New Efficient Calixarene Amide Ionophores for the Selective Removal of Strontium Ion from Nuclear Waste: Synthesis, Complexation, and Extraction Properties

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Received July 12, 2001

Abstract: Three novel *lower rim* hexamide derivatives $\mathbf{5_6}$, $\mathbf{7_6}$, and $\mathbf{9_6}$ of *p*-hydroxycalix[6]arene and four octamides $\mathbf{5_8}$, $\mathbf{7_8}$−$\mathbf{9_8}$ derived from the corresponding *p*-hydroxycalix[8]arene were synthesized, and their potential as extractants in radioactive waste treatment was evaluated, in comparison with *upper rim* analogues $\mathbf{12_6}$ and $\mathbf{12_8}$ and other existing selective neutral ionophores currently used in radioactive waste treatment. Extraction of alkali and alkaline earth metal picrates from water to dichloromethane, and of the corresponding nitrates from acidic water solution simulating radioactive waste, to 2-nitrophenyl hexyl ether (NPHE), showed that the *lower rim* amides extract divalent cations much better than monovalent ones. The *upper rim* hexa-$\mathbf{12_6}$ and octamide $\mathbf{12_8}$ are very inefficient ligands, hardly extracting any cation. In all cases, *p*-alkoxy octamides are more efficient and selective extractants than the corresponding hexamides. In the case of simulated waste solutions, the distribution coefficients for strontium removal by octamides ($6.5 < D_{Sr} < 30$) are much higher than the corresponding value (D_{Sr}) found for dicyclohexyl-18-crown-6 (DC18C6), and the same applies for the strontium/sodium selectivity, which is $6500 < D_{Sr}/D_{Na} < 30\,000$ for octamides and 47 for DC18C6. ESI-MS, UV−vis, and X-ray crystal structure studies give consistent results and indicate the formation of 2:1 (cation/ligand) strontium complexes for all octamides tested. Stability constants were determined in homogeneous methanol solution for alkali metal ($\log \beta_{11} \leq 2$), calcium ($4.3 \leq \log \beta_{11} \leq 6.0$; $9.4 \leq \log \beta_{21} \leq 12.0$), and strontium ($5.6 \leq \log \beta_{11} \leq 12.3$) ions using a UV−vis competition method with 1-(2-pyridylazo)-2-naphthol (PAN). They confirm the high efficiency and high divalent/monovalent selectivity found in metal ion extraction experiments for the new octamide ligands. Evidence for a positive cooperative effect between the two metal ion binding sites was obtained in the case of the Ca^{2+} complex of octamide $\mathbf{1_8}$.

Introduction

Nuclear fuel reprocessing operations produce both high and medium activity liquid wastes (HLW/MLW).[1,2] The major nuclides are long-lived β/γ emitters (^{99}Tc, ^{129}I, ^{135}Cs, ^{137}Cs, ^{90}Sr) or α emitters such as transuranium elements. Medium-level wastes are treated by evaporation or other conventional techniques such as chemical precipitation, ion exchange, and so forth to concentrate their radioactivity into the smallest possible volume. Nevertheless, this treatment leads to large volumes of concentrate solutions containing $NaNO_3$ (4 M) and HNO_3 (1 M) as an inactive matrix. Because of the presence of the long-life radionuclides, the great part of these concentrates has to be disposed in geological formation after embedding. One of the major goals of the radioactive nuclear waste treatment is to selectively remove β/γ emitters, in particular ^{137}Cs and ^{90}Sr radionuclides, to allow decategorization of MLW. In this context, the use of selective extraction appears particularly promising.[3] However, extremely high Cs^+/Na^+ and Sr^{2+}/Na^+ selectivity of the ligands is required, because sodium is usually present at high concentration (2−4 M), while cesium and strontium ions are much more diluted ($\sim 10^{-3}$ M).

We have previously found that calix[4]arene crowns-6 in the *1,3-alternate* conformation are extremely selective for cesium over sodium,[4] and their application to the treatment of nuclear waste is currently under development.[5] However, there is still need for efficient ligands displaying high strontium/sodium selectivity. Previous studies from our and other laboratories have shown that calix[4]arene tetramides $\mathbf{1_4}$ and $\mathbf{2_4}$ (Chart 1) are efficient ligands for alkaline earth metal ions, but they also

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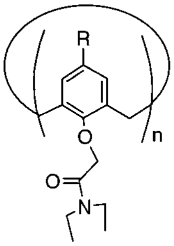
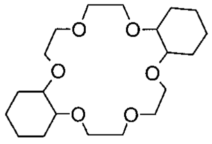
10.1021/ja016597f CCC: $20.00

Chart 1



$\mathbf{1}_n$:R = t-Bu, n = 4, 6, 8
$\mathbf{2}_n$:R = H, n = 4, 6, 8



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strongly bind sodium ions.[6] The replacement of two distal tertiary amide binding groups in *p-tert*-butylcalix[4]arene derivative $\mathbf{1_4}$ by secondary or primary amides strongly decreases the binding efficiency and does not significantly improve the Sr^{2+}/Na^+ selectivity.[7] On the other hand, the replacement of two amide groups in $\mathbf{1_4}$ with ionizable carboxylic acids gives the calix[4]arene diamide−dicarboxylic acids which are ionophores having a high Sr^{2+}/Na^+ selectivity but only at $4 < pH < 7$.[8]

Calix[6]arene amide derivatives $\mathbf{1_6}$ and $\mathbf{2_6}$ were shown to be able to complex strontium cation.[9,10] The X-ray crystal structure of the strontium complex of *p-tert*-butylcalix[6]arene hexamide $\mathbf{1_6}$ in the solid state shows that the metal cation is eight-coordinated by the oxygen atoms of the ligand and that one amide group does not participate in the coordination.[10] Extraction and complexation studies have shown that the Sr^{2+}/Na^+ selectivity of calix[6]arene amides depends on the nature of the alkyl groups present at the upper rim of calixarene, with the *p*-H derivative $\mathbf{2_6}$ being the most selective.[9] This compound presents a Sr^{2+}/Na^+ selectivity slightly higher than that of dicyclohexyl-18-crown-6 (DC18C6) **3** which is known to be one of the most selective extractants for strontium ion.[11,12] However, the Sr^{2+}/Na^+ selectivity of these ligands has not been considered sufficient for their application in the radioactive waste treatment. We have recently developed an efficient one-step procedure for the synthesis of *p*-alkoxy calix[8]arenes by condensing *p*-benzyloxy phenol and formaldehyde in basic conditions.[13] During the present work, we were also able to isolate (5% yield) the *p*-benzyloxycalix[6]arene which is a key intermediate product for the synthesis of other *p*-alkoxycalix[6]arene derivatives. This circumstance allowed us to explore the possibility of synthesizing various calix[6]- and calix[8]arene amides and to evaluate their potential in radioactive waste treatment.

