absorption spectrophotometry. The results show that (i) the stoichiometry of formed complexes varies with the nature of the cations, alkali or alkaline earth; (ii) the ligands bearing glycol groups are likely to form 1 : 2 complexes with Li$^+$, Na$^+$ and Ca^{2+} cations, accompanied in some cases by 1 : 1 complexes; (iii) size effect is not the only factor of the complex stability; the density charge of cations and their solvation seems to be other important factors of the complexation, as well as the number and nature of donor sites; (iv) the most important selectivities are those of the tetramethoxy **1** and the mixed [2 + 2′] methoxy–benzyl derivative **3** for Li^+ and Na^+ with respect to all studied cations.

The calorimetric study of the complexation of alkali cations by ligands **2**, **5** and **7** confirms the stoichiometry of the complexes obtained from spectrophotometric measurements. The determined $\Delta_c H°_{xy}$ and $\Delta_c S°_{xy}$ terms, suggest that the formation of the 1 : 1 species is generally enthalpy controlled, whereas the stability of the 1 : 2 species is entropy controlled.

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