Binding properties of *p-tert*-butyldihomooxacalix[4]arene tetra(2-pyridylmethoxy) derivative towards alkali, alkaline earth, transition and heavy metal cations

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The binding properties of tetra(2-pyridylmethoxy) (**2**) derived from *p-tert*-butyldihomooxacalix[4]arene, in the cone conformation, towards alkali, alkaline earth, transition (Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) and heavy (Ag^{+}, Cd^{2+}, Hg^{2+} and Pb^{2+}) metal cations have been assessed by extraction studies of metal picrates from water into dichloromethane and stability constant measurements in methanol and acetonitrile. Results concerning the calorimetric study of K^{+}, Ba^{2+}, Cu^{2+} and Ag^{+} complexes in acetonitrile are presented. The affinity of **2** for some cations (K^{+}, Ag^{+}, Zn^{2+}, Hg^{2+} and Pb^{2+}) has also been investigated by proton NMR spectrometry. The analogous derivative (**3**) of *p-tert*-butylcalix[4]arene was also studied, and the results of both compounds are compared. Towards the hard alkali and alkaline earth metal cations ligands **2** and **3** display a low efficiency of extraction. The complexation levels are also low in methanol becoming, however, much higher in acetonitrile. The highest stability is found for Ca^{2+} with ligand **2** in this solvent. Both ligands show a very high affinity for the soft heavy metal ions with preference for Ag^{+}, but other ions such as Hg^{2+}, Pb^{2+} and Cu^{2+} are also well bound. Proton NMR titrations confirm the formation of 1 : 1 complexes between **2** and all the cations studied, also indicating that they should be located inside the cavity defined by the phenoxy oxygen and the pyridyl nitrogen atoms.

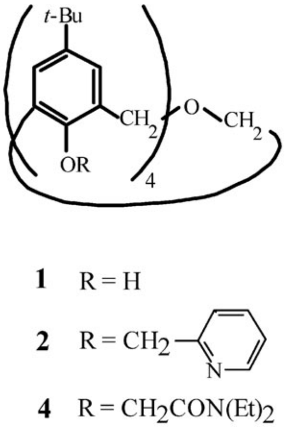
Introduction

The increasing interest of calixarenes[1–3] in the field of host–guest and supramolecular chemistry is well known. This is due to their extreme versatility to bind and transport selectively ions and neutral molecules, and also to their use as building blocks for the design of more sophisticated host molecules.

The ability of carbonyl containing substituents on the lower rim of calixarenes to bind metal ions, predominantly alkali and alkaline earth cations, has been largely studied.[4] The introduction of suitable binding groups with softer donor atoms than oxygen, such as nitrogen,[5] favours complexation of transition and heavy metal cations. This is of current interest owing to the harmful impact that some of these cations (such as cadmium, mercury and lead), due to their toxicity, can produce on environmental quality and consequently on human health.

In particular, the functionalisation of calix[*n*]arenes with 2-pyridylmethyl pendant groups at the lower rim has been performed.[6] Thus, pyridino-calix[4]-,[7–12] -[5]-,[13] -[6]-[14–16] and -[8]arene[16] derivatives, as well as, pyridino-homo-[17,18] and -homooxacalixarene[19,20] derivatives have been obtained.

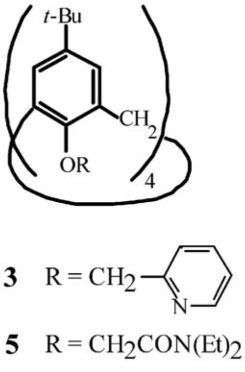
Dihomooxacalix[4]arenes are compounds closely related to calix[4]arenes, differing by two more atoms (oxygen and carbon) in the macrocycle ring. Thus, they are more flexible molecules than calix[4]arenes, but still possess a cone conformation. In the course of the studies of binding and transport properties of dihomooxacalix[4]arenes bearing carbonyl groups at the lower rim[21–24] towards alkali, alkaline earth, transition and heavy metal cations, we have extended our research into the interaction of dihomooxa derivatives containing softer donor atoms, such as nitrogen, with the previous cations. We synthesised the tetra(2-pyridylmethoxy) derivative **2**[20] from *p-tert*-butyldihomooxacalix[4]arene (**1**), in the cone conformation.



1 R = H

2 R = CH_2–

4 R = $CH_2CON(Et)_2$



3 R = CH_2–

5 R = $CH_2CON(Et)_2$

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This paper reports the binding properties of ligand **2** towards alkali, alkaline earth, transition (Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) and heavy (Ag^{+}, Cd^{2+}, Hg^{2+} and Pb^{2+}) metal cations. These properties have been established by extraction studies of metal picrates from an aqueous solution into dichloromethane and stability constant measurements in methanol and acetonitrile based on UV absorption spectrophotometry. For some cases, the thermodynamic parameters of complexation have been determined by microcalorimetric studies. The affinity of ligand **2** for some cations has also been investigated by proton NMR titration experiments. The tetra(2-pyridylmethoxy) derivative of *p*-*tert*-butylcalix[4]arene (**3**) is also studied in this work and the results of both derivatives are compared. The data are discussed in the light of those obtained with other dihomooxacalix[4]arene derivatives, namely those containing the carbonyl group at the lower rim.

