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Synthesis, conformational behaviour, alkali and alkaline-earth metal cation extraction and transport studies of *p-tert*-butyldihomooxacalix[4]crowns

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Abstract—1,3-Dimethoxy-*p-tert*-butyldihomooxacalix[4]arene-crown-6 (**4**) was synthesized for the first time. **4** was isolated in a partial cone A conformation in solution at room temperature, as established by NMR measurements (^{1}H, ^{13}C, COSY and NOESY). Conformational behaviour of **4** and *p-tert*-butyldihomooxacalix[4]-crown-5 (**2**) and crown-6 (**3**) was studied by dynamic ^{1}H NMR and by MD/MM calculations. Two-phase (water/CH_2Cl_2) picrate extraction studies and transport experiments with the same salts through a CH_2Cl_2 membrane were performed to evaluate the binding properties of these ligands towards alkali and alkaline earth metal cations. **2** and **3** are poor phase transfer agents for all cations, while **4** is a reasonable extractant for the alkali cations, showing preference for Cs^+. However, all three calixcrowns are good carriers for the alkali cations and display a very selective transport for Ba^{2+}. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Much attention has been lately paid to calixarenes,[1–3] mainly in the field of host–guest chemistry. The parent compounds are readily available and can be further lower rim functionalised into a large variety of derivatives.

In particular, the calixcrowns, where a poly(oxyethylene) chain links two phenolic oxygens of the calixarene framework, have been prepared. Due to their 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 or lower rims, the design and synthesis of these molecules have been very developed in the last few years.

Most of these compounds are calix[4]monocrown[3a–10] and biscrown[3a,11–18] derivatives, although some calix[5],[3b,19–21] calix[6][3c,22–26] and calix[8]crowns[3d,26–28] have also been described. Their binding abilities towards alkali and other metal ions have been assessed by extraction studies, transport experiments and stability constant measurements. 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^+, respectively.

The exceptional selectivity towards Cs^+ shown by some calix[4]-crown-6 derivatives, has led to their application as, for example, ion-selective electrodes[29] and mainly as selective carriers in the treatment of radioactive liquid wastes.[3e,30,31]

Inspired by these results and in the course of the studies of alkali and alkaline earth metal cation binding properties of *p-tert*-butyldihomooxacalix[4]arene (**1**)[3f] derivatives bearing the carbonyl group at the lower rim,[32] we prepared the first dihomooxacalix[4]-crown-5 (**2**) and crown-6 (**3**).[33] In this paper is first presented the synthesis and characterization of 1,3-dimethoxy-*p-tert*-butyldihomooxacalix[4]-arene-crown-6 (**4**). Then, is reported the conformational behaviour of derivatives **2**–**4** by variable temperature ^{1}H NMR spectroscopy and by molecular dynamics/molecular mechanics (MD/MM) calculations. Finally, the binding properties of these ligands towards alkali and alkaline earth metal cations were determined by extraction studies with metal picrates from aqueous solutions into dichloromethane and transport experiments with the same salts, through a dichloromethane membrane.

Keywords: calixcrowns; conformational analysis; metal cations; extraction; transport properties.

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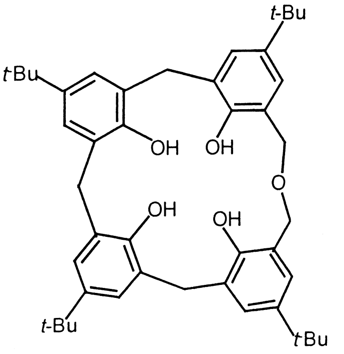

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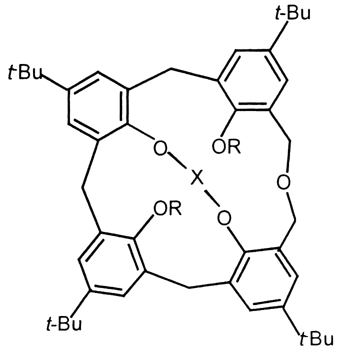


2 $X = (CH_2CH_2O)_3CH_2CH_2$, $R = H$

3 $X = (CH_2CH_2O)_4CH_2CH_2$, $R = H$

4 $X = (CH_2CH_2O)_4CH_2CH_2$, $R = CH_3$

2. Results and discussion

2.1. Synthesis and NMR characterization

Calixcrowns **2** and **3** were obtained from *p-tert*-butyldihomooxacalix[4]arene (**1**) and possess the cone conformation in solution, as reported before.[33]

Treatment of compound **3** with iodomethane and sodium hydride in THF/DMF at room temperature furnished calixcrown **4**.