We report in this paper the synthesis, complexation, and extraction data for these ligands which appear to be quite useful in the selective removal of $^{90}Sr^{2+}$ from radioactive waste.

Experimental Section

General. Most of the solvents and all reagents were obtained from commercial supplies and used without further purification. DMF employed in the synthesis was stored over 3 Å molecular sieves. All reactions were performed with efficient stirring in a nitrogen atmosphere. Melting points were obtained in a nitrogen-sealed capillary on Electrothermal Apparatus. TLC was performed on precoated silica gel plates (Merck 60 F_{254}), while silica gel 60 (Merck, particle size 0.040−0.063 mm, 230−240 mesh) was used for preparative column chromatography. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR 300 MHz and ^{13}C NMR 75 MHz) were recorded on a Bruker AC300 spectrometer. Chemical shifts are reported as δ values in ppm from tetramethylsilane as internal standard. Analytical thin-layer chromatography was carried out on silica gel plates (SiO_2, Merck 60 F_{254}). Mass spectra were performed with FINNIGAN MAT SSQ 710 (CI, CH_4) and FINNIGAN MAT 90 (FAB, NBA). Mass spectra of the Sr^{2+} complexes were obtained in methanol using ESI mode on a ZMD Micromass QUATTRO LC spectrometer (experimental conditions: capillary voltage 3.01 kV, cone voltage 15 V, extractor voltage 6 V, source block temperature 100 °C, desolvation temperature 180 °C).

The general procedures for the synthesis and the characterization of 5,11,17,23,29,35,41,47-octabenzyloxy-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene ($\mathbf{4_8}$), 5,11,17,23,29,35,41,47-octabenzyloxy-49,50,51,52,53,54,55,56-octakis[(*N,N*-diethylaminocarbonyl)methoxy]calix[8]arene ($\mathbf{5_8}$), 5,11,17,23,29,35,41,47-octahydroxy-49,50,51,52,53,54,55,56-octakis[(*N,N*-diethylaminocarbonyl)methoxy]calix[8]arene ($\mathbf{6_8}$), 5,11,17,23,29,35,41,47-octabenzyloxy-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene ($\mathbf{10_8}$), and 5,11,17,23,29,35,41,47-octahydroxy-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene ($\mathbf{11_8}$) are reported in details in ref 13.

5,11,17,23,29,35-Hexabenzyloxy-37,38,39,40,41,42-hexahydroxycalix[6]arene ($\mathbf{4_6}$). Compound $\mathbf{4_6}$ was obtained as a byproduct of the previously reported[13] preparation of $\mathbf{4_8}$, and its synthesis was not optimized. The dichloromethane filtrate after the precipitation of compound $\mathbf{4_8}$ was distilled off, the solid residue washed with 50 mL of ethyl ether and filtered on a Buchner funnel to yield 1.1 g (5%) of hexamer $\mathbf{4_6}$: mp > 300 °C; ^{1}H NMR (DMSO-d_6, 300 K) δ 8.52 (s, 6H, OH), 7.29 (m, 30H, PhH), 6.64 (s, 12H, ArH), 4.83 (s, 12H, CH_2-Ph), 3.75 (s, 12H, $ArCH_2Ar$); ^{13}C NMR (DMSO-d_6, 300 K) δ 151.7, (s, Ar para), 144.9 (s, Ar ipso), 137.2 (s, Ph), 128.6 (s, Ar ortho), 128.5, 128.1, 127.6 (d, Ph), 114.3 (d, Ar meta), 69.3 (t, OCH_2Ph), 31.2 (t, $ArCH_2Ar$); MS (CI) *m/z* (%) 1273.4 (100) $[M + H]^+$. Anal. Calcd for $C_{84}H_{72}O_{12}$ (1273.49): C, 79.23; H, 5.69. Found: C, 79.18; H, 5.77.

General Procedure for the Alkylation of Calixarenes with α-Chloro-*N,N*-diethylacetamide. A solution of 0.40 mmol of the proper calixarene, dissolved in 20 mL of dry DMF, was heated at 90 °C under stirring with Cs_2CO_3 (4 mol for each mole of OH) and α-chloro-*N,N*-diethylacetamide (6 mol for each mole of OH). After 15−20 h, the cooled reaction mixture was quenched with 1 N HCl (75 mL), and the crude product was filtered on a Buchner funnel and washed with water. The solid was dissolved in 20 mL of CH_2Cl_2, and the organic solution washed with 2 N HCl (2 × 25 mL) and water (2 × 25 mL). The organic phase was dried over $MgSO_4$ and CH_2Cl_2 and distilled off, and products $\mathbf{1_8}$, $\mathbf{2_8}$, $\mathbf{5_6}$, and $\mathbf{12}_n$ ($n = 6, 8$) were purified as reported in following sections.

5,11,17,23,29,35,41,47-Octakis(1,1-dimethylethyl)-49,50,51,52,53,54,55,56-octakis[(*N,N*-diethylaminocarbonyl)methoxy]calix[8]arene ($\mathbf{1_8}$). Compound $\mathbf{1_8}$ was obtained by crystallization from methanol. Yield 64%; mp > 300 °C; ^{1}H NMR ($CDCl_3$, 300 K) δ 6.69 (s, 16H, ArH), 4.37 (s, 16H, OCH_2CO), 4.13 (s, 16H, $ArCH_2Ar$), 3.21 (bs, 32H, NCH_2CH_3), 1.05 (s, 72H, tBu), 1.22 (t, $^3J = 7$ Hz, 24H, NCH_2CH_3), 0.84 (t, $^3J = 7$ Hz, 24H, NCH_2CH_3); ^{13}C NMR ($CDCl_3$, 300 K) δ 167.0 (s, OCH_2CO), 153.4 (s, Ar ipso), 146.0 (s, Ar para), 132.5 (s, Ar ortho), 125.9 (d, Ar meta), 71.1 (t, OCH_2CO), 41.1, 39.9 (t, NCH_2CH_3), 34.1 (s, $C(CH_3)_3$), 31.2 (t, $ArCH_2Ar$), 31.4 (s, $C(CH_3)_3$), 14.0, 12.8 (q, NCH_2CH_3); MS (CI) *m/z* (%) 2201 (100) $[M]^+$. Anal. Calcd for

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$C_{136}H_{200}N_8O_{16}$ (2203.14): C, 74.14; H, 9.15; N, 5.09. Found: C, 74.07; H, 9.22; N, 5.18.

