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Synthesis, NMR characterization and ion binding properties of 1,3-bridged *p-tert*-butyldihomooxacalix[4]crown-6 bearing pyridyl pendant groups

Paula M. Marcos[a,b,*] and José R. Ascenso[c]

[a]*Departamento de Química/CCMM, Faculdade de Ciências da Universidade de Lisboa, Edifício C8, 1749-016 Lisboa, Portugal*
[b]*Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*
[c]*Instituto Superior Técnico, Complexo I, Av. Rovisco Pais, 1049-001 Lisboa, Portugal*

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Abstract—1,3-Di(2-pyridylmethoxy)-*p-tert*-butyldihomooxacalix[4]arene-crown-6 (**2**) was synthesized for the first time. **2** was isolated in a cone conformation in solution at room temperature, as established by NMR spectroscopy (^{1}H, ^{13}C and NOESY). Complete assignment of both proton and carbon NMR spectra was achieved by a combination of COSY, HSQC and HMBC experiments. The binding properties of ligand **2** towards alkali, alkaline earth, transition and heavy metal cations have been assessed by phase transfer and proton NMR titration experiments. The results are compared to those obtained with other dihomooxacalix[4]arene-crowns-6 and closely-related calix[4]arene-crown derivatives. **2** shows a preference for the soft heavy metal cations (except for Cd^{2+}), with a very strong affinity for Ag^+. Some transition metal cations are also well extracted. **2** forms 1:1 complexes with K^+, Ca^{2+} and Ag^+, and ^{1}H NMR titrations indicate that they should be encapsulated into the cavity defined by the crown ether unit and by the two pyridyl pendant arms. A 1:2 (ML_2) complex is formed with Zn^{2+} and two species, probably 1:1 and 1:2 complexes, are obtained with Pb^{2+}.

1. Introduction

Calixarenes[1–3] are an extremely versatile class of macrocyclic receptors, able to bind and transport selectively ions and neutral molecules, and to serve as building blocks for the design of more elaborate structures. The parent compounds are readily available and can be further lower rim functionalised into a large variety of derivatives.

In particular, the calixcrowns,[4] where a poly(oxyethylene) chain links two phenolic oxygens of the calixarene framework, have been widely investigated since their first synthesis in 1983.[5] Calixcrowns have shown remarkable ionophoric properties towards, mainly, alkali metal cations. They exhibit highly selective metal ion recognition, which depends on the crown size, on the macrocyclic conformation (especially for calix[4]arene derivatives) and on the substituents at the upper and lower rims. It has been shown that calix[4]-crowns-4 show a preference for Na^+, while calix[4]-crowns-5 and -crowns-6 are selective for K^+ and Cs^+ cations, respectively. Thus, the design and synthesis of these molecules have been extensively developed in the last few years.

Among these compounds, some calix[4][6–9] and calix[5]-crowns[10,11] bearing pyridyl pendant groups at the lower rim have been synthesised, which combine within the same molecule two potential binding sites with hard and soft character: a crown ether moiety and *N*-heteroaromatic rings, respectively. Therefore, these compounds are potential receptors for a large variety of cations, including alkali, alkaline earth, transition and heavy metal ions. This kind of molecular association has already been successfully studied with pyridine-armed diaza-crown ethers.[12]

Following our studies on metal cation binding and transport properties of *p-tert*-butyl dihomooxacalix[4]arene derivatives containing the carbonyl group at the lower rim,[13–16] we have extended these studies to dihomooxacalix[4]-crowns,[17,18] as well. This paper presents the synthesis, the NMR conformational analysis and the binding properties towards alkali, alkaline earth, transition and heavy metal cations of the 1,3-di(2-pyridylmethoxy)-*p-tert*-butyldihomooxacalix[4]arene-crown-6 (**2**). These properties have been assessed by extraction studies of metal picrates

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Keywords: Calixcrowns; Conformational analysis; Metal cations; Extraction; ^{1}H NMR titration.

* Corresponding author. Tel.: +351 21 7500111; fax: +351 21 7500979; e-mail: pmmarcos@fc.ul.pt

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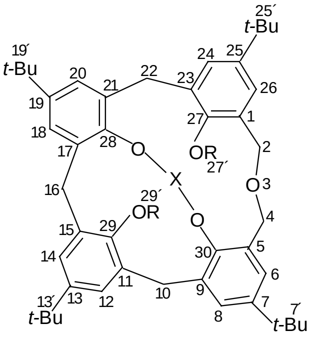
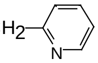
from an aqueous solution into dichloromethane and by proton NMR titration experiments. The results are discussed in the light of those obtained with other dihomooxacalix[4]-arene-crowns-6 and also with closely-related calix[4]arene-crown derivatives.