Proton, carbon-13, COSY and NOESY NMR experiments were carried out in chloroform at room temperature with compound **4** to establish its conformation.

The ^1H NMR spectrum displays four singlets for the *tert*-butyl groups, two singlets for the methoxy groups, five AB quartets for the CH_2 bridge protons, a multiplet for the CH_2 crown protons and four pairs of doublets for the aromatic protons. The AB systems were substantiated by cross-peak correlations in a COSY spectrum (Fig. 1).

Due to overlapping of signals in the ^{13}C NMR spectrum, less lines were obtained than those expected. Thus, this spectrum shows a pattern containing 23 of the 24 expected downfield resonances arising from the aromatic carbons, 14 midfield resonances arising from the methylene carbons of the CH_2OCH_2 group and the crown moiety and also the methyl carbons of the methoxy groups, and 10 of the 11 expected upfield resonances arising from the quaternary carbons $C(CH_3)$, the methyl carbons of the *tert*-butyl groups $C(CH_3)$ and the methylene carbons $ArCH_2Ar$. All resonances were assigned by DEPT experiment. The three $ArCH_2Ar$ resonances appear at 29.7, 30.9 and 36.5 ppm, indicating a partial cone A conformation[34] for calixcrown **4**. Further confirmation of this conformation was provided by a NOESY spectrum. The more relevant NOE enhancements are shown in Fig. 2.

2.2. Conformational behaviour

The conformational behaviour of dihomooxacalixcrowns-6 **3** and **4** was evaluated by dynamic ^1H NMR in solvents with

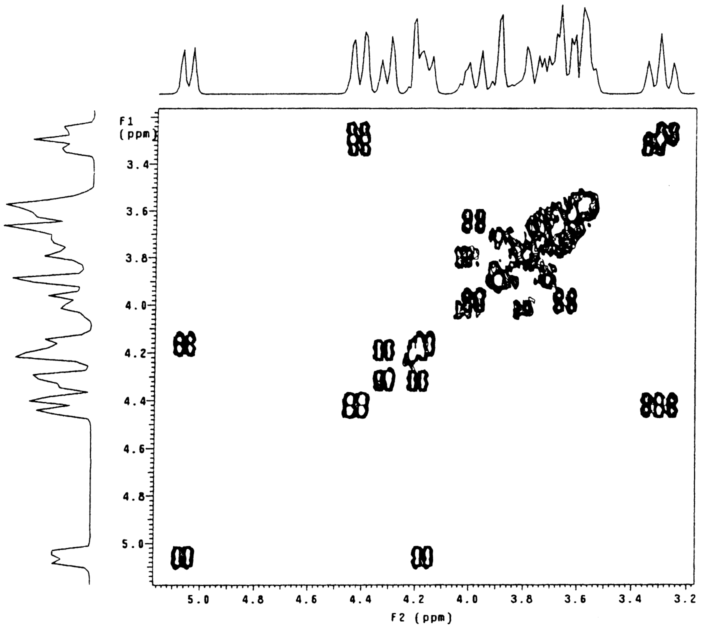


Figure 1. Methylene region of the COSY spectrum of **4** in $CDCl_3$ at 22°C and 300 MHz.