Results and discussion

Extraction studies

The results of phase transfer of alkali, alkaline earth, transition and heavy metal cations were obtained by the standard picrate method.[25] These data, expressed as a percentage of cation extracted (%*E*), for the tetrapyridyl derivatives **2** and **3** are reported in Tables 1 and 2.

The results obtained with derivative **2** range from 5 to 17% for the alkali cations and are less than 10% for all the alkaline earth cations. These percentages are slightly higher than those of derivative **3** for both types of cations. However, **2** due to its larger cavity size compared to that of **3**, shows some preference for K^{+}, while **3** exhibits preference for Na^{+}. This is the usual behaviour of these derivatives (dihomooxacalix[4]arenes and calix[4]arenes) towards this type of cation. If we compare ligand **2** with dihomooxacalix[4]arenes containing carbonyl groups at the lower rim (namely ketone[21] and amide[22] derivatives), we observe that **2** displays a low efficiency of extraction, which can be attributed to the nature of its donor atoms. The majority of the alkali and alkaline earth cations, being hard Lewis acids,[26] prefer to associate with hard donor atoms, such as oxygen. Thus, the softer character of the nitrogen donor atoms may account for these differences. The extraction of alkali metal cations by ligand **3** had already been carried out.[10] Although those values are slightly lower than those determined in this work, both follow the same selectivity order ($Na^{+} > K^{+} > Rb^{+} > Cs^{+} > Li^{+}$).

For the transition cations, Lewis acids of intermediate nature (except for Mn^{2+}, that is considered hard),[26] the percentages of extraction are also low, except in the cases of Fe^{2+} and Cu^{2+} (29 and 18%, respectively, for **2**). Again, these percentages are higher than those of derivative **3**, with the exception of Fe^{2+}, whose value is the same with both derivatives.

Both ligands show very high extraction levels for the soft heavy metal cations (except for Cd^{2+}). They exhibit a strong preference for Ag^{+} (90%) and Hg^{2+} (72%). Towards Pb^{2+}, of intermediate nature,[26] ligand **2** is much more efficient (40%) than ligand **3** (17%), although **3** shows a higher Ag^{+}/Pb^{2+} selectivity (S = 2.3 and 5.4, respectively) but a lower Pb^{2+}/Zn^{2+} selectivity (S = 4.4 and 3.5, respectively). As it was expected for this type of cation, the extraction levels exhibited by the tetrapyridyl derivatives **2** and **3** are higher than those obtained with carbonyl containing ligands,[23] though tetra(diethyl)amide derivatives[22] are still better phase transfer agents.

Complexation studies

UV absorption spectrophotometric titrations of both dihomooxa tetrapyridyl derivative **2** and its calix[4]arene homologue **3** against alkali, alkaline earth, transition and heavy metal ions in methanol and acetonitrile were performed and could be interpreted by the formation of 1 : 1 complexes. The logarithms of their stability constants are collected in Tables 1 and 2. Table 3 summarizes the thermodynamic parameters determined by microcalorimetry for the complexation of K^{+}, Ba^{2+}, Cu^{2+} and Ag^{+} with both ligands in acetonitrile.

Alkali and alkaline earth metal ions. Complexation results confirm the rather low affinity of ligand **2** for the hard alkali metal ions already observed in extraction. No significant complexation extent of these cations could be detected in methanol ($\log\beta \leq 2$). Even in acetonitrile, a less solvating solvent in which the stability constants are expected to be higher,[27] they could be determined only with the first three cations of the series, ranging from 3.4 to 3.9 log units. Only the stability constants of Na^{+} and K^{+} complexes with ligand **3** were determined in methanol, and the values obtained are close to three log units. In acetonitrile, the stability constants

Table 1 Percentage extraction (%*E*)[a] and stability constants ($\log\beta$)[b] of alkali and alkaline earth metal complexes in methanol and acetonitrile at 25 °C

		Li^{+}	Na^{+}	K^{+}	Rb^{+}	Cs^{+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
Ligand	Ionic radius[c]/Å	0.78	0.98	1.33	1.49	1.65	0.78	1.06	1.27	1.43
2	%*E*	4.9	13.1	17	12.5	12.5	1.2	8.2	5.1	7.4
	$\log\beta$ (MeOH)	≤2	≤2	≤2	≤2	≤2	2.66 ± 0.04	2.60 ± 0.07	3.0 ± 0.3	3.2 ± 0.3
	$\log\beta$ (MeCN)	3.37 ± 0.01	3.9 ± 0.1	3.87 ± 0.08	≤2	≤2	4.71 ± 0.04	≥ 7	6.29 ± 0.06	5.9 ± 0.3
3	%*E*	3.7	13.3	11.2	10.3	9.8	0.3	7.9	2.7	5.2
	$\log\beta$ (MeOH)	—	2.98 ± 0.03	3.11 ± 0.02	—	—	—	2.89 ± 0.06	3.0 ± 0.3	—
	$\log\beta$ (MeCN)	5.95[d]	6.0 ± 0.1	3.22 ± 0.01	2.48[d]	—	—	5.6 ± 0.2	4.67 ± 0.01	4.4 ± 0.1

