SYNTHESIS OF NEW CALIX[4]ARENE-BASED IONOPHORES

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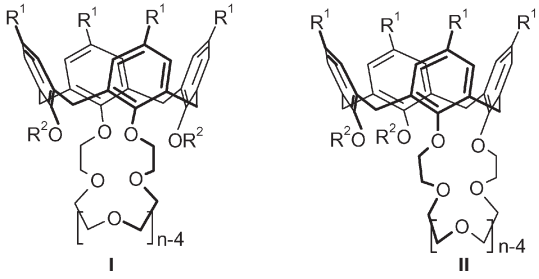
Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday in recognition of his outstanding contribution to the area of supramolecular chemistry.

A synthesis of new calix[4]arene-based ionophores is reported. These ligands are characterized by the presence of two types of coordination sites on their lower rim: one crowning unit of different length, linking two proximal calix[4]arene phenolic oxygens, and two esters or amide groups acting as additional hard binding sites. The choice of the proper reaction conditions, such as the base counterion and the solvent polarity, during the functionalization of the macrocycle lower rim, allows to modulate the stereochemistry of the final ligands. In this way the ligands in *cone* and *1,2-alternate* conformations were obtained in good yields. Complexation properties of these new compounds towards alkali and alkaline-earth cations were studied by means of liquid–liquid extraction experiments. The X-ray solid state structure of the *p-tert*-butylcalix[4]arene-*N*,*N*-diethylacetamide-crown-5 (**6a**) complex with strontium picrate shows the effective cooperativity among the two type of coordination site in the binding event.

Keywords: Supramolecular chemistry; Calixarenes; Ionophores; Alkali metals; X-ray diffraction; Complexation; Strontium.

Calixarenes[1] are a versatile class of phenolic macrocycles widely used as molecular platforms for the construction of efficient and selective hosts for neutral and charged guests. The common synthetic strategy followed for the construction of such receptors is based on the regio- and stereoselective functionalization protocols to introduce and orient onto the macrocycle skeleton suitable binding sites. In this way several milestone achievements in the recognition of alkali and alkaline-earth metal ions recognition have been obtained[1].



n = 4–7; R^1 = *t*-Bu, H; R^2 = H, alkyl, CH_2COR^3

Calix[4]arene monocrown ethers are one of the most widely investigated class of calixarene-based ligands for complexation of cations[2], whose first member synthesized was the "distal" *p-tert*-butylcalix[4]arene-1,3-monocrown-5 [3]. Starting from this pioneering work, many studies have been performed on complexation properties of compounds having different lengths and rigidity of the crown chain[2,4]. Their derivatives were obtained introducing additional binding sites, such as acetamide or acetate functions, on the two phenolic OH groups present in 2 and 4 position of the calix lower rim (**I**)[5]. On the contrary, the "proximal" *p-tert*-butylcalix[4]arene-1,2-monocrown derivatives (**II**) have been less studied in comparison with the distal 1,3-derivatives. In fact, only one class of such derivatives, obtained through the functionalization of the two phenolic OH groups in the proximal positions with picolyl groups, have been synthesized and their complexation properties toward cations studied[6]. However, although these compounds are less efficient ligands than calix[4]arene-1,3-monocrown, their selectivity towards alkali metal cations is remarkably interesting. It thus appeared to us that a better comprehension of the role played by this particular arrangement of coordination sites on the calix lower rim still merits fundamental studies. In this paper we describe the synthesis and extraction properties toward alkali and alkaline-earth metal picrates, of a series of calix[4]arene derivatives having different stereochemistry, bearing one crowning unit of different length, linking two proximal calix[4]arene phenolic oxygens and two additional hard binding sites, acetamide or acetate groups.

EXPERIMENTAL

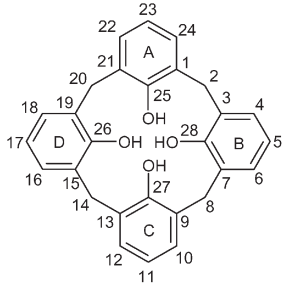
Spectroscopy

^{1}H NMR spectra (δ, ppm; *J*, Hz) were recorded in $CDCl_3$ unless otherwise indicated on Bruker AMX400 and AC300 spectrometers operating at 400 and 300 MHz, respectively, using the solvent residual signal as reference. ^{13}C NMR spectra were recorded on Bruker AC100

and AC300 spectrometers operating at 25 and 75 MHz, respectively. Mass spectra were determined in CI mode (CH_4) on a Finnigan Mass spectrometer. UV-VIS measurements were performed using a Uvikon 860 spectrophotometer.

Synthesis of the Calix[4]arene-Based Ionophores

All reactions were carried out under nitrogen; all solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use. All other reagents were of reagent grade quality as obtained from commercial suppliers and were used without further purification. Melting point are uncorrected. Compounds **1**[7] and **4**[8] were synthesized according to literature procedures. The nomenclature and numbering of the calixarene tetraol introduced by Gutsche[1a] was adopted through the Experimental.