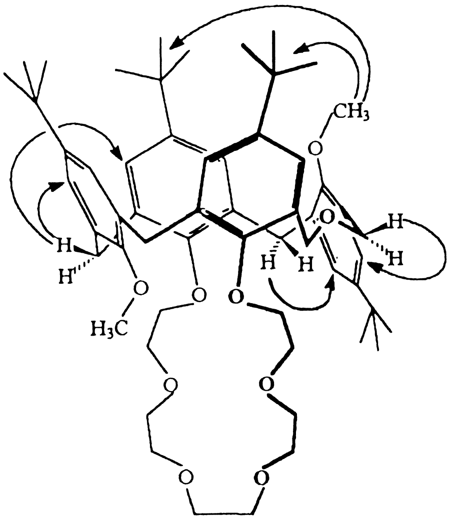


Figure 2. Relevant NOE enhancements used to confirm the partial cone A conformation in **4**.

different polarity, such as 1,1,2,2-tetrachloroethane or chloroform and pyridine.

In the nonpolar solvent $CDCl_2CDCl_2$, the methylenic proton signals for both derivatives broaden with increasing temperature. This effect is reversible, and is more evident for compound **3** than for compound **4** (Fig. 3). Analysis of these temperature dependent proton spectra indicates that derivative **4** is conformationally more rigid than derivative **3**. When the temperature is lowered until −40°C in $CDCl_3$, the ^{1}H NMR spectra of both derivatives show no evidence for the presence of conformations other than the existent at room temperature.

When $CDCl_3/CDCl_2CDCl_2$ are replaced by the more polar and basic solvent pyridine, it is expected that it interacts with the free OH groups of unsubstituted calixcrown **3**, disrupting the intramolecular hydrogen bond which contributes to hold the calixarene in the cone conformation. However, the coalesced spectrum is also not reached in this solvent until 110°C for compound **3**.

The conformational features of the three calixcrowns (**2**–**4**) were also studied by MD/MM calculations.

The set of MD/MM (MOPAC atomic charges) calculations performed for compounds **2**–**4** shows that they have different flexibilities. Analysis of the trajectory files of the MD/MM run shows that, within 5 kcal mol^{-1} of the global minimum, the four possible conformers (cone, partial cone A, partial cone B and 1,3-alternate) were found for compounds **3** and **4**, while the 1,3-alternate conformer was not found for compound **2**, thus indicating less flexibility of **2**.