[a] Metal picrates from H_2O into CH_2Cl_2; values with uncertainties less than 5%. [b] Standard deviation σ_{n-1} on the mean of several experiments. [c] V. M. Goldschmidt, *Skrifter Norske Videnskaps-Akad. Oslo, I*, Mat.-Naturv, K1, 1926; data quoted in I. Marcus, *Ion Properties*, Marcel Dekker, New York, 1997, pp. 46–47. [d] Data taken from ref. 8.

Table 2 Percentage extraction (%E)[a] and stability constants ($\log\beta$)[b] of transition and heavy metal complexes in methanol and acetonitrile at 25 °C

Ligand		Mn^{2+}	Fe^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Ag^{+}	Cd^{2+}	Hg^{2+}	Pb^{2+}
	Ionic radius[c]/Å	0.83	0.78	0.75	0.69	0.73	0.75	1.15	0.95	1.02	1.18
2	%E	6.8	29	5.1	7.1	18	9.0	90	5.4	72	40
	$\log\beta$ (MeOH)	3.63 ± 0.05	—	3.1 ± 0.1	3.8 ± 0.2	4.0 ± 0.2	2.2 ± 0.2	4.7 ± 0.2	3.2 ± 0.2	3.17 ± 0.05	4.12 ± 0.06
	$\log\beta$ (MeCN)	4.83 ± 0.05	—	5.3 ± 0.3	4.9 ± 0.2	3.53 ± 0.05	4.57 ± 0.03	4.79 ± 0.05	5.7 ± 0.1	3.9 ± 0.3	5.3 ± 0.2
3	%E	4.1	29	1.4	1.8	12.9	4.8	91	1.5	73	17
	$\log\beta$ (MeOH)	2.98 ± 0.07	—	2.9 ± 0.3	3.1 ± 0.2	2.8 ± 0.1	2.6 ± 0.1	4.66 ± 0.06	3.01 ± 0.03	3.33 ± 0.05	3.5 ± 0.1
	$\log\beta$ (MeCN)	4.5 ± 0.1	—	5.05 ± 0.03	4.41 ± 0.05	5.6 ± 0.1	5.89 ± 0.02	4.91 ± 0.03	6.0 ± 0.1	6.04 ± 0.06	6.5 ± 0.3

[a] Metal picrates from H_2O into CH_2Cl_2; values with uncertainties less than 5%. [b] Standard deviation σ_{n-1} on the mean of several experiments. [c] R. D. Shannon and C. T. Prewitt, *Acta Crystallogr., Sect. B* 1969, **25**, 925; 1970, **26**, 1046; data quoted in I. Marcus, *Ion Properties*, Marcel Dekker, New York, 1997, pp. 46–47.

of the alkali metal complexes were already published.[8] They were obtained by techniques other than the one used in this work, namely microcalorimetry ($\log\beta = 5.36$ and 3.10 for Na^+ and K^+, respectively) and competitive potentiometry ($\log\beta = 5.61$ and 3.17 for Na^+ and K^+, respectively). Our values for sodium and potassium complexes derived from spectrophotometric determinations (Table 1) are quite consistent with these previous data. Thus, ligand **3** forms more stable metal complexes than does dihomooxa ligand **2** in both solvents, except for K^+ cation in acetonitrile, whose value is slightly higher ($\log\beta = 3.87$).

Complexation level of alkaline earth metal ions is higher than the one observed with the alkali cations. In methanol, the stability constants of the complexes with ligand **2** are spread in a small range between 2.60 log units for Ca^{2+} and 3.2 log units for Ba^{2+}. Therefore, no significant selectivity is observed. Nevertheless, in acetonitrile the stability constants are much higher and the selectivity is clearly in favour of calcium ($\log\beta > 7$). In the case of ligand **3**, the stability constants of the calcium and strontium complexes have been evaluated in both solvents. The stability of the barium complex has also been determined in acetonitrile. These complexes are less stable than their homologues with dihomooxa derivative **2** (*e.g.* $\Delta\log\beta = 1.5$ for Ba^{2+} complex in acetonitrile), but it can be noted that the presence of a –CH_2O– group in **2** increases the complexation level without inducing changes in the selectivity profile. Thus, Ca^{2+} is the best complexed cation with both ligands, followed by Sr^{2+} and Ba^{2+}.