X = $(CH_2CH_2O)_4CH_2CH_2$

1 R = H

2 R = CH_2–



3 R = CH_3

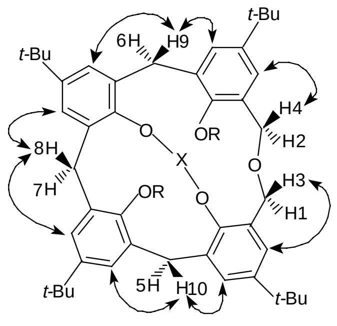
2. Results and discussion

2.1. Synthesis and NMR characterization

Calixcrown **2** was synthesized by the reaction of *p-tert*-butyldihomooxacalix[4]arene-crown-6 (**1**)[17] with 2-(chloromethyl)pyridine hydrochloride and NaH in dry DMF at 65 °C for 48 h. Proton, carbon-13, COSY, NOESY, HSQC and HMBC experiments were carried out in chloroform at room temperature to establish its structure and conformation.

The complete absence of symmetry in compound **2** is reflected by its proton and carbon NMR spectra. The ^1H NMR spectrum displays four singlets for the *tert*-butyl groups, five AB quartets for the CH_2 bridge protons, a complex multiplet for the polyether chain protons and four pairs of doublets for the aromatic protons. In addition, the OCH_2Py groups exhibit one AB quartet and one pseudo singlet for the CH_2 protons and only four of the eight expected multiplets, due to overlapping of some signals, for the heteroaromatic protons.

Due to overlapping of signals in the ^{13}C NMR spectrum, fewer lines than expected were obtained. Thus, this spectrum shows a pattern containing 33 of the 34 expected downfield resonances arising from the aromatic carbon atoms, 12 of the 14 expected midfield resonances arising from the methylene carbon atoms of the OCH_2Py and CH_2OCH_2 groups and crown moiety, and 11 upfield resonances arising from the quaternary carbon atoms $C(CH_3)$ (four lines), the methyl carbon atoms of the *tert*-butyl groups $C(CH_3)$ (four lines) and the methylene carbon atoms $ArCH_2Ar$ (three lines). All resonances were assigned by DEPT experiments. The three pertinent $ArCH_2Ar$ resonances appear in the range 29.5–30.8 ppm, indicating a cone conformation[19] for calixcrown **2**. Also the resonances of the OCH_2Py groups appear at $\approx$77.7 ppm, as observed for other pyridyl dihomooxa[20] and calix[4]arene[21] derivatives in the cone conformation. This conformation was further confirmed by proton–proton correlations observed in a NOESY spectrum. The more relevant NOE enhancements are shown in Figure 1. However, this conformation should be a distorted cone conformation, since the difference in the chemical shifts between the axial and equatorial protons of the $ArCH_2Ar$ bridges is larger than 0.9 ppm[22] ($\Delta\delta \geq 1.2$). Moreover, the peaks due to the *tert*-butyl and aromatic protons appear in a very large range (0.56–1.36 and 6.15–7.27 ppm, respectively), suggesting a less regular structure. A similar situation was found for the analogue di(2-pyridylmethoxy)-*p-tert*-butylcalix[4]arene-crown-5 derivative.[7]



X = $(CH_2CH_2O)_4CH_2CH_2$

2 R = CH_2–

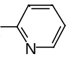


Figure 1. Relevant NOE enhancements used to confirm the cone conformation in calixcrown **2**.

The assignment for both proton and carbon spectra (Table 1) was obtained from cross-peak correlations in a COSY spectrum and by the analysis of a HSQC spectrum, which correlates directly bonded ^1H and ^{13}C

Table 1. Chemical shifts (δ, ppm) of protons and carbons of calixcrown **2**

Atom	δ_C	δ_H (eq), (ax)
2	68.8	4.58; 4.66
4	68.4	4.66; 4.94
10	29.5	3.18; 4.48
16	30.8	3.23; 4.43
22	30.2	3.21; 4.43
6	126.6	7.26
8	126.7	7.18
12	124.6	6.90
14	125.2	6.80
18	123.7	7.26
20	127.2	7.12
24	125.3	6.15
26	124.3	6.87
7′	31.7	1.30
13′	31.18	1.05
19′	31.6	1.36
25′	31.24	0.56
27	151.6	—
28	153.5	—
29	151.3	—
30	152.2	—
27′	77.0	4.74; 4.95
29′	78.5	4.89

nuclei. Identification of four pertinent quaternary carbon atoms (C27, C28, C29 and C30) was achieved by a HMBC spectrum, that correlates protons and carbons two and three bonds away. Thus, it was possible to confirm that the *t*-Bu and aromatic protons resonate at higher fields are on the aryl rings bearing the pyridyl substituents, and those resonate at lower fields are on the rings carrying the polyether chain.

2.2. Extraction studies

The ionophoric properties of dihomooxa calixcrown **2** towards alkali, alkaline earth, transition and heavy metal cations were first evaluated by the standard picrate extraction method.[23] The results, expressed as a percentage of cation extracted (*%E*), are reported in Tables 2 and 3. The corresponding values for calixcrowns **1** and **3** are included for comparison.