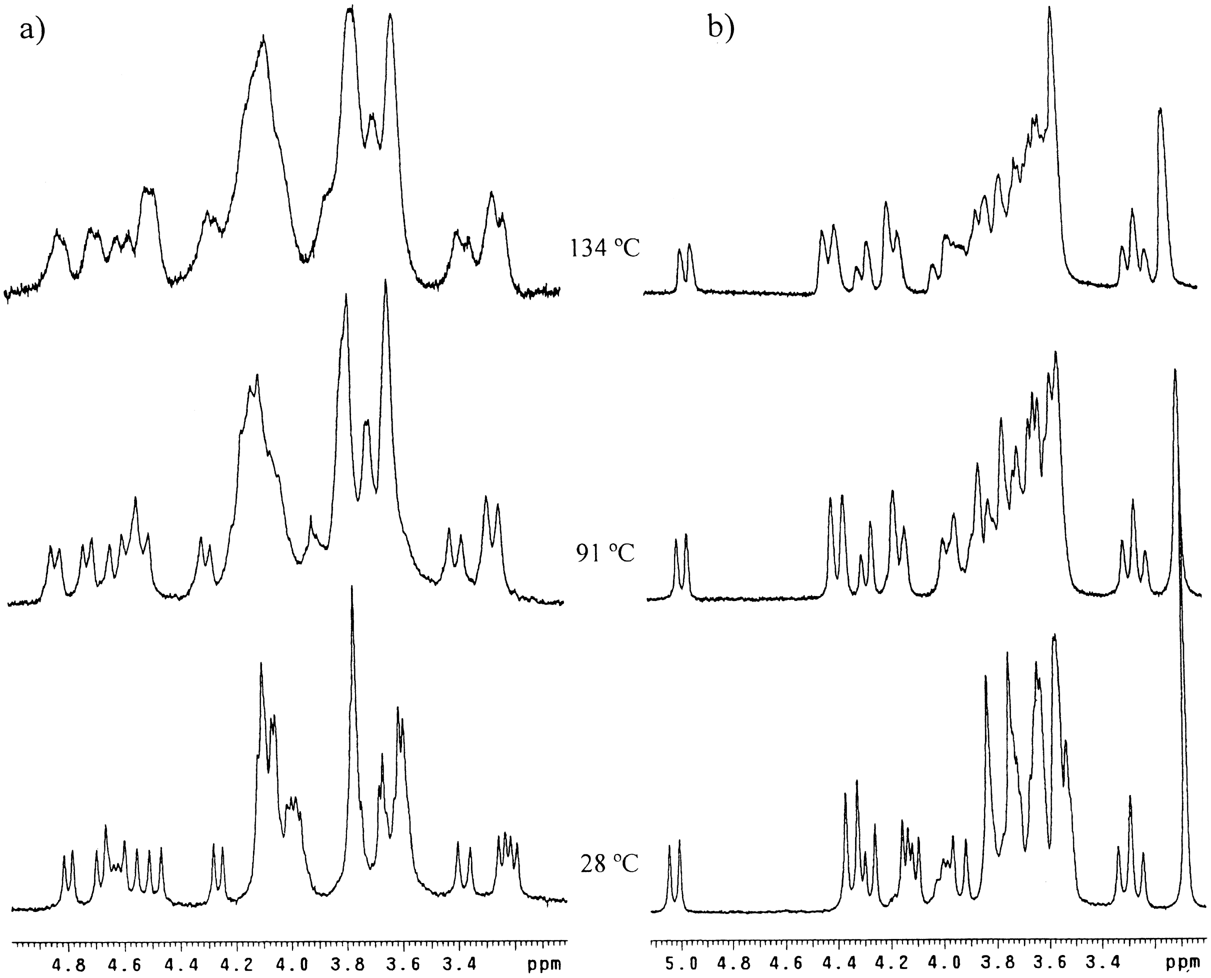
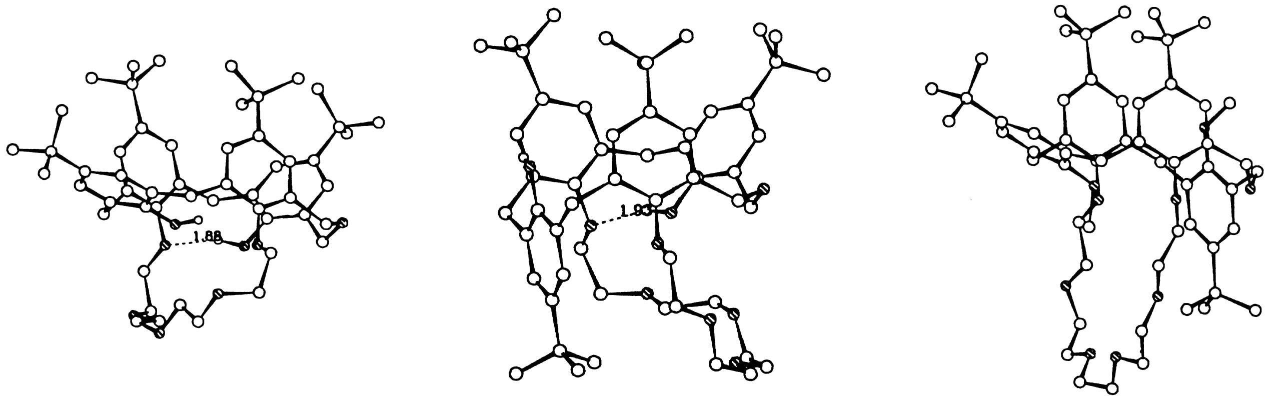


Figure 3. Variable temperature ^{1}H NMR spectra of **3** (a) and **4** (b) in $CDCl_2CDCl_2$ at 300 MHz.



a) b) c)

Figure 4. Stereoviews of the global minimum energy conformers calculated for compounds **2** (a), **3** (b) and **4** (c). Oxygen atoms are shaded. Hydrogen atoms are omitted, except those bound to oxygen atoms. The hydrogen bonds are shown as a dotted line.