The comparison with derivatives bearing hard carbonyl groups shows that the presence of softer pyridyl donor sites in ligands **2** and **3** contributes drastically to decrease their affinity for these cations. For example, the stability constants of the Na^+ and Ca^{2+} complexes in methanol decrease from 7.23 to ≤2 log units and from 5.0 to 2.60 log units, respectively, on going from dihomooxa diethylamide derivative (**4**)[22] to ligand **2**. A similar behaviour is observed with ligand **3** relative to calix[4]arene diethylamide derivative (**5**).[28]

Transition and heavy metal ions. Complexation data for transition metal ions are reported in Table 2. At first we can see that the behaviour of both ligands **2** and **3** is solvent dependent. In methanol, the stability of the complexes with dihomooxa derivative **2** follows the sequence: $Zn^{2+} \ll Co^{2+} < Mn^{2+} < Ni^{2+} < Cu^{2+}$, which is more or less in agreement with the Irving Williams rule.[29] The stability constants range from 2.2 to 4.0 log units for Zn^{2+} and Cu^{2+} complexes, respectively. These values are higher than those obtained with ligand **3**, except in the case of Zn^{2+}. All the complexes with **3** have about the same stability (close to an average value of 3.0 log units). Thus, although dihomooxa derivative **2** has a larger cavity size and greater flexibility compared to those of **3**, it seems that the presence of the oxygen bridge in **2** confers it some selectivity. For instance, the Cu^{2+} complex is 63 times more stable than its Zn^{2+} homologue. In acetonitrile, the stability constants for the complexes with ligands **2** and **3** are globally higher than in methanol, in agreement with the

Table 3 Thermodynamic parameters of complexation of some metal ions with ligands **2** and **3** in acetonitrile at 25 °C

Ligand		K^+	Ba^{2+}	Cu^{2+}	Ag^+
2	$\log\beta$	3.85 ± 0.02 (3.87)[a]	(5.9 ± 0.3)[a]	3.69 ± 0.02 (3.53)[a]	(4.79 ± 0.05)[a]
	$-\Delta G$/kJ mol^{-1}	21.9 ± 0.1	34 ± 2	21.04 ± 0.06	27.3 ± 0.3
	$-\Delta H$/kJ mol^{-1}	10.1 ± 0.3	30 ± 1	152.9 ± 0.6	23 ± 1
	$T\Delta S$/kJ mol^{-1}	11.8 ± 0.4	4 ± 3	−131.9 ± 0.7	4 ± 1
	ΔS/J K^{-1} mol^{-1}	40 ± 1	12 ± 10	−443 ± 2	14 ± 4
3	$\log\beta$	3.01 (3.22)[a]	4.1 ± 0.1	(5.6 ± 0.1)[a]	(4.91 ± 0.03)[a]
	$-\Delta G$/kJ mol^{-1}	17.7 ± 0.4 (17.90)[b]	23.4 ± 0.6	31.92 ± 0.02	28.0 ± 0.2 (29.06)[c]
	$-\Delta H$/kJ mol^{-1}	18.11[d] (18.47)[b]	34.5 ± 0.1	—[e]	19.2 ± 0.8 (19.04)[c]
	$T\Delta S$/kJ mol^{-1}	−0.38	−11.1 ± 0.7	—	8.8 ± 1.0
	ΔS/J K^{-1} mol^{-1}	−1.3 (−1.9)[b]	−37 ± 2	—	29 ± 4 (33.6)[c]

[a] Spectrophotometric result. [b] Data taken from ref. 8. [c] Data taken from ref. 9. [d] Single experiment. [e] Not interpretable thermograms.

respective donor numbers of the solvents.[27] Dihomooxa derivative **2** forms more stable complexes than its calix[4]arene homologue **3**, except with Cu^{2+} and Zn^{2+}. For instance, the **3**–Cu^{2+} complex is almost 120 times more stable than **2**–Cu^{2+} complex. The more symmetrical ligand **3** may be more adapted to the geometrical requirements of Cu^{2+} cation in this solvent.

Soft heavy metal ions are well complexed by ligand **2** in both solvents and the stability constants are close to those found for the complexes with ligand **3** (Table 2). For instance, with dihomooxa derivative **2** $\log \beta$ values range between 3.2 with Hg^{2+} and 4.7 with Ag^{+}, in methanol. They are slightly higher in acetonitrile, ranging from 3.9 to 5.7 log units for Hg^{2+} and Cd^{2+}, respectively. It can be pointed out that the stability constant of the **3**–Ag^{+} complex in acetonitrile was determined previously by calorimetry ($\log \beta = 5.00$) and potentiometry ($\log \beta = 5.18$) and that our value obtained from spectrophotometry is in perfect agreement with these values.[9]

As a consequence of the change in the stability order with the solvent, the selectivity of the ligands may be inverted on going from methanol to acetonitrile. For instance, **2** is selective for Ag^{+} over Cd^{2+} in methanol ($S = \beta_{Ag^{+}}/\beta_{Cd^{2+}} = 32$), whereas it is selective for Cd^{2+} in acetonitrile ($S = \beta_{Cd^{2+}}/\beta_{Ag^{+}} = 8$).