General Procedure for the Preparation of the Calix[4]arene-Based Ionophores in the *cone* Conformation

To a solution of the appropriate *p-tert*-butylcalix[4]arene-monocrown-*n* (**1** or **4**; 0.52 mmol) in dry toluene (30 ml), *t*-BuONa (0.15 g, 1.57 mmol) was added. An azeotropic distillation of the resulting heterogeneous mixture was performed using a Dean–Stark apparatus and the first 3 ml of distillate were discharged. After complete removal of *t*-BuOH formed during the reaction, the mixture was cooled to 70 °C and the alkylating reagent (*tert*-butyl bromoacetate or 2-chloro-*N*,*N*-diethylacetamide, 1.31 mmol) was added. After 12 h the solvent was completely removed under reduced pressure and the solid residue was taken up with a 10% solution of HCl (50 ml) and CH_2Cl_2 (100 ml). The separated organic phase was washed with distilled water to neutral reaction and evaporated to dryness under reduced pressure.

cone-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-mono(crown-4)-27,28-bis{[(1,1-dimethylethoxy)carbonyl]methoxy}-calix[4]arene (**2a**). Treatment of the solid residue with hot methanol afforded 0.26 g of **2a** (50%) as a white solid. M.p. 223–224 °C. ^{1}H NMR (300 MHz): 6.83 and 6.81 2d, *J* = 2.4, 4 H (H-16,18,22,24); 6.78 bs, 4 H (H-4,6,10,12); 4.88 d, *J* = 12.4, 1 H ($ArCH_2Ar$ ax.: H-8); 4.71 bs, 4 H ($ArOCH_2CO$-); 4.69 d, *J* = 12.3, 1 H ($ArCH_2Ar$ ax.: H-20); 4.61 d, *J* = 12.4, 2 H ($ArCH_2Ar$ ax.: H-2,14); 4.5–4.4, 4.2–4.1 and 4.1–3.7 3m, 12 H ($OCH_2CH_2OCH_2CH_2OCH_2CH_2O$); 3.20 d, *J* = 12.4, 1 H ($ArCH_2Ar$ eq.: H-8); 3.16 d, *J* = 12.3, 2 H ($ArCH_2Ar$ eq.: H-2,14); 3.12 d, *J* = 12.4, 1 H ($ArCH_2Ar$ eq.: H-20); 1.49 s, 18 H ($-OC(CH_3)_3$); 1.08 s, 36 H ($ArC(CH_3)_3$). ^{13}C NMR (75 MHz): 169.6, 153.5, 153.2, 134.3, 133.6, 133.3, 125.3, 125.1, 124.9, 80.8, 73.1, 72.6, 70.2, 33.9, 33.8, 31.6, 31.4, 28.1. MS-CI(+), *m/z*: 991 (MH^+).

cone-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-mono(crown-4)-27,28-bis{[(N,N-diethylamino)carbonyl]methoxy}-calix[4]arene (**3a**). Treatment of the solid residue with hot methanol afforded 0.33 g of **3a** (65%) as a white solid. M.p. 127–128 °C. ^{1}H NMR (300 MHz): 6.84 and 6.81 2d, *J* = 2.4, 4 H (H-16,18,22,24); 6.78 s, 4 H (H-4,6,10,12); 5.00 and 4.69 2d, *J* = 14.3, 4 H (ArOCH$_2$CO-); 4.86 d, *J* = 12.4, 2 H, (ArCH$_2$Ar ax.: H-2,14); 4.77 d, *J* = 12.9, 1 H (ArCH$_2$Ar ax.: H-20); 4.64 d, *J* = 12.3, 1 H (ArCH$_2$Ar ax.: H-8); 4.5–4.4, 4.1–4.0 and 3.9–3.7 3m, 12 H (OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$O); 3.5–3.3 m, 8 H (-CON(C**H**$_2$CH$_3$)$_2$); 3.22 d, *J* = 12.9, 1 H (ArCH$_2$Ar eq.: H-20); 3.17 d, *J* = 12.4, 2 H (ArCH$_2$Ar eq.: H-2,14); 3.12 d, *J* = 12.3, 1 H (ArCH$_2$Ar eq.: H-8); 1.2–1.1 m, 12 H (-CON(CH$_2$C**H**$_3$)$_2$); 1.10 and 1.06 2s, 36 H (ArC(CH$_3$)$_3$). ^{13}C NMR (75 MHz): 168.5, 153.6, 153.1, 144.7, 134.4, 132.8, 125.4, 124.9, 72.9, 72.3, 68.9, 40.8, 38.9, 33.8, 33.7, 31.4, 30.9, 14.4, 13.1. MS-CI(+), *m/z*: 989 (MH$^+$).

cone-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-mono(crown-5)-27,28-bis{[(1,1-dimethylethoxy)carbonyl]methoxy}-calix[4]arene (**5a**). Treatment of the solid residue with hot methanol afforded 0.32 g of **5a** (60%) as a white solid. M.p. 153–154 °C. ^{1}H NMR (300 MHz): 6.76 bs, 8 H (H-4,6,10,12,16,18,22,24); 4.88 d, *J* = 12.7, 1 H (ArCH$_2$Ar ax.: H-20); 4.75 s, 4 H (ArOCH$_2$CO-); 4.58 d, *J* = 12.7, 2 H (ArCH$_2$Ar ax.: H-2,14); 4.47 d, *J* = 12.3, 1 H (ArCH$_2$Ar ax.: H-8); 4.2–4.0 and 3.9–3.6 2m, 16 H (OCH$_2$CH$_2$(OCH$_2$CH$_2$O)$_3$); 3.2–3.1 m, 4 H (ArCH$_2$Ar eq.: H-2,8,14,20); 1.44 s, 18 H (-OC(CH$_3$)$_3$); 1.06 s, 36 H (ArC(CH$_3$)$_3$). ^{13}C NMR (75 MHz): 169.6, 153.4, 153.3, 144.7, 134.1, 133.7, 133.5, 125.2, 80.7, 73.6, 72.2, 71.1, 70.5, 33.8, 31.7, 31.4, 28.1. MS-CI(+), *m/z*: 1035 (MH$^+$).