Table 1. Percentage extraction of alkali and alkaline earth metal picrates into CH_2Cl_2 at 25°C

	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
Ionic radius (Å)[a]	0.78	0.98	1.33	1.49	1.65	0.78	1.06	1.27	1.43
2	1.0	7.9	9.5	14	6.9	1.5	3.9	4.8	3.5
3	4.4	4.4	3.6	5.8	6.1	4.8	4.8	3.7	5.8
4	5.4	12	22	36	40	1.0	3.0	3.3	2.5
Me[4]-C6[b]	1.4	1.6	2.2	3.1	19	–	–	–	–
Me[5]-C6[c]	n.d.	0.7	0.8	1.9	4.0	–	–	–	–

Values with uncertainties less than 5%.

[a] Goldschmidt, V. M. Skrifter Norske Videnskaps-Akad. Oslo, I, Mat.-Naturv. Kl, 1926; data quoted in Ref. 39.

[b] Data taken from Ref. 5.

[c] Data taken from Ref. 20.

These calculations further indicate that compound **2** adopts the cone as the global minimum energy conformation, even within 2 kcal mol^{-1} above that global minimum. However, within 5 kcal mol^{-1} of the global minimum other conformations were also found (50.0% partial cone A, 37.5% cone and 12.5% partial cone B). Partial cone B conformation is the global minimum energy conformation for compound **3**, although the conformers with energies within 2 kcal mol^{-1} of the global minimum are mostly in the cone conformation (66.7% cone, 33.3% partial cone B). All these minimum energy conformers show one or two hydrogen bonds with H–O distances of 1.9–2.2 Å. Concerning the methoxy derivative **4**, partial cone A is the global minimum energy conformation, which is also adopted by the most stable conformers within 2 kcal mol^{-1} of the global minimum (71.4% partial cone A, 28.6% cone).

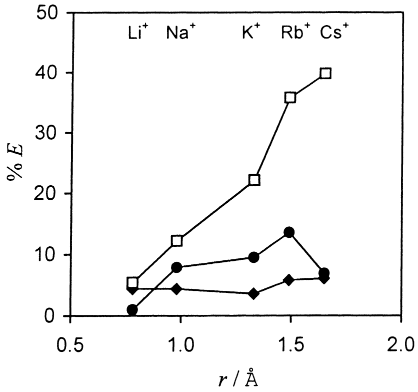


Figure 5. Percentage extraction (% E) of alkali metal picrates into CH_2Cl_2 at 25°C vs the cation ionic radius (r) for compounds 2 (●), 3 (◆) and **4** (□).

Fig. 4 shows the stereoviews of the global minimum energy conformers calculated for compounds **2**–**4**.

2.3. Extraction studies

The ionophoric properties of calixcrowns **2**–**4** towards alkali and alkaline earth metal cations were determined by the standard picrate extraction method.[35] The results, expressed as a percentage of cation extracted (% E), are collected in Table 1 and shown in Fig. 5.

These data reveal that both unsubstituted calixcrowns **2** and **3** are weaker extractants than the 1,3-dimethoxycalixcrown **4** for all the alkali metal cations. Calixcrown-5 (**2**) shows a preference for Rb^+ (14% E) and K^+ (9.5% E), while calixcrown-6 (**3**) displays only a very slight preference for Cs^+ (6.1% E) and Rb^+ (5.8% E). The value obtained for compound **2** towards K^+ is similar to that showed by the analogous *p-tert*-butylcalix[4]-crown-5 (11.8% E),[36] although this derivative presents a K^+/Na^+ selectivity much higher than compound **2**. Both derivatives also exhibited a very poor efficiency for Li^+.