49,50,51,52,53,54,55,56-Octakis[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[8]arene (2_8). Compound **2_8** was obtained by flash chromatography (SiO$_2$; AcOEt/NEt$_3$ = 10/0.5) and crystallization from cold ethyl acetate. Yield 75%; mp 84−86 °C; ^{1}H NMR (CDCl$_3$, 300 K) δ 6.61 (bs, 24H, ArH), 4.40 (s, 16H, OCH$_2$CO), 4.10 (s, 16H, ArCH$_2$Ar), 3.31−3.01 (m, 32H, NC*H*$_2$CH$_3$), 1.10−0.77 (m, 48H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 166.8 (s, OCH$_2$*C*O), 155.4 (s, Ar ipso), 133.8 (s, Ar ortho), 129.0 (s, Ar meta), 124.3 (d, Ar para), 71.5 (t, O*C*H$_2$CO), 40.9, 39.7 (t, N*C*H$_2$CH$_3$), 30.4 (t, ArCH$_2$Ar), 13.9, 12.7 (q, NCH$_2$*C*H$_3$); MS (CI) *m/z* (%) 1753 (100) [M]$^+$. Anal. Calcd for $C_{104}H_{136}N_8O_{16}$ (1754.28): C, 71.20; H, 7.81; N, 6.39. Found: C, 71.15; H, 7.79; N, 6.44.

5,11,17,23,29,35-Hexabenzyloxy-37,38,39,40,41,42-hexakis[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[6]arene (5_6). Product **5_6** was purified by crystallization from CH$_2$Cl$_2$/CH$_3$OH. Yield 75%; mp 246−247 °C; ^{1}H NMR (CDCl$_3$, 300 K) δ 7.52−7.11, 6.81, 6.80, 6.19 and 5.97 (m, 42H, PhH and ArH), 5.07−4.23 (m, 27H, OC*H*$_2$Ph, OC*H*$_2$CO, ArC*H*$_2$Ar), 3.96, 3.79, 3.40 (bs, 25H, NC*H*$_2$CH$_3$, ArC*H*$_2$Ar), 3.08, 2.49 (q, ^3J = 7 Hz, 2H each, NC*H*$_2$CH$_3$), 1.86 (bs, 30H, NCH$_2$C*H*$_3$), 0.75 and −0.51 (t, ^3J = 7 Hz, 3H each, NCH$_2$C*H*$_3$), 0.90, 0.70, −0.19, −1.61 (bs, 1H, NC*H*$_2$CH$_3$); ^{1}H NMR (DMSO-d_6, 373 K) δ 7.31 and 7.24 (s, 30H, PhH), 6.88 (bs, 12H, ArH), 4.88 (s, 12H, OC*H*$_2$Ph), 4.45 (s, 12H, OC*H*$_2$CO), 3.91 (bs, 12H, ArC*H*$_2$Ar), 3.26 (bs, 24H, NC*H*$_2$CH$_3$), 1.01 (bs, 36H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 168.0, 167.6, 167.5, 167.3, 166.9 (s, OCH$_2$*C*O), 155.1, 154.9, 154.3 (s, Ar ipso), 151.4, 150.7, 148.9 (s, Ar para), 138.1, 137.6, 137.1 (s, Ph), 135.4, 134.8, 134.5 (s, Ar ortho), 133.7, 133.5, 128.5, 128.1, 127.9, 127.4, 127.1, 126.9 (d, Ph), 117.4, 116.9, 116.5, 116.0, 115.3, 113.8, 113.5 (d, Ar meta), 74.7, 72.5, 71.4, 70.3, 69.8, 69.2 (t, O*C*H$_2$CO), 41.62, 41.42, 41.0, 40.1, 39.5 (t, N*C*H$_2$CH$_3$), 32.5, 32.1, 31.1 (t, ArCH$_2$Ar), 14.5, 12.9, 12.3, 12.1 (q, NCH$_2$*C*H$_3$); MS (CI) *m/z* (%) 1952 (100) [M + H]$^+$. Anal. Calcd for $C_{120}H_{138}N_6O_{18}$ (1952.45): C, 73.82; H, 7.12; N, 4.30. Found: C, 73.78; H, 7.18; N, 4.39.

5,11,17,23,29,35-Hexakis[(*N*,*N*-diethylaminocarbonyl)methoxy]-37,38,39,40,41,42-hexamethoxycalix[6]arene (12_6). Compound **12_6** was obtained by flash chromatography (SiO$_2$; AcOEt/Et$_3$N = 12/1). Yield 50%; ^{1}H NMR (CDCl$_3$, 300 K) δ 6.43 (s, 12H, ArH), 4.40 (s, 12H, OCH$_2$CO), 3.78 (bs, 12H, ArCH$_2$Ar), 3.36−3.05 (m, 42H, OC*H*$_3$ and NC*H*$_2$CH$_3$), 1.12−0.94 (m, 36H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 166.8 (s, OCH$_2$*C*O), 153.9 (s, Ar ipso), 150.7 (s, Ar para), 134.9 (s, Ar ortho), 114.8 (d, Ar meta), 67.5 (t, O*C*H$_2$CO), 60.4 (q, OCH$_3$), 41.6, 40.4 (t, N*C*H$_2$CH$_3$), 30.6 (t, ArCH$_2$Ar), 14.4, 13.0 (q, NCH$_2$*C*H$_3$); MS (CI) *m/z* (%) 1495.5 (100) [M + H]$^+$. Anal. Calcd for $C_{84}H_{114}N_6O_{18}$ (1495.86): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.56; H, 7.55; N, 5.81.

5,11,17,23,29,35,41,47-Octakis[(*N*,*N*-diethylaminocarbonyl)methoxy]-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene (12_8). Compound **12_8** was obtained by crystallization from AcOEt at −10 °C followed by flash chromatography (SiO$_2$; AcOEt/Et$_3$N = 10/1). Yield 80%; mp 72−75 °C; ^{1}H NMR (CDCl$_3$, 300 K) δ 6.47 (s, 16H, ArH), 4.45 (s, 16H, OCH$_2$CO), 3.90 (s, 16H, ArCH$_2$Ar), 3.42 (s, 24H, OCH$_3$), 3.37−3.20 (m, 32H, NC*H*$_2$CH$_3$), 1.09−1.04 (m, 48H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 166.9 (s, OCH$_2$*C*O), 154.0 (s, Ar ipso), 150.8 (s, Ar para), 134.7 (s, Ar ortho), 114.8 (d, Ar meta), 67.3 (t, O*C*H$_2$CO), 60.7 (q, OCH$_3$), 41.4, 40.2 (t, N*C*H$_2$CH$_3$), 30.4 (t, ArCH$_2$Ar), 14.2, 12.8 (q, NCH$_2$*C*H$_3$); MS (CI) *m/z* (%) 1994 (100) [M + H]$^+$. Anal. Calcd for $C_{112}H_{152}N_8O_{24}$ (1994.49): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.60; H, 7.52; N, 5.80.