In general, ligands **2** and **3** also form less stable complexes with these cations than do the corresponding diethylamide derivatives **4**[22] and **5**.[4b] For example, the stability in methanol increases by 2.3 and 2.5 log units for Cd^{2+} and Ag^{+}, respectively, on moving from ligand **2** to **4** and by 3.7 and 5.5 log units for Cu^{2+} and Cd^{2+}, respectively, on moving from ligand **3** to **5**. Apparently, the complexation with these softer cations is not favoured despite the presence of softer donor atoms in these ligands.

Calorimetric studies. Complexation of one cation of each series (K^{+}, Ba^{2+}, Cu^{2+} and Ag^{+}) with dihomooxa derivative **2** has been followed by microcalorimetric titrations. This technique allows the determination of ΔH, the enthalpy of complexation, and the calculation of ΔS, the corresponding entropy of complexation knowing ΔG, the free energy of complexation. These data are given in Table 3 together with the corresponding values for ligand **3**. Our results for K^{+} and Ag^{+} with the latter ligand are in full agreement with the values determined previously by other authors.[8,9]

The stability constant of the potassium complex with dihomooxa ligand **2** derived from the microcalorimetric measurements is in full agreement with the value obtained from spectrophotometry. The results show that the enthalpy and the entropy of complexation are responsible for the stabilisation of this complex, both contributions being of the same order of magnitude. As compared to the corresponding calix[4]arene **3**, the enthalpy term is less favourable ($-\Delta H = 10.1$ instead of 18.11 kJ mol^{-1} with **3**). However, the more favourable entropy ($T\Delta S = 11.8$ kJ mol^{-1} instead of close to zero with **3**) suggests that ligand **2** keeps part of its freedom even when complexed in contrast to ligand **3**, which is more ordered upon complexation.

The stabilisation of the divalent barium complex with **2** is clearly enthalpically driven. This term is higher than that for K^{+} or even for Ag^{+}. It is also less negative than the enthalpy change for ligand **3**. The entropy change is slightly positive, whereas it is clearly negative with **3**. As in the case of K^{+} discussed above, these parameters indicate the higher flexibility of dihomooxa ligand **2** compared to that of calix[4]arene ligand **3**.

The complexation process of Ag^{+} with dihomooxa derivative **2** is also enthalpically controlled. The entropy is still favourable but much lower. The enthalpy term is more than twice that for K^{+} complex. It is well known that silver strongly interacts with acetonitrile and the corresponding energy should be paid prior to complexation, resulting in a decrease in the enthalpy term. The reverse situation is observed which can be interpreted by the strength of the interaction between the soft silver ion and the nitrogen atoms of the ligand. The lower entropy change relative to K^{+}, may be interpreted by the fact that silver ion may still keep part of its solvation shell in the complex. In the case of ligand **3**, this would not be possible because of its smaller size and this would explain the more favourable entropy and the less favourable enthalpy terms, as a consequence to the desolvation of the cation before entering the hydrophilic cavity of the ligand.[9]

The case of the divalent copper cation is quite different. The formation of its complex with **2** is characterized by a very high and favourable $-\Delta H$ contribution, overcoming the strongly negative and unfavourable entropy change. Such high enthalpy values have already been found with related derivatives and transition metal cations.[30] This shows that the strong interaction between Cu^{2+} and the binding sites of the ligand is compensated by an important loss of freedom of the ligand, which must conform to the coordination requirements of this cation. No comparison can be made with the related calixarene **3**, as difficulties were encountered during the interpretation of the calorimetric titration curves.

Proton NMR studies

To obtain further information on the cation binding behaviour of tetrapyridyl derivative **2**, namely concerning the binding sites, proton NMR studies were performed. The cations studied were K^{+}, Zn^{2+}, Ag^{+}, Hg^{2+} and Pb^{2+}. Variable amounts of the salts were added to **2** and the proton spectra recorded after each addition.

Two different situations were found after the addition of the salts to ligand **2**. Titrations of tetrapyridyl **2** with K^{+}, Zn^{2+}, Ag^{+} and Hg^{2+} salts initially induce broadening of the signals until the [salt]/[ligand] ratio reaches the unity value, when the signals become sharp. This indicates a fast exchange rate between the two species on the NMR time scale, at room temperature. In the case of K^{+} and Zn^{2+}, that observation also indicates a weak affinity of ligand **2** towards these cations, which is in agreement with the extraction and stability constant results. The kinetic stability of Ag^{+} and Hg^{2+} complexes is also low, although they show higher stability constant values. The ^{1}H NMR titration experiments suggest a 1 : 1 metal-to-ligand stoichiometry, since all signals remain unchanged after subsequent additions of the salts. In contrast, the titration of **2** with Pb^{2+} cation shows that with [salt]/[ligand] ratios lower than 1 both signals of the complexed and uncomplexed ligand are present in the spectra, indicating that on the NMR time scale the exchange rate between the two species is slow, at room temperature. Upon reaching a 1 : 1 ratio, all signals for the free ligand disappear and those of the complexed ligand remain

Table 4 Proton chemical shifts (δ, ppm) of ligand **2** and its 1 : 1 metal complexes