The data reveal that calixcrown **2** is a reasonably good phase transfer agent for the alkali cations (*%E* ranges from 22 to 34), displaying a slight preference for Cs^+(34%). This cation is usually preferred by the calix[4]-crown-6 derivatives. Within the alkaline earth cations, compound **2** is a weak extractant, showing a plateau selectivity from Mg^{2+} to Ba^{2+} with almost no discrimination among the four cations of the series (*%E* ranges from 14 to 17).

The comparison with the unsubstituted calixcrown **1** shows that ligand **2** is a much stronger extractant for both kinds of cations, especially for the alkali ones. The larger size of the pyridyl groups and the possibility of acting cooperatively with the crown ether moiety on cation binding, may account for this behaviour of **2**. When the comparison is made with calixcrown **3** a similar situation is observed for the alkaline earth and the smaller alkali cations. However, this derivative exhibits slightly higher extraction percentages for the larger alkali cations Rb^+ and Cs^+. This can be due to its partial cone conformation.[18] The binding efficiency of this type of compounds is strongly conformationally dependent. Among calix[4]-crowns-5 and crowns-6, the partial cone conformation is preferred over cone conformation.[7,24,25] The former conformation is less polar and less solvated than the cone,[25] and the bound cations can interact not only with the crown ether moiety but also with one rotated aromatic nucleus (cation/π interaction) of the partial cone conformation.[24]

A comparison with pyridino derivative analogues of the calix[4]-crown-6 and calix[5]-crown-6 is not possible since, to our knowledge, no extraction studies with these compounds exist in the literature. Extraction studies toward a variety of metal picrates were done with the monopyridyl of the 1,2-bridged *p-tert*-butylcalix[4]-crown-6 (**1Py[4]-C6**) in the cone conformation.[6] However, a direct comparison with ligand **2** can not be made due to the superior efficiency of 1,3-bridged calix[4]crowns as ionophores. But, if we compare ligand **2** with dipyridyl derivative of the *p-tert*-butylcalix[4]-crown-5 (**2Py[4]-C5**) also in the cone conformation,[7] we observe that **2** is a better extractant than **2Py[4]-C5**, except for K^+ (Table 2). The comparison between these two derivatives allows the evaluation of the effect of two control factors of selectivity in cation binding: the crown size and the conformational flexibility of the calixarene. While **2Py[4]-C5** shows a peak selectivity for K^+, dihomooxa derivative **2**, with a larger macrocyclic cavity and crown size, displays a plateau selectivity with a slight preference for Cs^+.

For the transition metal cations, Lewis acids of intermediate nature (except Mn^{2+}, that is considered hard),[26] calixcrown **2** ranges from being a weak to an efficient extractant, mainly for Fe^{2+}(43%) and Cu^{2+}(37%). The highest percentages are shown towards the soft heavy metal cations (except for Cd^{2+}). **2** displays a very high extraction level for Ag^+(87%) and a good level for Hg^{2+}(44%). Towards Pb^{2+}, of intermediate nature,[26] ligand **2** also displays a significant preference (37%). The comparison of these results with those obtained with calixcrown derivatives **1**

Table 2. Percentage extraction of alkali and alkaline earth metal picrates into CH_2Cl_2 at 25 °C[a]

	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
Ionic radius (Å)[b]	0.78	0.98	1.33	1.49	1.65	0.78	1.06	1.27	1.43
1[c]	4.4	4.4	3.6	5.8	6.1	4.8	4.8	3.7	5.8
2	22	29	32	29	34	15	17	14	14
3[c]	5.4	12	22	36	40	1.0	3.0	3.3	2.5
2Py[4]-C5[d]	3.3	8.5	37.5	7.2	3.0	—	—	—	—

[a] Values with uncertainties less than 5%.

[b] Goldschmidt, V. M. *Skrifter Norske Videnskaps-Akad. Oslo, I, Mat.-Naturv. Kl*, **1926**; data quoted in Marcus, I. *Ion Properties*, Marcel Dekker: New York, 1997; pp 46–47.

[c] Data taken from Ref. 18.

[d] Data taken from Ref. 7.

Table 3. Percentage extraction of transition and heavy metal picrates into CH_2Cl_2 at 25 °C[a]

	Mn^{2+}	Fe^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Ag^+	Cd^{2+}	Hg^{2+}	Pb^{2+}
Ionic radius (Å)[b]	0.83	0.78	0.75	0.69	0.73	0.75	1.15	0.95	1.02	1.18
1	5.8	1.7	1.4	2.5	2.2	2.2	1.5	1.5	6.5	2.5
2	14	43	15	13	37	17	87	11	44	37
3	7.9	1.3	1.6	3.2	9.6	4.6	18	3.2	9.1	7.3

[a] Values with uncertainties less than 5%.

[b] Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr., Sect. B* **1969**, *25*, 925; **1970**, *26*, 1046; data quoted in Marcus, I. *Ion Properties*, Marcel Dekker: New York, 1997; pp 46–47.