The results obtained with the 1,3-dimethoxy derivative (**4**) range from 5% E for Li^+ to 40% E for Cs^+. This compound is a reasonable phase transfer agent, displaying a plateau

Table 2. Transport rate (V, μmol h^{-1}) of alkali and alkaline earth picrates through a CH_2Cl_2 liquid membrane at 25°C

	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
2	0.24	0.7	2.4	1.8	0.9	0.11	0.06	0.06	1.4
3	0.17	0.42	2.5	3.1	3.7	0.12	0.10	0.16	2.1
4	2.1	3.2	3.3	2.0	1.9	0.46	0.32	0.9	3.1

Reproducibility of ±10%.

selectivity between Rb^+ and Cs^+. As their analogous 1,3-dimethoxy-*p*-*tert*-butylcalix[4]-crown-6 (Me[4]-C6)[5] and 1,3-dimethoxy-*p*-*tert*-butylcalix[5]-crown-6 (Me[5]-C6),[20] derivative **4** also shows a preference for Cs^+ cation, but also a higher efficiency for all the alkali cations than those compounds (see Table 1). This can be due to its conformation. **4** presents a fixed partial cone conformation in solution, while the other derivatives, including unsubstituted calixcrowns **2** and **3**, possess a cone conformation. The efficiency of this type of compounds is strongly conformationally-dependent. Among calix[4]-crowns-6 and crowns-5, the partial cone conformation is preferred over cone conformation.[6,7] The former conformation is less polar and less solvated than the cone,[7] and the complexed 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.[6] Thus, although derivatives Me[4]-C6 and Me[5]-C5 are mobile and their conformations may change upon complexation, compound **4** will be a more preorganized ligand,[4] and therefore less conformational changes will occur upon binding.

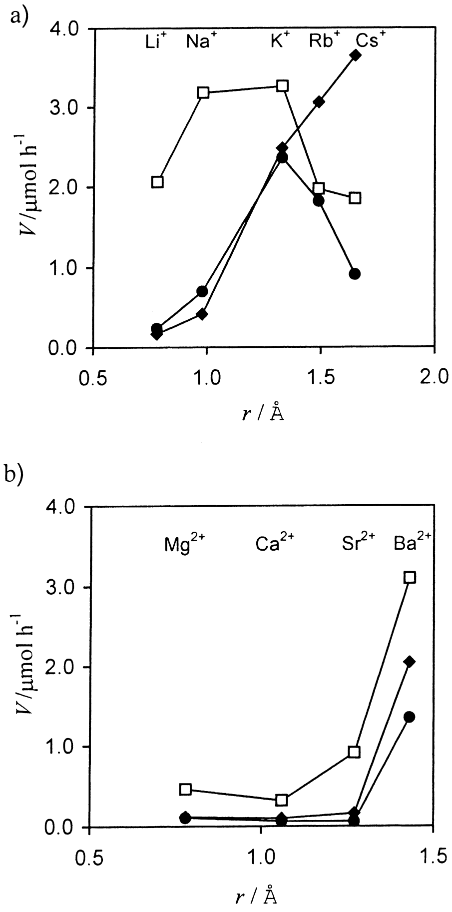


Figure 6. Transport rate (V, μmol h^{-1}) of metal picrates through a CH_2Cl_2 liquid membrane vs the cation ionic radius (r) for compounds **2** (●), **3** (◆) and **4** (□). (a) Alkali and (b) alkaline earth metals.

These trends found with dihomooxacalix[4]crowns **2**–**4** are similar to those already observed for calix[4]crown derivatives, where crowns-5 favouring K^+ and crowns-6 Cs^+.

Within the alkaline earth series, all three compounds are very poor phase transfer agents (never exceeding 6% E), with dimethoxycalixcrown **4** being now slightly less efficient than the others. This agrees with the majority of the calixcrowns that, in general, exhibit weak affinity for the alkaline earth cations.

2.4. Ion transport

Transport experiments were carried out in a dichloromethane liquid membrane system, similar to that employed by Lamb et al.[37] Table 2 and Fig. 6 present the transport rates V, in μmol h^{-1}, for calixcrowns **2**–**4**.

Table 2 shows that the three ligands range from reasonable to quite good neutral carriers within the alkali series. Calixcrown-5 (**2**) displays the slowest transport rate for Li^+ (0.24 μmol h^{-1}) and the highest for K^+ (2.4 μmol h^{-1}) although, rather than a peak selectivity, **2** shows a plateau selectivity increasing from Rb^+ to K^+. Li^+ is also the least carried cation by calixcrown-6 (**3**), while Cs^+ is the most transported one. This transport rate (3.7 μmol h^{-1}) is the highest value found with these three dihomooxacalix[4]crowns for all the cations studied. The trend found in transport for compounds **2** and **3** seems to follow that previously found in extraction studies.