		ArCH$_2$Ar		CH$_2$OCH$_2$				PyH							
	t-Bu	eq	ax	eq	ax	OCH$_2$Py	ArH	3′	4′	5′	6′	3	4	5	6
2	0.93, 1.25	3.17, 3.24	4.32, 4.43	4.63	4.75	4.48, 4.61, 4.83, 4.97	6.69, 7.05, 7.06, 7.14	6.93	7.40	7.05	8.44	7.52	7.40	7.12	8.50
2 + K$^+$	1.16, 1.21	3.27, 3.36	4.26, 4.23	3.72	4.32	4.71, 4.84, 4.97, 5.14	6.89, 7.24, 7.34, 7.37	7.08	7.64	7.22	8.38	7.18	7.76	7.41	8.65
2 + Ag$^+$	1.00, 1.17	3.01, 3.29	4.28, 4.33	4.16	4.61	4.91,[a] 4.96, 5.19	6.80, 6.86, 6.91, 7.03	7.07	7.57	7.30	8.53	7.54	7.81	7.51	8.91
2 + Zn^{2+}	1.00, 1.21	3.18, 3.07	3.90, 3.90	4.10	4.83	4.74, 4.97, 4.97, 5.20	6.79, 6.95, 7.07, 7.09	7.07	7.77	7.44	8.47	7.62	7.97	7.58	8.81
2 + Hg^{2+}	0.98, 1.24	3.10, 3.26	4.16, 4.16	[b]	4.26	4.79, 4.79, 4.90, 5.01	6.81, 6.89, 7.06, 7.15	7.30	7.82	7.43	8.48	7.82	8.01	7.65	8.71
2 + Pb^{2+}	1.14, 1.24	3.62, 3.64	4.11, 4.34	3.56	4.05	4.77, 4.89, 5.25, 5.81	6.85, 7.40, 7.44, 7.51	7.07	7.80	7.57	8.93	7.56	7.92	7.63	9.17

[a] Singlet corresponding to two protons. [b] Not possible to assign.

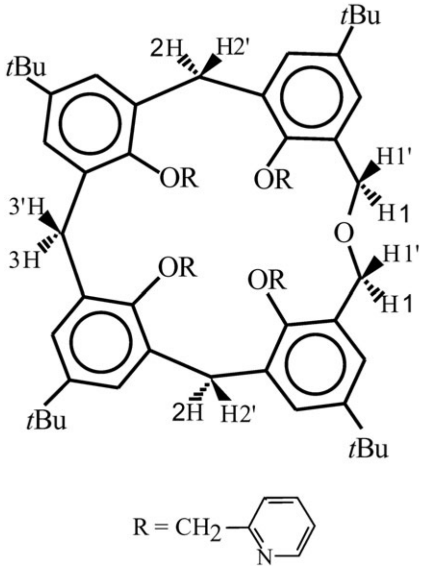
unaltered after subsequent additions of the salts, indicating a 1 : 1 metal-to-ligand stoichiometry, as well.

Proton NMR data of the free and complexed ligand **2** are collected in Table 4. Complexation of the five cations affects all the proton chemical shifts in the ligand. The largest downfield variations are observed for the heteroaromatic H4, H4′, H5, H5′, H6, H6′ and the methylene protons of the OCH$_2$Py groups, and the aromatic protons (mainly for Pb^{2+} and K$^+$). The oxygen bridge equatorial and axial methylene protons (CH$_2$OCH$_2$) and the bridging axial methylene protons (ArCH$_2$Ar) show the largest upfield shifts. Similar observations have been made for related pyridino-calixarenes,[8,10,17–19,30] as well as for other dihomooxa derivatives.[22,31]

A closer examination of the spectral changes upon complexation indicates very small variations ($\Delta\delta \approx 0.05$ ppm) for the *tert*-butyl groups. However, for K$^+$ and Pb^{2+} cations the upfield *tert*-butyl group experiences considerable downfield shift variations ($\Delta\delta = 0.23$ and 0.21 ppm, respectively). Thus, upon complexation the difference in the chemical shifts between the two *t*-Bu groups decreases significantly. Moreover, the difference in the chemical shifts between the axial and equatorial protons of the ArCH$_2$Ar bridges in ligand **2** ($\Delta\delta = 1.19$, 1.15 ppm) also decreases, being closer to 0.9 ppm [32] mainly for K$^+$ ($\Delta\delta = 0.87$, 0.99 ppm), suggesting that the ligand adopts a more symmetrical cone conformation upon complexation. In the cases of Pb^{2+} and Zn^{2+} the chemical shift separations are significantly lower than 0.9 ppm ($\Delta\delta = 0.70$, 0.49 and 0.83, 0.72 ppm, respectively), indicating that upon complexation with these cations the pendant arms of the ligand move closer together in a larger extent, resulting in a more flattened cone conformation.