General Procedure for the Preparation of the Calix[4]arene-Based Ionophores in the *1,2-alternate* Conformation

The same procedure as adopted for the synthesis of *cone* conformers is applied but using *t*-BuOCs (0.32 g, 1.57 mmol) as a base.

1,2-alternate-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-mono(crown-4)-27,28-bis{[(1,1-dimethylethoxy)carbonyl]methoxy}-calix[4]arene (**2b**). The desired product was isolated by filtration in 35% yield (0.18 g) as a white solid after treatment of the crude product with hot methanol (concentration and standing of the filtrate overnight afforded 0.06 g of **2a**, 14% yield, after filtration). M.p. 81–83 °C. ^{1}H NMR (300 MHz): 7.20 bs, 4 H (H-4,6, 10,12); 7.10 and 6.96 2d, *J* = 1.9, 4 H (H-16,18,22,24); 4.74 d, *J* = 12.7, 1 H (ArCH$_2$Ar ax.: H-20); 4.39 d, *J* = 12.4, 1 H (ArCH$_2$Ar ax.: H-8); 4.16 d, *J* = 16.2, 2 H (ArOCH$_2$CO-); 4.10 d, *J* = 13.5, 2 H (ArCH$_2$Ar ax.: H-2,14); 3.81 d, *J* = 16.2, 2 H (ArOCH$_2$CO-); 3.66 d, *J* = 13.5, 2 H (ArCH$_2$Ar eq.: H-2,14); 3.7–3.6 and 3.5–3.4 2m, 10 H (OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$O); 3.23 d, *J* = 12.4, 1 H (ArCH$_2$Ar eq.: H-20); 3.11 d, *J* = 12.7, 1 H (ArCH$_2$Ar eq.: H-8); 2.9–2.8 m, 2 H (OC**H**$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$C**H**$_2$O); 1.34, 1.30 and 1.26 3s, 54 H (ArC(CH$_3$)$_3$ and -OC(CH$_3$)$_3$). ^{13}C NMR (75 MHz): 169.5, 154.1, 153.4, 144.4, 143.9, 134.2, 133.3, 131.8, 126.6, 125.7, 80.4, 70.7, 70.5, 38.9, 34.0, 33.9, 31.7, 31.5, 28.1. MS-CI(+), *m/z*: 991 (MH$^+$).

1,2-alternate-5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-mono(crown-4)-27,28-bis{[(N,N-diethylamino)carbonyl]methoxy}-calix[4]arene (**3b**). Treatment of the residue with methanol afforded 0.12 g of **3b** (24%) as a white solid (after concentration and standing overnight, 0.05 g of **3a**, 11% yield, precipitated from the filtrate). M.p. 124–125 °C. ^{1}H NMR (300 MHz): 7.29, 7.15, 7.09 and 6.98 4d, *J* = 2.4, 8 H (H-4,6,10,12,16,18,22,24); 4.81 d, *J* = 12.4, 1 H (ArCH$_2$Ar ax.: H-20); 4.42 d, *J* = 13.7, 2 H (ArCH$_2$Ar ax.: H-2,14); 4.36 d, *J* = 12.5, 1 H (ArCH$_2$Ar ax.: H-8); 4.14 d, *J* = 16.4, 2 H (ArOCH$_2$CO-); 4.00 d, *J* = 12.5, 2 H (ArCH$_2$Ar eq.: H-2,14); 3.80 2d, *J* = 16.4, 2 H (ArOCH$_2$CO-); 3.7–3.5 and 3.5–3.2 2m, 11 H

($OCH_2C\mathbf{H}_2OC\mathbf{H}_2C\mathbf{H}_2OC\mathbf{H}_2CH_2O$, $ArCH_2Ar$ eq.: H-8); 3.12 d, *J* = 12.4, 1 H ($ArCH_2Ar$ eq.: H-20); 3.1–2.9 m, 8 H ($-CON(C\mathbf{H}_2CH_3)_2$); 2.7–2.8 m, 2 H ($OC\mathbf{H}_2CH_2OCH_2CH_2OCH_2C\mathbf{H}_2O$); 1.33 and 1.28 2s, 36 H ($ArC(CH_3)_3$); 1.04 and 0.84 2t, *J* = 6.8, 12 H ($-CON(CH_2C\mathbf{H}_3)_2$). ^{13}C NMR (75 MHz): 168.4, 154.7, 153.5, 144.4, 144.1, 134.5, 132.2, 131.4, 126.2, 125.6, 71.2, 70.7, 69.4, 67.9, 41.2, 40.1, 34.0, 31.6, 30.1, 29.5, 14.5, 13.1. MS-CI(+), *m/z*: 989 (MH^+).