1,3-Dimethoxy derivative (**4**) is an efficient carrier for all the alkali cations being, however, the least selective of the three compounds. **4** shows preference for K^+ (3.3 μmol h^{-1}) and Na^+ (3.2 μmol h^{-1}) with very little discrimination between them. Towards the other cations (Li^+, Rb^+ and Cs^+) there is practically no differentiation in their transport rates either. The transport rate sequence shown by derivative **4** seems to be the reverse of that for the extraction efficiency. For example, while Cs^+ and Rb^+ are the most extracted cations, they are the least carried by this ligand.

In the alkaline earth cation series, calixcrowns **2** and **3** are inefficient neutral carriers for Mg^{2+}, Ca^{2+} and Sr^{2+} (V ranging from 0.06 up to 0.16 μmol h^{-1}), while calixcrown **4** displays reasonable transport rates for those cations (V ranging from 0.32 up to 0.9 μmol h^{-1}). The most significant aspect towards these divalent cations is the very selective transport shown for Ba^{2+} by all three compounds. **2** is the most selective carrier for Ba^{2+} (Table 3) with the lowest

Table 3. Transport selectivities, $S=V_{\mathrm{M}_1^{2+}}/V_{\mathrm{M}_2^{2+}}$

Compd	Ba^{2+}/Sr^{2+}	Ba^{2+}/Ca^{2+}	Ba^{2+}/Mg^{2+}
2	23	23	13
3	13	21	17
4	3.4	10	7

transport rate (1.4 μmol h^{-1}), while **4** shows the highest value (3.1 μmol h^{-1}) and the least selectivity for that cation.

3. Conclusions

Dimethoxycalixcrown **4** was synthesized and obtained in a partial cone A conformation in solution at room temperature. Variable temperature ^{1}H NMR studies have shown that compound **4** is conformationally more rigid than compound **3**, although no significant conformational interconversion is observed for **3** until 130°C in $CDCl_2CDCl_2$ or 110°C in pyridine.

Molecular modelling calculations performed with calixcrowns **2**–**4** seem to support their conformational preferences previously found in solution by NMR measurements (cone conformation for **2** and **3**, and partial cone A conformation for **4**).

Extraction studies with metal picrates from an aqueous solution into CH_2Cl_2 have shown that dimethoxycalixcrown **4** is the best extractant for the alkali cations, probably because of its conformation. Calixcrowns-6 show preference for Cs^+ and Rb^+, and calixcrown-5 for Rb^+ and K^+. Concerning transport experiments, all derivatives are good carriers for the alkali cations and present a very selective transport for Ba^{2+}. **4** is the best carrier for all cations, **3** shows the highest transport rate for Cs^+ (3.7 μmol h^{-1}) and **2** is the most selective for Ba^{2+}. The trend found in transport for calixcrowns **2** and **3** seems to follow that of extraction, but it seems to be the reverse of that observed in extraction for calixcrown **4**.

4. Experimental

4.1. Synthesis

All chemicals were reagent grade and were used without further purification. Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. ^{1}H 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 phase sensitive NOESY experiment was collected as 256×2K complex points and a mixing time of 1 s. The COSY experiment was run with gradients to achieve a much higher sensitivity over the classical experiments, and was acquired with four transients, a delay of 1 s and as 512×2K complex points. All temperatures were corrected to MeOH or ethylene glycol, and the readouts are considered accurate to ±1°C. Elemental analysis was determined on a Fisons EA 1108 microanalyser.