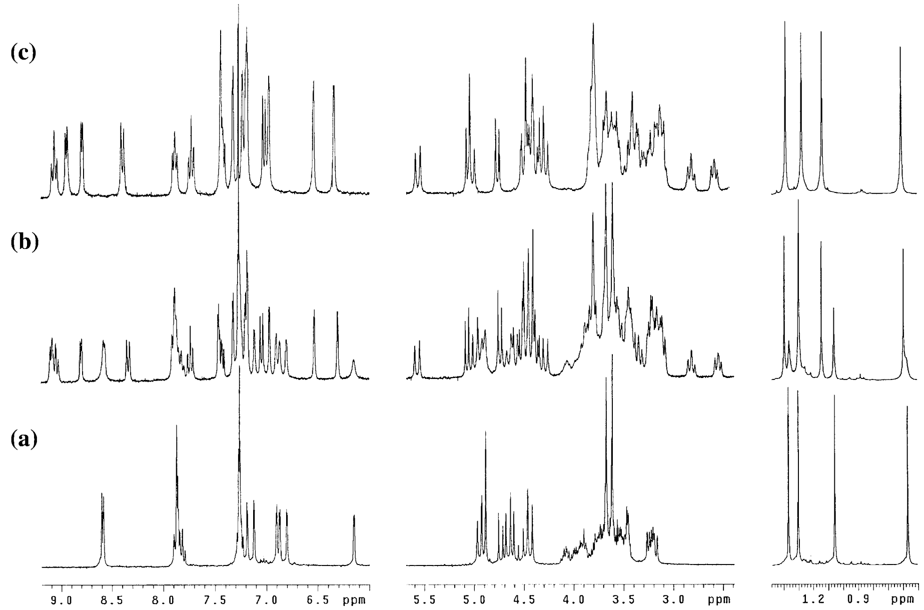


Figure 2. 300 MHz. ^{1}H NMR spectra of **2** in $CDCl_3$ at 22 °C. (a) Free ligand, (b) upon addition of 0.25 and (c) 0.5 equiv of Zn triflate 300MHz.

and **3** clearly shows the higher extraction ability of ligand **2** towards transition and heavy metal cations. The softer character of the nitrogen donor atoms may explain this behaviour. Interestingly, among the nineteen cations studied in this work, the six exhibiting the highest extraction percentages are soft Lewis acids or of intermediate nature ($Ag^+ \gg Hg^{2+} \approx Fe^{2+} > Pb^{2+} = Cu^{2+} > Cs^+$).

2.3. Proton NMR studies

To obtain further information on the cation binding behaviour of calixcrown **2**, namely concerning the binding sites, ^{1}H NMR studies were performed. The cations studied were K^+, Ca^{2+}, 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.

Different situations were found after the addition of the salts to ligand **2**.

Titrations of calixcrown **2** with K^+ and Ca^{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, and consequently a weak affinity of ligand **2** towards these two cations. This is in agreement with the extraction results, mainly in the case of Ca^{2+}. 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 Ag^+ 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. This reflects the high binding ability of ligand **2** towards Ag^+, as previously observed in extraction. Upon reaching a 1:1 ratio, all signals for the free ligand disappear and those of the complexed ligand remain unaltered after subsequent additions of the salts, indicating a 1:1 metal-to-ligand stoichiometry. In the case of Zn^{2+}, the addition of 0.25 equiv of the salt shows that both signals of the complexed and uncomplexed ligand are present in the spectrum with the same intensity (Fig. 2). Upon the addition of 0.5 equiv all the signals for the free ligand disappear and those of the complexed ligand remain unchanged after subsequent additions of the salt. This indicates a 1:2 metal-to-ligand stoichiometry. In order to confirm this stoichiometry a Job plot based on ^{1}H NMR data between calixcrown **2** and Zn^{2+}cation was carried out. As shown in Figure 3, the curve maximum appears between 0.6 and 0.7 mol fraction of **2**, clearly indicating that Zn^{2+} forms a ML_2 complex with ligand **2**. A complex between Zn^{2+} and **1Py[4]-C6** was obtained some time ago,[27] but with a 1:1 stoichiometry.

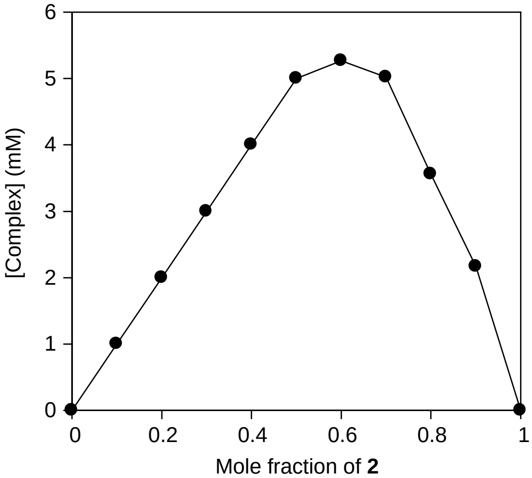


Figure 3. Job's plot based on ^{1}H NMR data for the system $\mathbf{2}+Zn^{2+}$; total concentration 1×10^{-2} M in $CDCl_3$–CD_3OD (9/1, v/v).