5,11,17,23,29,35-Hexahydroxy-37,38,39,40,41,42-hexakis[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[6]arene (6_6). A 0.5 g sample of compound **5_6** was suspended in a mixture of ethanol (10 mL) and cyclohexene (9 mL) in a Schlenk tube under nitrogen. After the addition of 0.1 g (20% w/w to respect with the calixarene) of Pd(OH)$_2$/C (20%, Pearlman's catalyst), the reaction mixture was heated at 90 °C for 15−18 h. Then, the catalyst was removed by filtration on a Celite filter and the filter carefully washed with CH$_2$Cl$_2$ and C$_2$H$_5$OH and again with CH$_2$Cl$_2$. The collected filtrates were evaporated under vacuum to dryness, leaving the crude product in nearly quantitative yields (>90%). Product **6_6** can be crystallized from hexane. Yield 80%; mp 255 °C (dec); ^{1}H NMR (DMSO-d_6, 300 K) δ 8.3 (bs, 6H, ArOH), 6.6 (bs, 12H, ArH), 4.21 (bs, 12H, OC*H*$_2$CO), 3.85 (bs, 12H, ArC*H*$_2$Ar), 3.30 (bs, 24H, NC*H*$_2$CH$_3$), 1.0 (bs, 36H, NCH$_2$C*H*$_3$); ^{1}H NMR (DMSO-d_6, 343 K) δ 8.11 (s, 6H, ArOH), 6.35 (s, 12H, ArH), 4.35 (s, 12H, OC*H*$_2$CO), 3.81 (s, 12H, ArC*H*$_2$Ar), 3.20 (bs, 24H, NC*H*$_2$CH$_3$), 0.90 (bs, 36H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 166.8 (s, OCH$_2$*C*O), 152.5 (s, Ar ipso), 147.8 (s, Ar para), 133.6 (s, Ar ortho), 115.8 (d, Ar meta), 79.4 (t, O*C*H$_2$CO), 40.71 (t, N*C*H$_2$CH$_3$), 30.3 (t, ArCH$_2$Ar), 13.7, 12.6 (q, NCH$_2$*C*H$_3$); MS (FAB) *m/z* (%) 1410.9 (100) [M]$^+$. Anal. Calcd for $C_{78}H_{102}N_6O_{18}$ (1411.70): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.44; H, 7.33; N, 6.02.

General Procedure for Alkylation of Calixarenes 4_6, 6_6, and 6_8. To a stirred solution of 0.5 mmol of compounds **4_6** or **6_n** (n = 6−8), dissolved in 80 mL of dry DMF, were added Cs$_2$CO$_3$ (3 mol for each mole of OH) and the appropriate (CH$_3$I, *n*-C$_5$H$_{11}$I, or *n*-C$_8$H$_{17}$OTs) alkylating agent (3 mol for each mole of OH). The reaction mixture was heated at 90 °C under nitrogen for 18 h. Then DMF was removed under reduced pressure and the residue treated with a 10% HCl aqueous solution (75 mL). Dichloromethane (75 mL) was added and the organic layer separated and washed with water (2 × 50 mL). The organic phase was dried over MgSO$_4$ and the solvent removed under reduced pressure.

5,11,17,23,29,35-Hexamethoxy-37,38,39,40,41,42-hexakis[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[6]arene (7_6). Yield 95%; mp 108−110 °C; ^{1}H NMR (DMSO-d_6, 300 K) δ 7.3−6.8 and 5.7 (bs, 12H, ArH), 4.63 (bs, 12H, OC*H*$_2$CO), 4.3 (bs, 12H, ArC*H*$_2$Ar), 3.9−3.4 (bs, 42H, OCH$_3$ and NC*H*$_2$CH$_3$), 1.10 (bs, 36H, NCH$_2$C*H*$_3$); ^{1}H NMR (DMSO-d_6, 343 K) δ 6.70 (s, 12H, ArH), 4.43 (s, 12H, OC*H*$_2$CO), 3.85 (s, 12H, ArC*H*$_2$Ar), 3.54 (s, 18H, OCH$_3$), 3.17 (bs, 24H, NC*H*$_2$CH$_3$), 0.96 (bs, 36H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 167.1, 166.7 (s, OCH$_2$*C*O), 155.9, 155.8 (s, Ar ipso), 148.5, 148.3 (s, Ar para), 136.2, 135.3, 135.1, 134.5, 134.2 (s, Ar ortho), 116.6, 116.0, 115.7, 114.8, 114.6, 113.9 (d, Ar meta), 72.4, 72.2 (t, O*C*H$_2$CO), 57.4, 56.8, 55.3 (q, OCH$_3$), 41.2, 39.9 (t, N*C*H$_2$CH$_3$), 31.7 (t, ArCH$_2$Ar), 14.5, 12.8 (q, NCH$_2$*C*H$_3$). MS (CI) *m/z* (%) 1496 (100) [M + H]$^+$. Anal. Calcd for $C_{84}H_{114}N_6O_{18}$ (1495.86): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.38; H, 7.75; N, 5.73.

5,11,17,23,29,35,41,47-Octamethoxy-49,50,51,52,53,54,55,56-octakis[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[8]arene (7_8). Yield 70%; mp 96−97 °C; ^{1}H NMR (CDCl$_3$, 300 K) δ 6.43 (s, 16H, ArH), 4.43 (s, 16H, OCH$_2$CO), 4.04 (s, 16H, ArCH$_2$Ar), 3.45 (s, 24H, OCH$_3$), 3.29 (d, ^3J = 6.3 Hz, 16H, NC*H*$_2$CH$_3$), 3.13 (d, ^3J = 6.3 Hz, 16H, NC*H*$_2$CH$_3$), 1.04 (t, ^3J = 6.3 Hz, 24H, NCH$_2$C*H*$_3$), 0.90 (t, ^3J = 6.3 Hz, 24H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 166.9 (s, OCH$_2$*C*O), 155.9 (s, Ar ipso), 148.9 (s, Ar para), 134.6 (s, Ar ortho), 113.9 (d, Ar meta), 72.0 (t, O*C*H$_2$CO), 54.9 (s, OCH$_3$), 41.0, 39.8 (t, N*C*H$_2$CH$_3$), 30.5 (t, ArCH$_2$Ar), 14.0, 12.6 (q, NCH$_2$*C*H$_3$); MS (CI) *m/z* (%) 1994 (100) [M + H]$^+$. Anal. Calcd for $C_{112}H_{152}N_8O_{24}$ (1994.49): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.54; H, 7.56; N, 5.77.