4.1.1. 7,13,19,25-Tetra-*tert*-butyl-27,29-dimethoxy-28,30-crown-6-2,3-dihomo-3-oxacalix[4]arene (4). A suspension of 0.41 g (0.46 mmol) of *p*-*tert*-butyldihomooxacalix[4]arene-crown-6 (**3**), 0.10 g (2.5 mmol) of sodium hydride (60% oil dispersion) and 1.0 ml (16 mmol) of iodomethane in 44 ml of THF/DMF (10:1, v/v) was stirred at room temperature for ca. 15 h. The solvent was evaporated and a brown oily residue was obtained and poured into water. The precipitated material was filtered, taken up in dichloromethane and washed with 0.1 M HCl, brine and water and dried with anhydrous Na_2SO_4. Evaporation of the solvent gave a light yellow solid, which was recrystallized from acetone/methanol, affording 0.412 g (97%) of **4** as white crystals: mp 151–152°C; ^{1}H NMR ($CDCl_3$) δ 1.06, 1.13, 1.36, 1.38 (4s, 36H, $C(CH_3)_3$), 1.95, 3.11 (2s, 6H, OCH_3), 3.27, 4.43 (ABq, 2H, $J=13.8$ Hz, $ArCH_2Ar$), 3.32, 4.42 (ABq, 2H, $J=13.6$ Hz, $ArCH_2Ar$), 3.54–3.92 (m, 20H, crown), 3.64, 3.98 (ABq, 2H, $J=13.9$ Hz, $ArCH_2Ar$), 4.16, 5.06 (ABq, 2H, $J=11.8$ Hz, CH_2OCH_2), 4.19, 4.32 (ABq, 2H, $J=11.3$ Hz, CH_2OCH_2), 6.92 (1d, 1H, ArH), 6.99 (3d, 3H, ArH), 7.17, 7.19, 7.24, 7.26 (4d, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ 29.68, 30.91, 36.47 ($ArCH_2Ar$), 31.23, 31.32, 31.68 ($C(\mathit{CH}_3)$), 33.92, 33.94, 34.14, 34.23 ($\mathit{C}(CH_3)$), 59.77, 60.18 (OCH_3), 64.18, 68.21, 70.56, 70.77, 70.84, 70.88, 70.94, 71.08, 71.35, 71.57, 73.04, 73.75 (CH_2OCH_2 and crown), 125.15, 125.67, 126.46, 126.50, 126.60, 126.78, 127.60, 127.65 (ArH), 129.84, 131.17, 133.15, 133.28, 133.44, 134.38, 134.52, 135.05, 145.04, 145.10, 145.21, 153.32, 153.84, 154.81, 154.91 (Ar). Anal. calcd for $C_{57}H_{80}O_9$: C, 75.30; H, 8.87. Found: C, 75.35; H 8.93.

Dihomooxacalixcrowns **2** and **3** had already been synthesized in a previous work.[33]

4.2. Molecular modelling studies

Theoretical calculations were performed with the programs included in the INSIGHT/MSI package of software.[38] The molecules were built up on the Builder and were first optimised on Discover with the default charges and parameters of the consistent valence force-fields (CVFF). Then, MOPAC calculations gave the optimised geometries and the atomic charges. Finally, all molecules were subjected to a molecular dynamics calculation (100 ps) at a temperature of 2000 K in vacuum (500 iterations using steepest descendents). One hundred conformations of each molecule were saved at 1 ps ranges and were later refined by molecular mechanics, using VA09A until the maximum derivative was less than 0.01 kcal mol^{-1}.

4.3. Picrate extraction measurements

5 ml of a 2.5×10^{-4} M aqueous solution of metal picrate and 5 ml of a 2.5×10^{-4} M solution of calixarene 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 four times. Blank experiments showed that no picrate extraction occurred in the absence of a calixarene derivative. The

details of metal picrates preparation have already been described.[32a]

4.4. Transport experiments

The ion transport across a liquid membrane was done using an apparatus similar to that employed by Lamb et al.[37] The membrane phase (50 ml of a 7×10^{-5} M solution of the calixarene in CH_2Cl_2), the receiving phase (25 ml of doubly distilled and deionized water) and the source phase (7 ml of a 5×10^{-3} M aqueous solution of metal picrate), were placed in a thermostated vessel. The apparatus was maintained at 25°C and the phases stirred at 150 rpm. The experiments were repeated, at least, three times. The appearance of the picrate ion in the receiving phase was followed by UV spectrophotometry at regular time intervals. Experiments with no carrier present were performed, indicating no transport of metal picrates. The experimental procedure has already been described elsewhere,[32a]as well.

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