A systematic observation of the data reveals that the axial methylene proton opposite to the bridging oxygen atom (H3, Scheme 1) exhibits larger upfield shifts than the ones displayed by the axial methylene proton H2, as observed by us before for other dihomooxa derivatives.[21,22,31] Complexation with Pb^{2+} shows an inverse situation. As observed for other calixarene derivatives, the variation in chemical shift experienced by the equatorial methylene protons (ArCH$_2$Ar) is downfield and smaller than that of the axial protons. Again, the exception is Pb^{2+} complexation that shows higher shift variations for the former proton ($\Delta\delta \approx 0.43$ and 0.15 ppm, respectively). The CH$_2$OCH$_2$ resonances behave differently, as reported before.[19,21–23,31] The axial and equatorial methylene protons of the oxygen bridge move upfield and the equatorial protons experience larger shift variations than the axial ones. In the case of the Zn^{2+} cation, the axial proton even shows a small downfield shift. The highest values, though with the less pronounced difference, were recorded for Pb^{2+} ($\Delta\delta = 1.07$ and 0.70 ppm, respectively). These results suggest that the oxygen bridge conformation changes significantly upon complexation, with the equatorial protons undergoing a higher shielding effect. Concerning the heteroaromatic protons, one of the groups exhibits slightly higher chemical shift variations. However, these differences are more pronounced between the 6-PyH and 6′-PyH protons. Complexation with Ag$^+$ shows the highest difference ($\Delta\delta = 0.41$ and 0.09 ppm, respectively), whereas complexation with Pb^{2+} displays large downfield shifts for both protons ($\Delta\delta = 0.67$ and 0.49 ppm, respectively).

The deshielding effect observed for the aromatic protons indicates the involvement of the phenolic oxygens in complexation, as reported previously.[33] Also the largest downfield shift changes shown by the methylene, H4, H4′, H5, H5′, H6 and H6′ protons of the OCH$_2$Py groups indicate an interaction of the cations with both, oxygen and nitrogen atoms of the pyridyl groups,[19] resulting in a deshielding effect on the protons adjacent to these donor atoms. Therefore, this suggests that all the cations must be inside the cavity defined by the phenoxy oxygens and the pyridyl pendant arms. The cations should be bound into that cavity composed by four



Scheme 1

oxygen and four nitrogen atoms through metal–oxygen and metal–nitrogen interactions, in a geometrical arrangement that should depend on the nature of the cations.

Ligand **2** displayed the highest chemical shift variations for the complexation with Pb^{2+}, and comparable spectral changes for the other cations ($Ag^+ \approx Hg^{2+} \approx K^+ \approx Zn^{2+}$). A similar observation has been reported by us before for a dipyridyl-dihomooxacalixcrown derivative.[31] This preference of ligand **2** seems to be the result of the combination of three main factors affecting complexation: charge, size and nature of the cations.

Conclusions

Extraction studies from an aqueous solution into CH_2Cl_2 and stability constant measurements in methanol and acetonitrile have shown that tetrapyridyl ligands **2** and **3** behave similarly, although **2** is a slightly better binder than **3**. Towards the hard alkali and alkaline earth metal ions both ligands are weak binders. However, in acetonitrile and for the alkaline earth cations, their stability constants are much higher and ligand **2** even shows a clear preference for Ca^{2+}. Towards transition and heavy metal cations **2** and **3** are strong binders, displaying a high affinity for the soft metal ions Ag^+ and Hg^{2+}, but also for some ions of intermediate nature as Pb^{2+} and Cu^{2+}. The softer character of the nitrogen donor atoms may explain this behaviour. The larger cavity size of dihomooxa ligand **2** compared to that of **3** does not change significantly the selectivity order relative to that of ligand **3**, making **2** even more selective. Both complexation processes of Ag^+ and Ba^{2+} cations with ligand **2** are enthalpically controlled, whereas the enthalpy and entropy terms are responsible for the stabilisation of the K^+ complex. In the particular case of Cu^{2+}, the complex stabilisation is due to a balance between the very high enthalpy and the strongly negative entropy terms. Proton NMR studies confirmed the formation of 1 : 1 complexes between tetrapyridyl **2** and all the cations, also suggesting that they should be encapsulated into the cavity composed by the phenoxy oxygen and the pyridyl nitrogen atoms.

Experimental

Extraction studies

Equal volumes (5 mL) of aqueous solutions of metal picrates (2.5×10^{-4} M) and solutions of the calixarenes (2.5×10^{-4} M) in CH_2Cl_2 were vigorously shaken for 2 min, and then thermostated in a water bath with mechanical stirring, at 25 °C overnight. After complete phase separation, the concentration of picrate ion in the aqueous phase was determined spectrophotometrically ($\lambda_{max} = 354$ nm). For each cation-calixarene system the absorbance measurements were repeated, at least, four times. Blank experiments showed negligible picrate extraction in the absence of a calixarene. The details of metal picrate preparation have already been described.[23,24]

Stability constant determination

The stability constants β defined as the concentration ratio $[ML^{n+}]/([M^{n+}][L])$ (where M^{n+} = cation and L = ligand) were determined in methanol (Carlo Erba, 99.9%, water content 0.1%) and acetonitrile (Riedel-deHaën, analytical reagent, water content <0.1%) used without further purification by UV absorption spectrophotometry, at 25 °C and constant ionic strength provided by 0.01 M Et_4NClO_4 (Fluka, purum), Et_4NCl (Fluka, purum) or Et_4NNO_3 (Acros) according to the procedure already described.[28] The spectra were recorded on a Shimadzu UV-2101-PC or a Perkin Elmer Lambda 11 spectrophotometer. The ligand concentrations were *ca.* 10^{-4} M and the spectra were treated by programs Letagrop[34] and/or Specfit.[35] The treatment of the same experiment by both programs led to similar values within the experimental error. By analogy to similar compounds,[36] ligands **2** and **3** were assumed to be fully unprotonated in methanol and under our experimental conditions.