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-mono(crown-5)-27,28-bis{[(N,N-diethylamino)carbonyl]methoxy}-calix[4]arene (**6a**). To a solution of **4** (0.2 g, 0.25 mmol) in DMF (20 ml), NaH (0.02 g, 0.75 mmol) was added. The reaction mixture was vigorously stirred at room temperature for 1 h, and the 2-chloro-*N*,*N*-diethylacetamide (0.09 g, 0.62 mmol) was added. After 48 h at 50 °C, the reaction was quenched by adding a small amount of methanol (CAUTION!). Then the solvent was completely removed under reduced pressure and the solid residue was taken up with a 10% solution of HCl (50 ml) and CH_2Cl_2 (50 ml). The separated organic phase was washed with water to neutral reaction and evaporated to dryness under reduced pressure. Purification of the solid residue by chromatography (eluent hexane/ethyl acetate 9:1) afforded 0.15 g of **6a** (60%). M.p. 229–230 °C. ^1H NMR (300 MHz): 6.78 bs, 8 H (H-4,6,10,12,16,18,22,24); 4.95 d, *J* = 14.5, 2 H ($ArOCH_2CO$-); 4.9–4.7 m, 3 H ($ArOCH_2CO$-, $ArCH_2Ar$ ax.: H-20); 4.71 d, *J* = 13.2, 2 H ($ArCH_2Ar$ ax.: H-2,14); 4.56 d, *J* = 12.5, 1 H ($ArCH_2Ar$ ax.: H-8); 4.3–4.2, 4.2–4.0 and 3.8–3.6 3m, 16 H ($OCH_2CH_2(OCH_2CH_2O)_3$); 3.6–3.4 m, 8 H ($-CON(C\mathbf{H}_2CH_3)_2$); 3.19 d, 1 H ($ArCH_2Ar$ eq.: H-20); 3.18 d, *J* = 13.2, 2 H ($ArCH_2Ar$ eq.: H-2,14); 3.11 d, *J* = 12.5, 1 H ($ArCH_2Ar$ eq.: H-8); 1.3–1.1 m, 12 H ($-CON(CH_2C\mathbf{H}_3)_2$); 1.08 and 1.06 2s, 36 H ($ArC(CH_3)_3$). ^{13}C NMR (75 MHz): 168.5, 153.5, 153.4, 144.5, 134.2, 133.8, 125.3, 125.0, 73.5, 71.6, 70.6, 41.0, 39.8, 33.8, 31.7, 31.4, 31.0, 14.5, 13.1. MS-CI(+), *m/z*: 1033 (MH^+).

X-ray Studies

A yellow single crystal suitable for the X-ray experiments was isolated and mounted on an Enraf–Nonius CAD4 diffractometer equipped with a CuKα radiation source (λ = 1.54178 Å) monochromated with graphite crystal. Cell parameters were obtained by a least-squares fit of 28 $I(\theta\kappa\phi)_{hkl}$ reflections in the range: $22.5 \le \theta \le 31.6°$. Crystal data and the most significant experimental details and parameters used in the crystal structure refinement are collected in Table I. One standard reflection monitored every 100 ones, indicated a decay of about 20% during the data collection. The intensities were corrected for Lorentz and polarization effects but not for absorption. No unusual trends were found in F_o^2 versus F_c^2 as a function of $(\sin\theta)/\lambda$, Miller indices, and F_o^2.

The structure was solved by direct methods using SIR92 [9]. At first two strontium cations and their nearest neighbor were located, then the structure was completed by successive cycles of Fourier Δ*F* maps. The compound is the co-crystallization product between the **6a** ⊃ $Sr(Pic)_2$ and the $Sr(Pic)_2$ salt. The crystal lattice is built up by one cationic and one anionic species: the cationic one is the **6a** ⊃ Sr^{2+} complex, whereas the anionic one is formed by the strontium picrate salt – whose metal ion also coordinates the two picrate anions from the first strontium ion – and a 2-propanol solvent molecule giving an anionic complex of formula $[Sr(Pic)_4 \supset CH_3CHOHCH_3]^{2-}$. The cationic complex showed severe static disorder in the crown moiety and in the *tert*-butyl groups and this prevented a low final value of *R*.

The structure was refined by full matrix least-squares on F^2 with SHELXL97 [10] using anisotropic atomic displacements for the two strontium atoms. All the hydrogen atoms were

added to the corresponding C atoms in the "riding" model, with the geometrical constraint C–H = 0.96 Å) and refined with isotropic atomic displacements. All the geometrical calculations were obtained by PARST [11]. All the calculations were carried out on a DEC Alpha 250 workstation.

TABLE I
Crystal data and details for data collection and crystal structure refinement

Empirical formla	$[C_{64}H_{90}N_2O_9Sr]^{2+}\cdot[Sr(C_6H_2N_3O_7)_4\cdot(C_3H_8O)]^{2-}$
Formula weight	2179.149
Crystal size, mm	0.3 × 0.2 × 0.4
Crystal system	triclinic
Space group	*P*-1(No.2)
a, Å	25.830(5)
b, Å	15.678(5)
c, Å	13.286(5)
α, °	99.43(2)
β, °	88.30(2)
γ, °	86.91(2)
V, Å^3	5296(3)
Z	2
ρ(calcd.), g cm^{-3}	1.366
F(000)	2260
T, K	298
λ, Å	CuKα 1.54178
μ, mm^{-1}	2.09
Diffractometer	Enraf–Nonius CAD4
Index ranges	$-30\leq h\leq 30$, $-18\leq k\leq 18$, $-4\leq l\leq 15$
Reflections collected	16 449
Independent reflections	15 501 (R_{int} = 0.0175)
Observed reflections	7512 [$F_0\geq\sigma(F_0)$]
Parameters, restraints	561, 5
R_1 [a]	0.136
wR_2	0.392
Goodness-of-fit on F^2 [b]	1.181
Highest peak, deepest hole, e Å^{-3}	1.50, –1.01

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4]^{1/2}$. [b] GOF = $[\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p the number of parameters.