5,11,17,23,29,35,41,47-Octapentyloxy-49,50,51,52,53,54,55,56-octakis[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[8]arene (8_8). Compound **8_8** was obtained by flash chromatography (SiO$_2$; AcOEt/MeOH = 10/1). Yield 65%; mp 68−70 °C; ^{1}H NMR (CDCl$_3$, 300 K) δ 6.49 (s, 16H, ArH), 4.37 (s, 16H, OCH$_2$CO), 4.00 (s, 16H, ArCH$_2$Ar), 3.65 (bs, 16H, OCH$_2$R), 3.24 (bs, 16H, NC*H*$_2$CH$_3$), 3.11 (bs, 16H, NC*H*$_2$CH$_3$), 1.55 (bs, 48H, (CH$_2$)$_3$), 1.28 (bs, 24H, RCH$_3$), 1.01 (t, ^3J = 6.5 Hz, 24H, NCH$_2$C*H*$_3$), 0.85 (t, ^3J = 6.5 Hz, 24H, NCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 166.9 (s, OCH$_2$*C*O), 155.3 (s, Ar ipso), 148.9 (s, Ar para), 134.3 (s, Ar ortho), 114.6 (d, Ar meta), 72.1 (t, O*C*H$_2$CO), 67.7 (s, OCH$_2$R), 41.0, 39.8 (t, N*C*H$_2$CH$_3$), 30.4 (t, ArCH$_2$Ar), 28.8 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 28.7 (t, *C*H$_2$CH$_2$CH$_3$), 22.3 (t, *C*H$_2$CH$_3$), 13.8 (q, CH$_3$), 14.0, 12.6 (q, NCH$_2$*C*H$_3$); MS (CI) *m/z* (%) 2442.8 (100) [M + H]$^+$. Anal. Calcd for $C_{144}H_{216}N_8O_{24}$ (2443.35): C, 70.79; H, 8.91; N, 4.59. Found: C, 70.83; H, 8.86; N, 4.66.

5,11,17,23,29,35-Hexaoctyloxy-37,38,39,40,41,42-hexakis[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[6]arene (9_6). Compound **9_6** was obtained by crystallization from MeOH. Yield 60%; mp 155−158 °C. ^{1}H NMR (DMSO-d_6, 393 K) δ 6.80 (bs, 12H, ArH), 4.41 (bs, 12H, OCH$_2$CO), 3.82 (bs, 12H, ArCH$_2$Ar), 3.33 (bs, 12H, OCH$_2$R), 2.81 (bs, 24H, NC*H*$_2$CH$_3$), 1.32 (m, 72H, (C*H*$_2$)$_6$CH$_3$), 1.09 (bs, 36H, NCH$_2$C*H*$_3$), 0.91−0.84 (m, 18H, O(CH$_2$)$_7$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 167.0 (s, OCH$_2$*C*O), 155.3 (s, Ar ipso), 148.7 (s, Ar para), 134.7, 133.6, 133.4 (s, Ar ortho), 117.2, 115.6, 113.0 (d, Ar meta), 71.7 (t, O*C*H$_2$CO), 68.4, 68.0 (t, O*C*H$_2$R), 41.7, 40.2 (t, N*C*H$_2$CH$_3$), 31.8 (t, OCH$_2$*C*H$_2$R), 31.2 (t, OCH$_2$CH$_2$*C*H$_2$R), 29.5 (t, ArCH$_2$Ar and OCH$_2$CH$_2$CH$_2$*C*H$_2$R), 29.3 (t, O CH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$R), 26.1 (t, *C*H$_2$CH$_2$CH$_3$), 22.7 (t, *C*H$_2$CH$_3$), 14.6, 13.0 (q, NCH$_2$*C*H$_3$), 14.1 (q, O(CH$_2$)$_7$*C*H$_3$); MS (CI) *m/z* (%) 2085 (100) [M + H]$^+$. Anal. Calcd for $C_{126}H_{198}N_6O_{18}$ (2084.99): C, 72.59; H, 9.57; N, 4.03. Found: C, 72.66; H, 9.50; N, 4.03.

5,11,17,23,29,35,41,47-Octaoctyloxy-49,50,51,52,53,54,55,56-octakis[(*N,N*-diethyaminocarbonyl)methoxy]calix[8]arene (9$_8$). Compound **9$_8$** was obtained by flash chromatography (SiO$_2$; AcOEt/MeOH = 10/0.1). Yield 57%; mp 68−70 °C; ^{1}H NMR (CDCl$_3$, 300 K) δ 6.47 (bs, 16H, ArH), 4.34 (bs, 16H, OCH$_2$CO), 3.99 (s, 16H, ArCH$_2$Ar), 3.65 (bs, 16H, OCH$_2$R), 3.22 (bs, 32H, NC*H*$_2$CH$_3$), 1.23 (bs, 96H, (C*H*$_2$)$_6$CH$_3$), 0.90 (bs, 24H, NCH$_2$C*H*$_3$), 0.86 (bs, 24H, NCH$_2$C*H*$_3$), 0.83 (t, ^3J = 6.5 Hz, 24H, (CH$_2$)$_7$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 166.9 (s, OCH$_2$*C*O), 155.2 (s, Ar ipso), 148.9 (s, Ar para), 134.4 (s, Ar ortho), 114.6 (d, Ar meta), 72.0 (t, O*C*H$_2$CO), 67.7 (s, OCH$_2$R), 41.0, 39.8 (t, N*C*H$_2$CH$_3$), 31.7 (t, *C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 30.4 (t, ArCH$_2$Ar), 29.5 (t, *C*H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 29.1 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 25.9 (t, *C*H$_2$CH$_2$CH$_3$), 22.4 (t, *C*H$_2$CH$_3$), 13.8 (q, CH$_3$), 14.0, 12.6 (q, NCH$_2$*C*H$_3$); MS (CI) *m/z* (%) 2779 (100) [M + H]$^+$; Anal. Calcd for $C_{168}H_{264}N_8O_{24}$ (2779.99): C, 72.58; H, 9.57; N, 4.03. Found: C, 72.62; H, 9.51; N, 4.12.

5,11,17,23,29,35-Hexabenzyloxy-37,38,39,40,41,42-hexamethoxycalix[6]arene (10$_6$). Product **10$_6$** can be crystallized from MeOH. Yield 90%; ^{1}H NMR (CDCl$_3$, 300 K) δ 7.36−7.21 (m, 30H, PhH), 6.58 (s, 12H, ArH), 4.83 (s, 12H, OCH$_2$Ph), 3.87 (bs, 12H, ArCH$_2$Ar), 3.20 (s, 18H, OCH$_3$); ^{1}H NMR (DMSO-*d*$_6$, 373 K) δ 7.33−7.22 (m, 30H, Ph), 6.60 (s, 12H, ArH), 4.86 (s, 12H, OCH$_2$Ph), 3.84 (s, 12H, ArCH$_2$Ar), 3.18 (s, 18H, OCH$_3$); ^{13}C NMR (CDCl$_3$, 300 K) δ 154.5 (s, Ar ipso), 150.3 (s, Ar para), 137.1 (s, Ph), 135.2 (s, Ar ortho), 128.4, 127.7, 127.6 (d, Ph), 115.0 (d, Ar meta), 70.1 (t, OCH$_2$Ph), 60.3 (q, OCH$_3$), 30.6 (t, ArCH$_2$Ar); MS (CI) *m/z* (%) 1357.8 (100) [M + H]$^+$; Anal. Calcd for $C_{90}H_{84}O_{12}$ (1357.65): C, 79.62; H, 6.24. Found: C, 79.88; H, 6.11.