The metal salts used were chlorides, perchlorates or nitrates according to their solubilities in the solvents used. The following salts were employed in methanol: LiCl, $ZnCl_2$, CsCl, $CoCl_2$, $CuCl_2$ and $Ni(NO_3)_2 \cdot 6H_2O$ (Fluka), NaCl, KCl, RbCl, $MgCl_2 \cdot 6H_2O$, $CaCl_2$, $SrCl_2 \cdot 6H_2O$, $BaCl_2$, $MnCl_2 \cdot 4H_2O$, $Cd(NO_3)_2 \cdot 4H_2O$ and $Pb(NO_3)_2$ (Merck, p.a.), $HgCl_2$ (Prolabo), $AgNO_3$ (Strem Chemicals). In acetonitrile the following perchlorates and nitrates were used: $LiClO_4$, $Ca(ClO_4)_2 \cdot 4H_2O$, $Co(ClO_4)_2 \cdot 6H_2O$, $Ni(ClO_4)_2 \cdot 6H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$ and $Hg(NO_3)_2$ (Fluka, purum), $KClO_4$ and $Ba(ClO_4)_2$ (Prolabo), $NaClO_4$ and $RbClO_4$ (Sigma), $CsClO_4$ and $Sr(ClO_4)_2 \cdot 6H_2O$ (Alfa Aesar), $Zn(ClO_4)_2 \cdot 6H_2O$ and $Pb(ClO_4)_2$ (Johnson Matthey Alfa Products), $AgNO_3$ (Strem Chemicals), $Mg(NO_3)_2 \cdot 6H_2O$, $Cd(NO_3)_2 \cdot 4H_2O$ and $Mn(NO_3)_2 \cdot 4H_2O$ (Merck). All these salts were dried under vacuum for at least 24 h before use. The concentrations of the stock solutions of the cations (except alkali cations and Ag^+) were standardized by complexometry using the appropriate coloured indicators.[37] The concentration of the Ag^+ solution was determined by potentiometry with addition of NaCl.

Calorimetric measurements

Microcalorimetric experiments were performed using the 2277 Thermal Activity Monitor Microcalorimeter (Thermometric). Titrations were carried out at 25 °C on 2.7 mL of *ca.* 10^{-4} M of the ligands in acetonitrile using a glass cell of 4 mL. The heats of formation of the complexes were measured after addition of 15×10 µL aliquots of 5.0×10^{-3}–1.5×10^{-2} M of $M(ClO_4)_n$ ($M^{n+} = K^+, Ba^{2+}, Cu^{2+}, Ag^+$) in the same solvent. Chemical calibration was made by determination of the complexation enthalpy of Ba^{2+} with 18C6 in water or of Rb^+ with 18C6 in methanol, as recommended.[38] In some cases, *e.g.* for K^+ complexes and for Ba^{2+} with **3**, the enthalpy of complexation and the stability constants were refined simultaneously from these data using the ligand binding analysis program DIGITAM version 4.1[39] and after correction for the heat of dilution of the metal salt determined in separate titrations without the ligands. The stability constant values thus obtained were in agreement with the values derived from spectrophotometric measurements when available. In the other cases, where the stability constants were high enough to consider the complexes totally formed after each addition of metal ion, *i.e.* for $\log\beta \geq 4.8$, the enthalpies of complexation were obtained from the slopes of the linear plots of the corrected cumulated heats exchanged against the number of moles of metal ions added until the 1 : 1 stoichiometry. The corresponding entropies of complexation were then calculated from the expression $\Delta G = \Delta H - T\Delta S$, knowing $\Delta G = -RT\ln\beta$ and β from spectrophotometry.

Proton NMR titration experiments

Several aliquots (up to 2–3 equiv.) of the salt solutions (0.5 M) in CD_3OD were added to $CDCl_3$ solutions (1×10^{-2} M) of ligand **2** directly in the NMR tube. The salts used were KSCN, Ag and Zn triflates, Hg and Pb perchlorates. Due to the low solubility of Hg perchlorate in MeOH, it was necessary to decrease the concentration of the ligand (0.5×10^{-3} M) and of the salt (5×10^{-3} M). In this case, the ligand was dissolved in a $CDCl_3$–CD_3OD (4 : 1, v/v). The spectra were recorded on a Varian Unity 300 Spectrometer after each addition of the salts. The temperature of the NMR probe was kept constant at 22 °C.

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