CCDC 225858 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

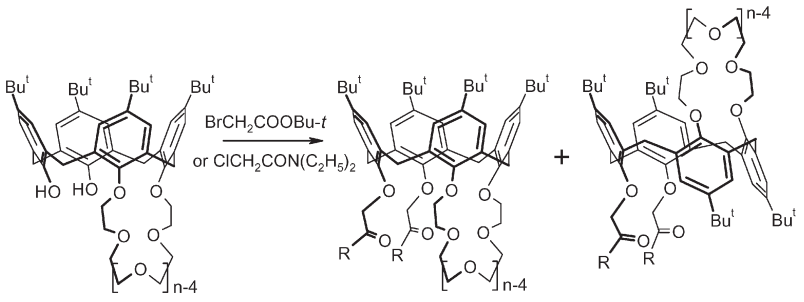
RESULTS AND DISCUSSION

Synthesis of Ionophores

In a previous paper we have shown the possibility to synthesize *p-tert*-butylcalix[4]arene-monocrown-*n* (*n* = 4, 5) derivatives by regioselective alkylation of two proximal phenolic groups of the macrocycle lower rim[7]. In the same study we also verified that a stereochemical control in the lower rim double 1,2-bridging process could be achieved through a careful choice of the base/solvent system employed in these alkylation reactions. In particular, *cone* and *1,2-alternate* conformers of the *p-tert*-butylcalix[4]arene-biscrown-4 were obtained in satisfactory yields using NaH in DMF or *t*-BuOK in toluene, respectively. The combination of such regio and stereoselective methodologies could lead to the synthesis of new calixarene-based ionophores in which two additional "hard" binding sites, such as esters or amide groups, and a "crown" unit are attached to the calix[4]arene fixed in different geometries.

The *p-tert*-butylcalix[4]arene-monocrown-4 (**1**) was employed as starting material to evaluate the scope of this synthetic approach. Therefore compound **1** was reacted with *tert*-butyl bromoacetate under several reaction conditions and with several base/solvent couples. We found that only by using NaH in DMF or *t*-BuONa in toluene the *cone*-diester-monocrown-4 **2a** could be isolated in 32 or 50% yield, respectively.

The ^{1}H NMR spectrum of **2a** is in agreement with a calix[4]arene derivative in the *cone* conformation having the lower rim tetrafunctionalized with two different types of substituents in the proximal positions (Scheme 1). In fact the bridging methylene protons of the calix resonate as three AX systems in the 1:1:2 integral ratio at δ 4.88, 4.69, 4.61 ppm (axial protons) and 3.20, 3.12, 3.16 ppm (equatorial protons), respectively, while the aromatic protons resonate at δ 6.83, 6.81 and 6.78 ppm, as two doublets and a singlet, respectively. When the insertion of the two ester functions was carried out using *t*-BuOCs as a base and dry toluene as solvent, both the *cone* (**2a**) and the *1,2-alternate* (**2b**) conformers of the diester-monocrown-4 were isolated in 14 and 35% yields, respectively (see Scheme 1).



1 n = 4
4 n = 5

2a n = 4, R = OBu-*t*
3a n = 4, R = $N(CH_2CH_3)_2$
5a n = 5, R = OBu-*t*
6a n = 5, R = $N(CH_2CH_3)_2$

2b n = 4, R = OBu-*t*
3b n = 4, R = $N(CH_2CH_3)_2$

Reaction conditions: base/solvent/*T*	yield (%) *cone* / *1,2-alt* **2a** / **2b**	**3a** / **3b**	**5a**	**6a**
t-BuOCs / toluene/ 80 °C	14 / 35	11 / 24	--	--
t-BuONa / toluene/ 80 °C	50 / --	65 / --	60	--
NaH / DMF/ 50 °C	32 / --	45 / --	16	60

SCHEME 1

In the ^{1}H NMR spectrum of **2b** ($CDCl_3$), the calixarene bridging methylene protons resonate as three AX systems at δ 4.74, 4.39, 4.10 ppm (axial protons) and 3.66, 3.23, 3.11 ppm (equatorial protons), which are in the 1:1:2 ratio, respectively. However, diagnostic for *1,2-alternate* conformation are the two symmetrical protons of the polyether chain in the α position to the two phenolic oxygens, which experience a substantial upfield shift ($\Delta\delta \approx 0.8$ ppm) as a consequence of the anisotropic shielding effect of the facing aromatic rings of the calix[6,7].

The diamide derivatives of the *p-tert*-butylcalix[4]arene-monocrown-4 were prepared by the reaction of **1** with 2-chloro-*N*,*N*-diethylacetamide adopting the same experimental conditions devised for the synthesis of the corresponding esters (see Scheme 1). Thus, the *cone* conformer **3a** was isolated in 65% yield using *t*-BuONa as the base and toluene as the solvent. The use of the more polar DMF as solvent with either NaH or *t*-BuONa slightly decreases the overall reaction yield. When *t*-BuOCs was used as a base in toluene, the *1,2-alternate* conformer **3b** was isolated in 24% yield. In this case, the *cone* **3a** still remains an important by-product of the reaction (11%). The NMR spectra of **3a**, **3b** show the same characteristic features described for the corresponding ester derivatives.

When *p-tert*-butylcalix[4]arene-monocrown-5 (**4**) was used as starting reagent for the preparation of the ionophores, a general improvement of the yields were obtained in the synthesis of the ester *cone* conformer **5a** using

t-BuONa/toluene system, whereas for the corresponding amide **6a** better results were found with NaH/DMF. Interestingly, the presence of a longer polyether chain on the calix[4]arene scaffold prevents the formation of the products in the *1,2-alternate* conformation, even when *t*-BuOCs was used as a base.