5,11,17,23,29,35-Hexahydroxy-37,38,39,40,41,42-hexamethoxycalix[6]arene (11$_6$). Compound **10$_6$** was debenzylated according to the synthesis of **6$_6$**. Product **11$_6$** was obtained by crystallization from hexane. Yield 80%; mp > 300 °C (dec); ^{1}H NMR (DMSO-*d*$_6$, 300 K) δ 8.90 (s, 6H, OH), 6.34 (s, 12H, ArH), 3.76 (bs, 12H, ArCH$_2$Ar), 3.36 (bs, 18H, OCH$_3$); ^{13}C NMR (DMSO-*d*$_6$, 300 K) δ 152.8 (s, Ar ipso), 148.5 (s, Ar para), 134.8 (s, Ar ortho), 115.1 (d, Ar meta), 60.0 (q, OCH$_3$), 29.6 (t, ArCH$_2$Ar); MS (CI) *m/z* (%) 817.6 (100) [M + H]$^+$. Anal. Calcd for $C_{48}H_{48}O_{12}$ (816.90): C, 70.57; H, 5.92. Found: C, 70.65; H, 6.01.

Physicochemical Measurements. Materials. The solvent methanol (Carlo Erba, max 0.01% water) was used without any further purification. The ionic strength was held constant at 10^{-2} M by addition of Et$_4$NClO$_4$ (Acros) twice recrystallized from bidistilled water and dried under vacuum for 24 h at room temperature. The metallic salts were chosen according to their solubility in the solvent: LiCl (Fluka, purum), NaCl (Merck, p.a.), KCl (Merck, p.a.), RbCl (Fluka, puriss.), CsCl (Merck, p.a.), Mg(ClO$_4$)$_2$·*x*H$_2$O (Merck, p.a.), Ca(ClO$_4$)$_2$·4H$_2$O (Fluka, purum), SrCl$_2$·6H$_2$O (Aldrich, 99%), Sr(NO$_3$)$_2$ (Merck, p.a.), Ba(ClO$_4$)$_2$ (Prolabo, Rectapur). All these salts were dried under vacuum for 24 h before use. The stock solutions of all the alkaline earth metal ions were standardized by complexometric titrations with EDTA in the presence of the appropriate indicator.[14] The preparations of all the picrate salts employed in extraction experiments have already been reported.[15] The solutions of the colored ligand, PAN, 1-(2-pyridylazo)-2-naphthol (Fluka puriss.), used in competitive complexation, were made from dissolution of a weighted quantity in methanol.[16] The base Et$_4$NOH was made from dilution of the commercial solution (25% in MeOH, Fluka) and standardized against potassium acid phthalate. The γ emitters (^{22}Na, ^{85}Sr simulating long-lived β emitter ^{90}Sr) used for spiking the simulated waste were obtained from Amersham. The solvent 2-nitrophenyl hexyl ether (NPHE), synthesized by Eras Labo, was used without any further purification.

Extraction from Simulated Waste. Calixarenes were dissolved in NPHE at a concentration of 10^{-2} M in NPHE. Liquid−liquid extraction experiments were performed by contacting for 1 h the same volumes of organic and aqueous phases inside agitated closed tubes placed in a thermostated cell (25 ± 0.2 °C). Complete separation of phases was ensured by placing the tubes into a centrifuge for 5 min. Then, aliquots of aqueous and organic phases were removed for analysis by γ spectrometry (Eurysis Mesures). The measurement times were adapted to obtain a reproducibility of ± 5%.

The distribution coefficients D_M were determined as the ratio of cation γ activity in the organic phase to cation γ activity in the aqueous phase. The selectivity for the cation M$_2$ over M$_1$ is expressed as α, the ratio of distribution coefficients of the two cations

$$D_M = \frac{\sum[M]_{org}}{\sum[M]_{aq}}$$

$$\alpha = \frac{D_{M_2}}{D_{M_1}}$$

where $\sum[M]_{org}$ and $\sum[M]_{aq}$ are the sums of all the species containing the metal ion at the equilibrium in the organic and aqueous phases, respectively.

Metal Picrate Extraction. The percentages of extraction of metal picrates (%*E*) and the corresponding distribution coefficient D_M (D_M = %*E*/(100 − %*E*)) from water into dichloromethane, at 20 ± 0.1 °C, were determined from the absorbance at 354 nm of the picrate anion remaining in the aqueous phase after extraction. The same concentration (2.5×10^{-4}M) was used for the ligand in the organic phase and the picrate salt in the aqueous phase as already described in detail.[17]

Stability Constant Determination. The stability constants of the complexes are expressed as concentration ratios, $\beta_{xy} = [M_xL_y]/[M]^x[L]^y$, and are related to the equilibrium

$$xM^{m+} + yL \rightleftharpoons M_xL_y^{\ xm+}$$

where M^{m+} = metallic cation and L = neutral ligand. They were determined in methanol, at 25 °C and constant ionic strength 0.01 M in Et$_4$NClO$_4$, by UV absorption spectrophotometry. The values given in the tables correspond to the arithmetic means of at least three independent determinations.

Direct Spectrophotometry. Upon complexation, the UV spectrum of the ligand very often undergoes small changes, in the range 250−300 nm, which, in most cases, are sufficient to allow a multiwavelength treatment of the data by the computer programs Sirko[18] and/or Specfit.[19]

Competitive Spectrophotometry. When complexation was associated with very small spectral changes or when the stability constants were too high to allow their direct spectrophotometric determination, a competitive method was devised using the colored ligand, PAN (1-(2-pyridylazo)-2-naphthol). This method applies only if the stability constants to be determined and those of the PAN complexes are of the same order of magnitude.

The procedure used was the following: a mixture of PAN and the ligand under study was titrated against a solution of the alkaline earth metal ions. The basic medium necessary to the complexation was ensured by the presence of Et$_4$NOH in 50-fold excess with respect to PAN. The UV−visible spectra recorded between 400 and 630 nm were interpreted with the program Specfit, knowing the stability constants for the PAN complexes determined from titrations of PAN alone by the metal ion. These constants for alkaline earth ions are given in Table 1.