Table 4. Relevant proton chemical shifts (δ, ppm) of ligand **2** and its metal complexes

	t-Bu	Crown	OCH_2Py	ArH	PyH							
					3	4	5	6	3′	4′	5′	6′
2	0.56, 1.05, 1.30, 1.36	3.43–4.13	4.66, 4.89,[a] 4.95	6.15, 6.80, 6.87, 6.90, 7.12, 7.18, 7.26, 7.27	7.87	7.81	7.25	8.59	7.87	7.87	7.25	8.59
2+K^+ (ML)	0.92, 1.18, 1.19, 1.25	3.54–4.11	5.03, 5.07, 5.16, 5.38	6.63, 6.87, 6.99, 7.13, 7.15, 7.17, 7.30, 7.31	7.20	7.70	7.33	8.68	7.35	7.83	7.43	8.91
2+Ca^{2+} (ML)	0.83, 1.10, 1.21, 1.26	3.72–4.31	4.96, 5.15, 5.46, 5.50	6.70, 6.74, 7.04, 7.13, 7.14, 7.21, 7.21, 7.29	7.08	7.75	7.51	8.84	7.25	7.86	7.51	9.08
2+Ag^+ (ML)	0.79, 0.87, 1.30, 1.36	3.14–3.93, 4.11–4.30	5.43, 5.59, 5.63, 5.73	6.63, 6.63, 6.65, 6.77, 7.12, 7.17, 7.21, 7.22	6.94	7.81	7.56	9.10	7.71	7.91	7.70	9.24
2+Zn^{2+} (ML_2)	0.61, 1.14, 1.28, 1.39	2.59, 2.82, 3.08–3.89	4.39, 4.51, 5.02, 5.57	6.34, 6.54, 6.98, 7.19, 7.21, 7.24, 7.33, 7.45	7.03	7.73	7.44	8.80	8.40	7.89	9.07	8.95
2+Pb^{2+} (ML) A	1.08, 1.15, 1.22, 1.24	3.45–4.22	5.17, 5.76,[a] 6.26	6.79, 7.06, 7.30, 7.36, 7.36, 7.40, 7.40, 7.45	7.24	7.84	7.64	9.01	7.74	8.14	[b]	9.73
2+Pb^{2+} (ML_2) B	0.64, 1.15, 1.27, 1.39	2.65, 2.84,b	[b]	6.38, 6.58, 6.98, 7.19, 7.20, 7.23, 7.33, 7.42	7.16	[b]	7.52	8.80	8.37	7.92	9.01	8.91

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

With Pb^{2+} a quite different situation was found. Three sets of sharp signals with approximately the same intensity, corresponding to the free ligand and to two other complexed species are present in the spectra from the addition of the first aliquot (0.5 equiv) of the salt. With 1 equiv all the peaks of the free ligand disappear, and further additions produce an increase of one of the complexes relative to the other. In this case, a Job plot was not possible to perform in order to determine the stoichiometry of these complexes, since a large number of peaks is present in every region of the proton spectrum and, therefore, no reliable integration of the signals was feasible. However, from a qualitative inspection of the spectra it is possible to verify that the chemical shifts of the minor complex (B) are identical to those of Zn^{2+} complex (Table 4), whereas the δ of the major complex (A) are similar to those of the other complexes, and that the intensity of B peaks decreases as the addition of the salt proceeds. Thus, it seems reasonable to assign the 1:1 stoichiometry for complex A and the 1:2 (ML_2) for complex B. A similar situation has already been observed by us before.[28]

Titration of calixcrown **2** with Hg^{2+} required a slightly different procedure, since the solubility of $Hg(ClO_4)_2$ in MeOH is very low. Thus, it was necessary to decrease the concentration of both ligand and salt (see Section 4). Upon the addition of 1 equiv of Hg^{2+} salt three sets of peaks with approximately the same intensity and apparently corresponding to three complexed species, are present in the spectra. As the addition of the salt proceeds (up to 4 equiv), the intensity of two of the three sets of signals decreases, but no further conclusions could be drawn due to the great complexity of the spectra.

Proton NMR data of the free and complexed ligand **2** are collected in Table 4. The complete interpretation of the spectra required additional COSY experiments. In the case of Pb^{2+} spectrum full proton assignment was not possible due to the presence of both complexed species. Nevertheless, the relevant protons of complexes A and B could be assigned. Complexation of the cations affects all the proton chemical shifts in the ligand. The largest downfield variations are observed for the methylene and heteroaromatic H6, H6′ protons of the OCH_2Py groups and the aromatic protons of the alkylated rings. The heteroaromatic H3, H3′ protons, the oxygen bridge equatorial methylene protons (CH_2OCH_2) and the bridging axial methylene protons ($ArCH_2Ar$), show the largest upfield shifts. Similar observations have been made for closely-related calix[4]-crown derivatives with K^{+}[8] and also for a homocalix[4]-arene[29] and a hexatrioxacalix[3]arene with Ag^+.[30]