Extraction Studies

In order to evaluate the binding properties of ligands **2a**, **2b**, **3a**, **3b**, **5a** and **6a**, we determined the energy of complexation (ΔG^0) with alkali picrates in chloroform using the Cram's method[12]. The results obtained have been summarized in Table II and in Fig. 1. As a general trend all these derivatives have shown distinct complexing abilities toward all the alkali metal picrates tested, even though with a general preference for the smaller cations of the series. However, some useful considerations on the effect of both the ligand geometry and the crown length could be drawn from a careful analysis of the results obtained. Among the compounds in the *cone* conformation, monocrown-5 derivatives **5a** and **6a** are more efficient than the corresponding monocrown-4 derivatives **2a** and **3a**, respectively. Furthermore, within this series, the substitution of the esters coordination sites with the more electron-donating amide groups (cf. **2a** and **5a** with **3a** and **6a**) results, as expected, in a general enhancement of the binding abilities.

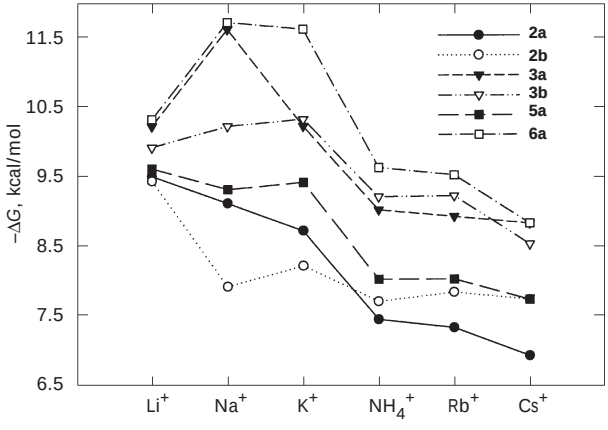


FIG. 1
ΔG^0 (in kcal/mol) of binding of the complexation of ligands **2a** (●), **2b** (○), **3a** (▼), **3b** (▽), **5a** (■) and **6a** (□) with alkali picrates in $CHCl_3$ at room temperature

TABLE II
Gibbs free energy of the formation of alkali metal picrate complexes of ligand **2a**, **2b**, **3a**, **3b**, **5a** and **6a** in $CHCl_3$ saturated with water at room temperature

Ligand	–Δ*G*°, kcal/mol					
	Li^+	Na^+	K^+	NH_4^+	Rb^+	Cs^+
2a	9.49 ± 0.03	9.1 ± 0.1	8.7 ± 0.3	7.42 ± 0.09	7.3 ± 0.2	6.9 ± 0.3
2b	9.42 ± 0.06	7.9 ± 0.3	8.2 ± 0.3	7.68 ± 0.07	7.81 ± 0.04	7.7 ± 0.2
3a	10.2 ± 0.3	11.6 ± 0.1	10.2 ± 0.1	9.0 ± 0.3	8.9 ± 0.4	8.8 ± 0.3
3b	9.9 ± 0.1	10.2 ± 0.2	10.3 ± 0.2	9.19 ± 0.09	9.2 ± 0.1	8.5 ± 0.1
5a	9.6 ± 0.2	9.3 ± 0.03	9.4 ± 0.1	8.0 ± 0.3	8.0 ± 0.4	7.7 ± 0.1
6a	10.3 ± 0.1	11.7 ± 0.3	11.6 ± 0.3	9.61 ± 0.03	9.5 ± 0.04	8.8 ± 0.3

The ligands in the *1,2-alternate* conformation **2b** and **3b**, in which the two different types of binding sites cannot cooperate in binding, showed, on the contrary, higher affinity to the cations with minor ionic radii. Although the diamide derivative **3b** exhibited, as expected, better efficiency than the geometrically analogous diester derivative **2b**, this latter compound evidenced an interesting selectivity for the lithium ion.

X-ray Studies

The ionophoric properties of the synthesized ligands were also evaluated with alkaline-earth picrates using extraction experiments from water into dichloromethane. Preliminary results showed, however, scarce selectivity among the picrates tested (Ca^{2+}, Sr^{2+} and Ba^{2+})[13,14], but we succeeded in obtaining suitable crystals for X-ray analysis by mixing strontium picrate with the *p-tert*-butylcalix[4]arene-*N*,*N*-diethylacetamide-crown-5 (**6a**) in 2-propanol. After a slow evaporation the ligand–strontium picrate complex was isolated as a yellow crystalline solid. Subsequently, X-ray crystal structure analysis showed that instead of the expected **6a** ⊃ $Sr(Pic)_2$ complex of the 1:1 stoichiometry, the crystallization gave a 1:2 ligand/salt ratio which is not simply the product of the co-crystallization of the $Sr(Pic)_2$ salt together with the complex of the 1:1 stoichiometry, but it is formed by one cationic and one anionic complex, both containing one Sr^{2+} ion.

The cationic complex is the [**6a** ⊃ $Sr]^{2+}$ unit (see Fig. 2a), whereas the anionic one is formed by the strontium picrate salt, whose metal ion also binds the two picrate anions released by the first strontium ion, and a 2-propanol molecule of overall formula $[Sr(Pic)_4 \cdot CH_3CHOHCH_3]^{2-}$ (see Fig. 2b). At the best of our knowledge this is the first example of formation of a co-crystallization product of calixarene-strontium picrate with the picrate salt. This phenomenon is somewhat surprising considering that an analogous behavior was not observed, for example, in the crystal structure of the *p-tert*-butylcalix[4]arene-tetra-*N*,*N*-diethylacetamide ⊃ $Sr(Pic)_2$ complex[15], in which the shielding effect of the calix[4]arene ligand on the strontium cation is similar to that exerted by **6a**. Further effort will be necessary to clarify this unexpected behavior.