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(14) *Méthode d'analyses complexométriques avec le Titriplex*, 3rd ed.; Merck, E., Ed.; Grafis: Darmstadt, 1992.

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(16) For examples of competitive spectrophotometry see: (a) Thompson, S. W.; Byrne, R. H. *Anal. Chem.* **1988**, *60*, 19. (b) Ohoyoshi, E.; Kohata, S. *Polyhedron* **1989**, *8*, 1561.

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(18) Vetrogon, V.; Lukyanenko, N. G.; Schwing-Weill, M.-J.; Arnaud-Neu, F. *Talanta* **1994**, *41*, 2105.

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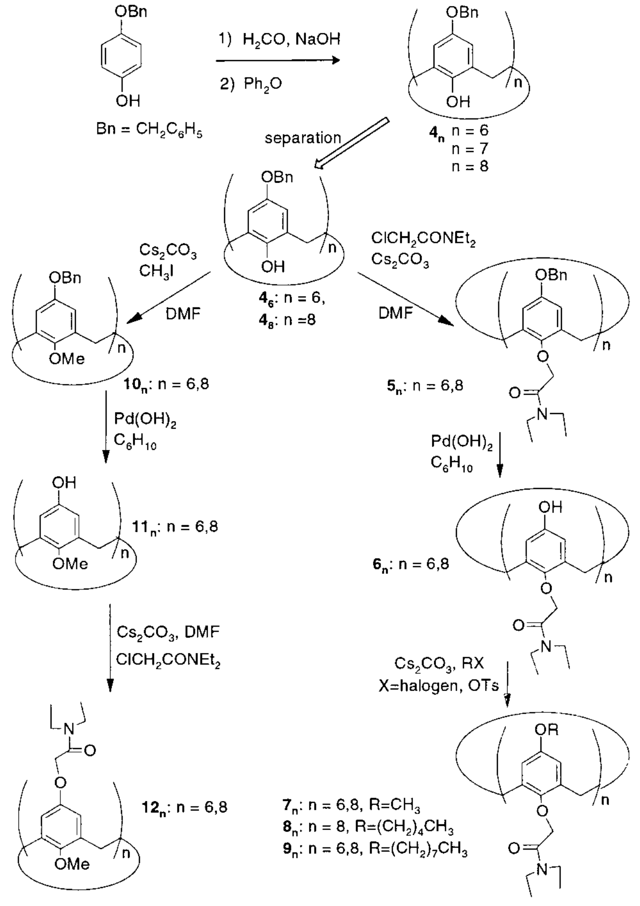
Table 1. Stability Constants (log $\beta \pm \sigma_{n-1}$) of PAN Complexes with the Alkaline Earth Metal Ions in Methanol at 25 °C ($I = 0.01$ M in Et_4NClO_4)

M:L	Ca^{2+}	Sr^{2+}	Ba^{2+}
1:1	5.67 ± 0.06	5.25 ± 0.04	3.9 ± 0.1
1:2	10.3 ± 0.2	9.73 ± 0.09	

Scheme 1



To check the validity of the competition method, complexation of $SrCl_2$ by the *p-tert*-butylcalix[4]arene diethylamide $\mathbf{1_4}$ was measured in the presence of tetraethylammonium perchlorate 0.01 M as supporting electrolyte. The value obtained by the competition method (log β_{11} = 5.1 ± 0.3) was in full agreement with the value obtained by direct spectrophotometry (5.4 ± 0.2).

Results and Discussion

Synthesis of the Ligands. The base-catalyzed condensation of *p*-benzyloxy phenol and formaldehyde produces mainly *p*-benzyloxycalix[8]arene $\mathbf{4_8}$, together with a minor amount of calix[6]- and calix[7]- derivatives (Scheme 1). From this mixture, we previously isolated the calix[8]arene derivative $\mathbf{4_8}$ by crystallization. From the mother liquor, we have now obtained and characterized the *p*-benzyloxycalix[6]arene $\mathbf{4_6}$.

Compounds $\mathbf{4}_n$ (n = 6, 8) were easily alkylated with α-chloro-*N,N*-diethylacetamide to afford the amides $\mathbf{5_6}$ and $\mathbf{5_8}$. Debenzylation of these compounds by transfer hydrogenation with $Pd(OH)_2/C$ and cyclohexene gave compounds $\mathbf{6}_n$, which are very useful intermediates for further functionalization but are poorly soluble in most organic solvents. However, alkylation of $\mathbf{6}_n$ with Cs_2CO_3 and RX in DMF (90 °C) affords highly soluble compounds $\mathbf{7}_n$−$\mathbf{9}_n$. The ^1H NMR spectra of all octamides show that they are conformationally very flexible in $CDCl_3$ at room temperature. On the other hand, the hexamide derivatives are conformationally mobile when small methoxy substituents are present at the upper rim (e.g., $\mathbf{7_6}$), but, because of the reduced size of the calixarene annulus, show restricted conformational mobility with bulkier benzyloxy ($\mathbf{5_6}$) or octyloxy ($\mathbf{9_6}$) groups, which causes a broadening of the ^1H NMR spectra at room temperature. The octamides $\mathbf{1_8}$ and $\mathbf{2_8}$ are easily prepared by alkylation of the corresponding calix[8]arenes with α-chloro-*N,N*-diethylacetamide using Cs_2CO_3 in DMF. For comparison, we also synthesized calixarenes $\mathbf{12_6}$ and $\mathbf{12_8}$ bearing amide groups at the upper and methoxy groups at the lower rims. In this case, we reversed the order of the alkylation steps: compounds $\mathbf{4}_n$ were first methylated to give $\mathbf{10}_n$, which were subsequently debenzylated and alkylated with α-chloro-*N,N*-diethylacetamide to give $\mathbf{12}_n$ in good yields (Scheme 1). Compounds $\mathbf{10}_n$−$\mathbf{12}_n$ are also conformationally mobile in solution at room temperature, thanks to the presence of the small methoxy group at the lower rim.

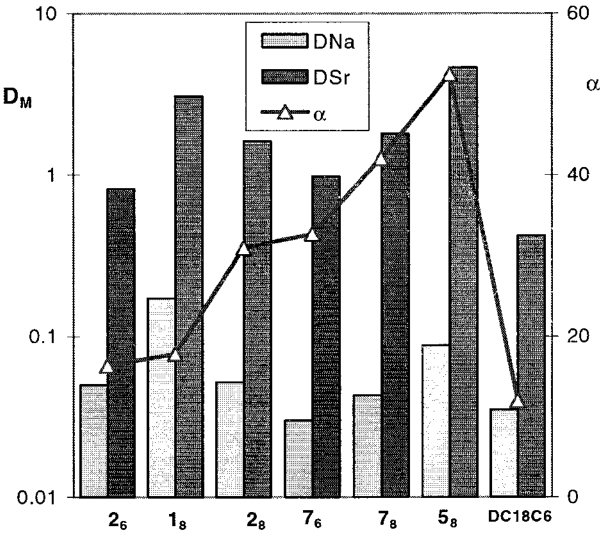


Figure 1. Sodium and strontium distribution coefficients in CH_2Cl_2 and Sr^{2+}/Na^+ selectivity (α) of calixarene ligands and DC18C6 (**3**).