A closer examination of the spectral changes upon complexation indicates very small variations ($\Delta\delta \approx 0.10$) for the three downfield *tert*-butyl groups. However, the fourth *t*-Bu group experiences considerable downfield shift variations, as those observed for Pb^{2+} (complex A) and K^+ ($\Delta\delta = 0.52$ and 0.36, respectively). Thus, upon complexation the difference in the chemical shifts among the four *t*-Bu groups decreases significantly. Identical situations were observed among the eight aromatic protons, with Δδ being after complexation approximately half of the value of the free ligand. This suggests that upon complexation ligand **2** should adopt a more symmetrical conformation. Similar results were obtained for a polyether calix[4]arene derivative, analogue of a calixcrown, and K^+ cation.[31] Zn^{2+} cation behaves differently upon complexation with calixcrown **2**, according to its different metal-to-ligand stoichiometry. This cation shows practically the same $\Delta\delta$ values as before complexation (0.78 and 1.11 ppm for *t*-Bu and aromatic protons, respectively).

A systematic observation of the data reveals that the upfield shift variations experienced by the axial methylene protons of the CH_2 bridges follow the order H5<H6<H7 (Fig. 1). The axial methylene proton (H7) opposite to the bridging oxygen atom exhibits the largest upfield shifts, with the highest value recorded for Ca^{2+} ($\Delta\delta=0.61$). Similar observations have been made by us before for dihomooxacalix[4]arene derivatives containing the carbonyl group at the lower rim.[16,28] As observed for other calixarene derivatives, the variation in chemical shift experienced by the equatorial methylene protons ($ArCH_2Ar$) is downfield and much smaller than that of the axial protons, but the CH_2OCH_2 resonances behave differently, as reported before.[15,16,28,30] The axial and equatorial methylene protons of the oxygen bridge move upfield and the equatorial protons experience larger shift variations than the axial ones. 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, their chemical shift variations are not the same in both groups. 3-PyH and 3′-PyH protons show similar upfield shifts for K^+ and Ca^{2+} ($\Delta\delta=0.79$ and 0.62, respectively, for Ca^{2+}), but very different for Ag^+ and Pb^{2+} in complex A ($\Delta\delta=0.93$ and 0.16, respectively, for Ag^+). In the case of Zn^{2+} this difference is even more pronounced, with 3-PyH undergoing an upfield shift of 0.84 ppm and 3′-PyH a downfield shift of 0.53 ppm. For 6-PyH and 6′-PyH a similar trend is observed, with the latter proton experiencing a higher downfield shift than the former. Complexation with Pb^{2+} (complex A) shows the highest difference ($\Delta\delta=1.13$ and 0.42, respectively). It is also to point out the very large downfield shift experienced by 5′-PyH proton ($\Delta\delta=1.82$) for Zn^{2+} complexation comparing to that of 5-PyH ($\Delta\delta=0.19$), as well as to those of both protons for the complexation of the other cations.

The deshielding effect observed for the aromatic protons indicates the involvement of the phenolic oxygens in complexation, as reported previously.[32] The largest shift changes shown by the methylene, H6, H6′, H3 and H3′ protons of the OCH_2Py groups indicate the participation of the pyridine nitrogen atoms in cation complexation. Therefore, this suggests that for 1:1 complexes all the cations must be inside the cavity defined by the crown ether unit and by the two pyridyl pendant arms. The cations should be bound into that cavity through metal–oxygen and metal–nitrogen interactions, in a geometrical arrangement that should depend on the nature of the cations.

In the case of Zn^{2+}, the unexpected 1:2 metal-to-ligand stoichiometry may be interpreted in terms of the too large size of the ionophoric cavity to accommodate that small cation. After complexation of Zn^{2+} the ionophoric cavity of **2** remains almost unchanged, as already pointed out by the invariance of *t*-Bu and aromatic protons. Moreover, the crown moiety protons undergo, in general, moderate downfield shifts, whereas complexation with Zn^{2+} induces a large upfield shift variation, mainly of two protons resonating at 2.59 and 2.82 ppm (Fig. 2). This clearly indicates a more effective coordination by the crown unit towards Zn^{2+} cation. Relative to the OCH_2Py groups, it seems that only one group from each calixcrown participates in complexation. Beyond the different behaviour observed by a set of heteroaromatic protons, also a CH_2 group shows an upfield variation (Table 4) contrary to all the others that undergo downfield shifts. Therefore, these facts suggest that Zn^{2+} cation is bound to some oxygen atoms of both crown ether units, placing the two ligands in an arrangement ‘tail-to-tail’, and also enveloped by one pyridine nitrogen atom from each calixarene.

Although comparable spectral changes had been observed for the complexation of the cations, ligand **2** showed some differences among them. The magnitude of the shift variations for protons adjacent to the donor atoms is higher for Pb^{2+} (complex A), followed by Ag^+ and Ca^{2+}. This preference of ligand **2** seems to be the result of the combination of three main factors affecting complexation: size, charge and nature of the cations. Thus, the different bound cations induce more or less marked conformational rearrangements on the ionophoric cavity of ligand **2**.