In the lattice, the $Sr_{cationic} \cdots Sr_{anionic}$ separation is 8.242(3) Å. The structure of the cationic complex is illustrated in Fig. 2a. The Sr^{2+} ion is nine-coordinated in the form of a slightly distorted capped square antiprism. The upper face of the antiprism is delimited by the four phenolic oxygens O1a, O1b, O1c, O1d which are coplanar within the estimated standard deviations; the lower face is defined by the two carbonyl oxygens O2a, O2b and by the two crown oxygens O1*, O3*. The latter four oxygen atoms are not rigorously coplanar, although the maximum out of plane value (0.11 Å

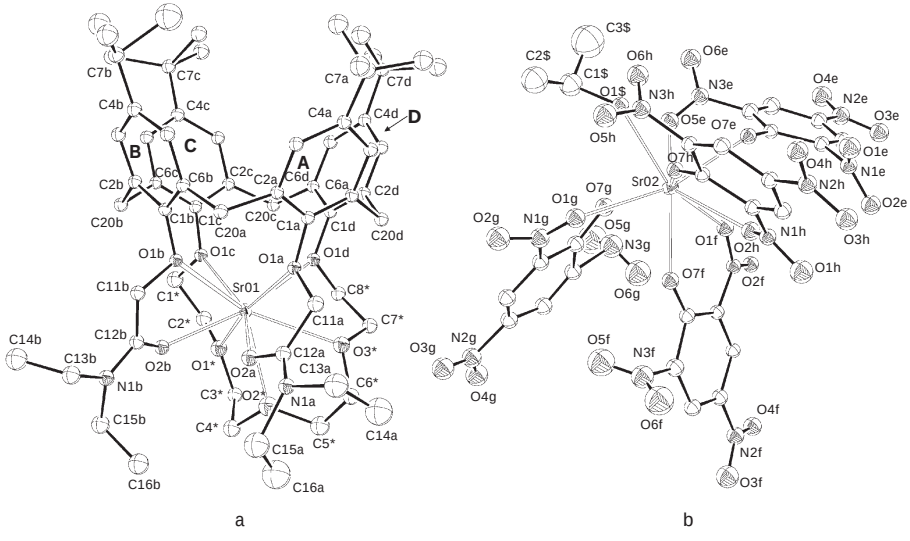


FIG. 2

a Perspective view of the cationic complex. b Perspective view of the anionic complex. In both figures hydrogen atoms have been omitted for clarity

for O1*) is quite small. The dihedral angle of 3.8(2)° between the upper and lower face of the antiprism indicates that the distortion of the coordination polyhedron is quite small. The ninth coordination site is supplied by the external atom of the crown (O2*) and is located nearly the ideal apical position for a capped square antiprism: the Sr–O2* bond is inclined by 17.3(2)° from the normal to the lower face of the antiprism. The calix[4]arene basket adopts a cone conformation in a pseudo C_4 symmetry. The whole conformation of the calix[4]arene basket is unequivocally described by the conformational parameters[16] reported in Table III and leads to the symbolic representation C_1 +-,+-,+-,+-.

The dihedral angles δ between the four phenolic units and the reference plane **R** (the weighted least-squares plane between the four CH_2 bridging groups according to standard rules for calixarenes[17] reported in Table III), together with the absolute values of the ϕ and χ angles (comparable in pairs), indicate a small distortion from the ideal C_4 symmetry.

The structure of the anionic complex $[Sr(Pic)_4 \cdot CH_3CHOHCH_3]^{2-}$ is shown in Fig. 2b. The strontium ion is nine-coordinated. Each picrate anion acts as a bidentate ligand and binds the cation through the phenoxy oxygen and one nitro oxygen. The coordination sphere is saturated by a 2-propanol molecule whose oxygen atom O1$ occupies the ninth coordination site. The most significant bond distances in the cationic and anionic complexes are collected in Table IV.

It has already been reported that the *p-tert*-butylcalix[4]arene-tetra-*N*,*N*-diethylacetamide ligand extracts the Sr^{2+} ion with higher efficiency than the *p-tert*-butylcalix[4]arene-di-*N*,*N*-diethylacetamide-crown-5. Thus it can be of some interest to compare the obtained geometry of the cationic com-

TABLE III
Conformational parameters (in °) and dihedral angles (in °) between the least-squares reference plane (**R**) and the least-squares planes through the aromatic rings

Conformational parameters, °			Dihedral angles, °	
	ϕ	χ		δ
A–B	83(1)	–79(1)	**R–A**	116.9(3)
B–C	79(1)	–80(1)	**R–B**	112.1(2)
C–D	78(1)	–78(1)	**R–C**	113.6(3)
D–A	76(1)	–83(1)	**R–D**	110.7(3)

plex to that of the analogous one in the *p-tert*-butylcalix[4]arene-tetra-*N*,*N*-diethylacetamide ⊃ $Sr(Pic)_2$, reported by us[15], to see whether the relative stability of the two complexes has a structural basis. In this comparison it is useful to separate the coordination sphere into two parts: (i) the common part – the amide-base coordination sites – in the two complexes, which involves $Sr–O_{phenyl}$ and $Sr–O_{C=O}$ bonds; (ii) the role of the crown-5 chain. Concerning (i), the $Sr–O_{phenyl}$ bond distances increase from 2.577(5) Å (on average) in the complex of the *p-tert*-butylcalix[4]arene-tetra-*N*,*N*-diethylacetamide to 2.689(7) Å (on average) in that of **6a**, whereas the $Sr–O_{C=O}$ bond distances are comparable within the standard deviations (2.502(6) Å (on average) in the former and 2.476(9) Å (on average) in the latter). Concerning the role of the crown-5 chain, even if the $Sr–O_{crown-5}$ bond distances are comparable, within the standard deviations, with those observed in the $[Sr(H_2O)(NO_3)_2(15\text{-crown-}5)]$ complex[18], they are all significantly longer (2.766(11) Å (on average)) than the $Sr–O_{C=O}$ bonds in the *p-tert*-butylcalix[4]arene-tetra-*N*,*N*-diethylacetamide ligand (2.502(6) Å (on average)) and, therefore, each of the crown oxygens binds the cation less strongly than one amidic carbonyl oxygen.

In conclusion, the balance of what is gained and what is lost in the coordination sphere of the metal cation due to the substitution of two amide-

TABLE IV
Bond distances (in Å) in the coordination sphere of the Sr^{2+} ion in the cationic and anionic complexes

		$[\mathbf{6a} \supset Sr]^{2+}$	
Sr01–O1a	2.728(7)	Sr01–O2b	2.474(9)
Sr01–O1b	2.715(7)	Sr01–O1*	2.725(7)
Sr01–O1c	2.695(7)	Sr01–O2*	2.780(12)
Sr01–O1c	2.617(7)	Sr01–O3*	2.794(10)
Sr01–O2a	2.477(8)		
		$[Sr(Pic)_4 \cdot CH_3CHOHCH_3]^{2-}$	
Sr02–O5e	2.721(13)	Sr02–O7e	2.520(10)
Sr02–O1f	2.648(9)	Sr02–O7f	2.488(11)
Sr02–O1g	2.792(13)	Sr02–O7g	2.466(11)
Sr02–O2h	2.766(10)	Sr02–O7h	2.521(8)
Sr02–O1$	2.613(10)		

based coordination chains with crown-5 seems to justify a decrease of the stability. This can be interpreted as the superposition of four effects: (i) the $Sr–O_{C=O}$ bond distances remain practically unchanged; (ii) the $Sr–O_{phenyl}$ bond distances increase and thus tends to reduce the stability of the complex; (iii) the lengthening of the $Sr–O_{crown}$ distances with respect to the $Sr–O_{C=O}$ ones also reduces the binding of the cation; (iv) these destabilizing effects are not compensated by the gain in the binding coming from the addition of the ninth coordination site O2*.

The crystal packing, illustrated in Fig. 3, is determined only by electrostatic interactions between cationic and anionic complexes without assistance of intermolecular hydrogen bonds.

CONCLUSIONS

Different conformers, *cone* and *1,2-alternate*, of *p-tert*-butylcalix[4]arene-1,2-monocrown-4 having either *tert*-butyl acetate (**2a**, **2b**) or *N*,*N*-diethylacetamide (**3a**, **3b**) coordination groups on the remaining phenolic oxygens of the lower rim have been synthesized through a careful choice of the base counterion during the alkylation reaction of *p-tert*-butylcalix[4]arene-1,2-monocrown-4 (**1**). The same stereochemical control could not be obtained when a calix[4]arene derivative having a longer crown chain (**4**) is employed as starting material, and only the respective *cone* conformers (**5a** and **6a**) have been obtained in satisfactory yields. Liquid–liquid extraction experiments of alkali picrates (from water to chloroform) have shown that the efficiency and selectivity of the synthesized ligands depend on (i) the

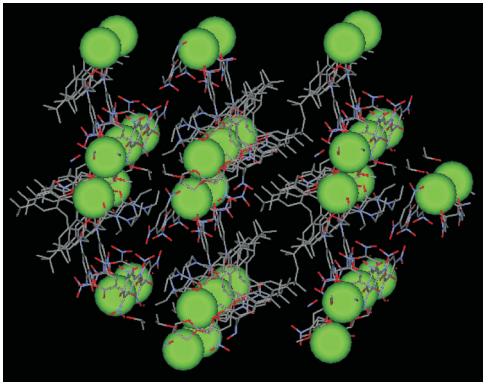


FIG. 3
Crystal packing of $[\mathbf{6a}]^{2+}[Sr(Pic)_4 \cdot CH_3CHOHCH_3]^{2-}$ compound. For clarity, the Sr^{2+} ions are represented by CPK spheres

length of the crown chain, (ii) the nature of the hard binding site and (iii) the geometry of the calix[4]arene scaffold. In particular, *N*,*N*-diethylacetamide substituents together with longer crown chain generally improve the extraction ability of these ligands. Concerning the ligand geometry, the *cone* derivatives, as expected, show a generally higher efficiency than the corresponding *1,2-alternate* derivatives, although these latter compounds are more efficient and selective to the smallest cation (Li^+) of the series. The solid state structure of the *p-tert*-butylcalix[4]arene-*N*,*N*-diethylacetamide-crown-5 (**6a**) complex with strontium picrate demonstrates that the binding event occurs through the formation of a coordination sphere in which the strontium cation is entrapped, through the cooperation between the ether oxygens belonging to the crown chain with the ether and carbon oxygens of the acetamide moieties.

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