3. Conclusions

Dipyridylcalixcrown **2** was synthesized and obtained in a cone conformation in solution at room temperature. Extraction studies with metal picrates from an aqueous solution into CH_2Cl_2 have shown that, for the alkali and alkaline earth cations, dihomooxacalixcrown **2** is, in general, a better extractant than the other calixcrowns. However, **2** is a less selective ligand comparing with **2Py[4]-C5**, due to its larger macrocyclic cavity and crown sizes. Towards transition and heavy metal cations **2** is clearly the best phase transfer agent, displaying a strong affinity for soft metal cations as Ag^+ and Hg^{2+}, but also for some of intermediate nature as Fe^{2+}, Pb^{2+} and Cu^{2+} cations. The softer character of the nitrogen donor atoms may explain this behaviour. **2** forms 1:1 complexes with K^+, Ca^{2+} and Ag^+, and a 1:2 (ML_2) complex with Zn^{2+}. The structure for 1:1 complexes deduced from NMR experiments shows that the cations should be encapsulated into the cavity composed by the crown ether unit and the two pyridyl groups. For ML_2 complex, Zn^{2+} should be placed between the crown ether units of both ligands in an arrangement ‘tail-to-tail’, being also surrounded by one pyridyl group from each calixarene. In the case of Pb^{2+}, two complexes with a 1:1 and probably a 1:2 stoichiometries were obtained.

4. Experimental

4.1. Synthesis

All chemicals were reagent grade and were used without further purification. Melting points were measured on a

Stuart Scientific apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer and on a Varian Inova 300 spectrometer, with TMS as internal reference. The gradient version of the COSY spectrum was collected as 512×2 K complex points. The phase sensitive NOESY experiment was collected as 256×2 K complex points with a mixing time of 0.7 s, a delay of 1.5 s and 32 transients. Gradient versions of HSQC and HMBC experiments for connecting ^1H and ^{13}C were run with 32 scans for the former and 64 scans for the latter. In both cases a delay of 1.5 s was used. Elemental analysis was determined on a Fisons EA 1108 microanalyser.

4.1.1. 7,13,19,25-Tetra-*tert*-butyl-27,29-bis[(2-pyridylmethyl)oxy]-28,30-crown-6-2,3-dihomo-3-oxacalix[4]arene (2). A mixture of **1** (0.50 g, 0.568 mmol) and NaH (95%, 0.216 g, 8.55 mmol) in dry DMF (20 mL) was stirred and gently warmed under N_2 for 30 min. After cooling, 2-(chloromethyl)pyridine hydrochloride (0.56 g, 3.41 mmol) was added to the mixture and the reaction was then heated at 60–65 °C with stirring under N_2 for 48 h. Addition of MeOH (1 mL) and water (70 mL) to the cooled reaction mixture gave a white precipitate, which was recrystallized from *n*-heptane to afford 0.32 g (53%) of **2**: mp 142–144 °C; ^1H NMR ($CDCl_3$) δ 0.56, 1.05, 1.30, 1.36 (4s, 36H, $C(CH_3)_3$), 3.18, 4.48 (ABq, 2H, $J=12.7$ Hz, $ArCH_2Ar$), 3.21, 4.43 (ABq, 2H, $J=14.1$ Hz, $ArCH_2Ar$), 3.23, 4.43 (ABq, 2H, $J=13.2$ Hz, $ArCH_2Ar$), 3.43–4.13 (m, 20H, crown), 4.58, 4.66 (ABq, 2H, $J=13.6$ Hz, CH_2OCH_2), 4.66, 4.94 (ABq, 2H, $J=13.6$ Hz, CH_2OCH_2), 4.74, 4.95 (ABq, 2H, $J=12.6$ Hz, OCH_2Py), 4.89 (s, 2H, OCH_2Py), 6.15, 6.80, 6.87, 6.90, 7.12, 7.18, 7.26, 7.27 (8d, 8H, ArH), 7.25 (m, 2H, 5-PyH and 5′-PyH), 7.81 (td, $J=7.7$, 1.7 Hz, 1H, 4′-PyH), 7.87 (m, 3H, 4-PyH, 3-PyH and 3′-PyH), 8.59 (m, 2H, 6-PyH and 6′-PyH); ^{13}C NMR ($CDCl_3$) δ 29.5, 30.2, 30.8 ($ArCH_2Ar$), 31.18, 31.24, 31.6, 31.7 ($C(CH_3)_3$), 33.8, 34.0, 34.2, 34.3 ($C(CH_3)_3$), 68.5, 68.9 (CH_2OCH_2), 69.4, 70.5, 70.7, 70.8, 70.9, 71.0, 71.5, 72.7 (crown), 77.0, 78.5 (OCH_2Py), 121.9, 122.66, 122.72, 123.2, 123.7, 124.3, 124.6, 125.2, 125.3, 126.6, 126.7, 127.2, 137.0, 137.1, 149.1 (ArH), 130.2, 132.4, 132.5, 132.6, 132.8, 134.0, 134.2, 135.4, 145.2, 145.4, 145.6, 145.7, 151.3, 151.6, 152.2, 153.5, 157.6, 157.7 (Ar). Anal. Calcd for $C_{67}H_{86}N_2O_9$: C, 75.67; H, 8.15; N, 2.63. Found: C, 75.69; H, 8.20; N, 2.63.

Dihomooxacalixcrowns **1**[17] and **3**[18] were synthesized in previous works.

4.2. 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 that no picrate extraction occurred in the absence of a calixarene. The details of metal picrate preparation have already been described.[13,15]

4.3. Proton NMR titration experiments

Several aliquots (up to 2–4 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, Ca, 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). 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. Job's method was performed for calixcrown **2** and Zn triflate. The total concentration was maintained at 1×10^{-2} M in $CDCl_3$–CD_3OD (9/1, v/v).

References and notes

1. Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998.
2. *Calixarenes for Separations*; Lumetta, G. J., Rogers, R. D., Gopalan, A. S., Eds.; ACS Symposium Series 757; American Chemical Society: Washington, 2000.
3. *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrofield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001.
4. Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Crown Ethers Derived from Calix[4]arenes*; Asfari, Z., Böhmer, V., Harrofield, J., Vicens, J., Eds.; Calixarenes 2001; Kluwer Academic: Dordrecht, 2001; pp 365–384.
5. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075.
6. Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041.
7. Arnaud-Neu, F.; Ferguson, G.; Fuangswasdi, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Petringa, A. *J. Org. Chem.* **1998**, *63*, 7770.
8. Ferguson, G.; Lough, A. J.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Petringa, A. *J. Org. Chem.* **1998**, *63*, 9703.
9. Ferguson, G.; Lough, A. J.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Resnati, G. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1109.
10. Caccamese, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Principato, G. *Tetrahedron* **1999**, *55*, 5505.
11. De Salvo, G.; Gattuso, G.; Notti, A.; Parisi, M. F.; Pappalardo, S. *J. Org. Chem.* **2002**, *67*, 684.
12. Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *J. Org. Chem.* **1991**, *56*, 268.
13. Marcos, P. M.; Ascenso, J. R.; Segurado, M. A. P.; Pereira, J. L. C. *J. Phys. Org. Chem.* **1999**, *12*, 695.
14. Marcos, P. M.; Ascenso, J. R.; Segurado, M. A. P.; Pereira, J. L. C. *Tetrahedron* **2001**, *57*, 6977.
15. Marcos, P. M.; Ascenso, J. R.; Segurado, M. A. P.; Pereira, J. L. C. *J. Inc. Phenom. Macrocyclic Chem.* **2002**, *42*, 281.
16. Marcos, P. M.; Félix, S.; Ascenso, J. R.; Segurado, M. A. P.; Pereira, J. L. C.; Khazaeli-Parsa, P.; Hubscher-Bruder, V.; Arnaud-Neu, F. *New J. Chem.* **2004**, *28*, 748.

17. Félix, S.; Ascenso, J. R.; Lamartine, R.; Pereira, J. L. C. *Synth. Commun.* **1998**, *28*, 1793.
18. Marcos, P. M.; Félix, S.; Ascenso, J. R.; Santos, M. A.; Segurado, M. A. P.; Pereira, J. L. C. *Tetrahedron* **2002**, *58*, 9223.
19. Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.
20. Marcos, P. M.; Ascenso, J. R.; Pereira, J. L. C. *Eur. J. Org. Chem.* **2002**, 3034.
21. Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611.
22. Gutsche, C. D. In *Calixarenes*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989.
23. Pedersen, C. *J. Am. Chem. Soc.* **1970**, *92*, 391.
24. Ungaro, R.; Arduini, A.; Casnati, A.; Pochini, A.; Ugozzoli, F. *Pure Appl. Chem.* **1996**, *68*, 1213.
25. Arnaud-Neu, F.; Deutsch, N.; Fanni, S.; Schwing-Weill, M. J.; Casnati, A.; Ungaro, R. *Gazz. Chim. Ital.* **1997**, *127*, 693.
26. Pearson, R. G. *Science* **1966**, *151*, 172.
27. Pappalardo, S.; Parisi, M. F. *Tetrahedron Lett.* **1996**, *37*, 1493.
28. Marcos, P. M.; Félix, S.; Ascenso, J. R.; Segurado, M. A. P.; Mellah, B.; Abidi, R.; Hubscher-Bruder, V.; Arnaud-Neu, F. *Supramol. Chem.* **2006**, in press.
29. Yamato, T.; Haraguchi, M.; Iwasa, T.; Tsuzuki, H.; Ide, S. *An. Quím., Int. Ed.* **1997**, *93*, 301.
30. Yamato, T.; Haraguchi, M.; Nishikawa, J. I.; Ide, S. *Can. J. Chem.* **1998**, *76*, 989.
31. Abidi, R.; Harrowfield, J. M.; Skelton, B. W.; White, A. H.; Asfari, Z.; Vicens, J. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1997**, *27*, 291.
32. Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreetti, G. D.; Ugozzoli, F. *Tetrahedron* **1986**, *42*, 2089.