Alkali and Alkaline Earth Picrates Extraction. To have a preliminary evaluation of the ionophoric properties of the ligands, extraction percentages and distribution coefficients of alkali and alkaline earth picrates from water to dichloromethane by all the calix[6]- and calix[8]arene amides were studied, and the results are reported in Table 2. The extraction data correspond to the mean values of at least four independent experiments.

With the exception of Mg^{2+}, which is poorly extracted by all ligands, the calix[6]- and calix[8]arene amides in general show a remarkable preference in the extraction of alkaline earth over alkali metal ions. In the case of calix[8]arene amides, the %*E* values for Ba^{2+} are higher than 80%, and the Sr^{2+}/Na^+ selectivity, which is relevant for radioactive waste treatment, is also very high. For the most selective ligands and for DC18C6 (**3**), we have determined, from the extraction data, the distribution coefficients D_{Sr} and D_{Na}, which are reported together with their ratio $\alpha_{Sr/Na}$ in Figure 1.

The Sr^{2+}/Na^+ selectivity increases according to the sequence $\mathbf{2_6} < \mathbf{1_8} < \mathbf{7_6} \approx \mathbf{2_8} < \mathbf{7_8} < \mathbf{5_8}$. The octamide $\mathbf{5_8}$ (α = 51.3) is much more selective (and efficient) than DC18C6 (α = 12) and *p*-H-calix[6]arene hexamide $\mathbf{2_6}$ (α = 16.4), which are the most selective extractants for strontium ion known so far. Calixarenes $\mathbf{12_6}$ and $\mathbf{12_8}$ bearing the amide groups at the upper rim do not significantly extract alkali and alkaline earth metal ions, as their %*E* values are usually far below 5%.

Table 2. Extraction Percentages and Distribution Coefficients (D_M) of Alkali, Alkaline Earth, Ag^+, and Eu^{3+} Picrates from Water into Dichloromethane for Calix[6]- and Calix[8]arene Amides (T = 20 °C, $C_L = C_{Pic} = 2.5 \times 10^{-4}$ M, Volume Aqueous/Organic Phase = 1)

cations	$\mathbf{5_6}$	$\mathbf{7_6}$	$\mathbf{9_6}$	$\mathbf{1_6}$[a]	$\mathbf{2_6}$[a]	$\mathbf{5_8}$	$\mathbf{7_8}$	$\mathbf{8_8}$	$\mathbf{9_8}$	$\mathbf{1_8}$	$\mathbf{2_8}$
Li^+	11.4 ± 0.3 (0.13)	4.3 ± 0.2 (0.04)	19.4 ± 0.3 (0.24)	23.4 (0.31)	5.2 (0.05)	5.9 ± 0.4 (0.06)	3.7 ± 0.7 (0.04)	22.7 ± 0.6 (0.29)	7.0 ± 1.0 (0.08)	13.2 ± 0.5 (0.15)	3.8 ± 0.2 (0.04)
Na^+	12.8 ± 0.6 (0.15)	2.9 ± 0.4 (0.03)	17.1 ± 0.2 (0.21)	27 (0.37)	4.8 (0.05)	8.1 ± 0.2 (0.09)	4.1 ± 0.8 (0.04)	26.8 ± 0.9 (0.37)	14.3 ± 0.9 (0.17)	14.7 ± 0.1 (0.17)	4.9 ± 1.6 (0.05)
K^+	11.0 ± 0.6 (0.12)	5.4 ± 0.3 (0.06)	12.9 ± 0.4 (0.15)	23.6 (0.31)	7.5 (0.08)	10.0 ± 0.4 (0.11)	4.9 ± 0.1 (0.05)	27.7 ± 0.7 (0.38)	17.9 ± 0.6 (0.22)	14.4 ± 0.1 (0.17)	5.5 ± 0.8 (0.06)
Rb^+	12.4 ± 0.3 (0.14)	5.1 ± 0.1 (0.05)	19.5 ± 0.4 (0.24)	22.4 (0.29)	17.2 (0.21)	17.6 ± 0.1 (0.21)	4.1 ± 0.1 (0.04)	25.0 ± 0.7 (0.33)	12.3 ± 0.2 (0.14)	10.6 ± 0.1 (0.12)	4.4 ± 0.1 (0.05)
Cs^+	24.3 ± 0.4 (0.32)	12.0 ± 0.2 (0.14)	38.4 ± 0.4 (0.62)	26.4 (0.36)	45.4 (0.83)	8.1 ± 0.5 (0.09)	6.2 ± 0.6 (0.07)	32.0 ± 0.8 (0.47)	14.4 ± 0.4 (0.17)	12.2 ± 0.9 (0.14)	61.8 ± 0.6 (1.62)
Mg^{2+}	3.7 ± 0.2 (0.04)	4.0 ± 0.3 (0.04)	13.9 ± 0.2 (0.16)	8.7 (0.10)	2.6 (0.03)	2.5 ± 0.3 (0.03)	≤1 (<0.01)	12.4 ± 0.1 (0.14)	≤1 (<0.01)	3.7 ± 0.2 (0.04)	2.7 ± 0.4 (0.03)
Ca^{2+}	44.8 ± 0.2 (0.81)	20.1 ± 0.3 (0.25)	61.8 ± 0.1 (1.62)	84.2 (5.33)	25.7 (0.35)	52.2 ± 0.1 (1.09)	22.2 ± 0.3 (0.29)	62.8 ± 0.1 (1.69)	63.0 ± 0.1 (1.70)	57.0 ± 0.3 (1.33)	27.0 ± 0.1 (0.37)
Sr^{2+}	60.7 ± 0.4 (1.54)	49.6 ± 0.3 (0.98)	72.1 ± 0.1 (2.58)	83.8 (5.17)	45.0 (0.82)	82.2 ± 0.3 (4.62)	64.4 ± 0.7 (1.81)	76.5 ± 0.2 (3.26)	80.1 ± 0.3 (4.03)	75.4 ± 0.2 (3.06)	61.7 ± 0.1 (1.61)
Ba^{2+}	64.1 ± 0.1 (1.79)	55.9 ± 0.2 (1.27)	75.1 ± 0.2 (3.02)	85.5 (5.90)	58.0 (1.38)	93.0 ± 0.2 (13.29)	83.8 ± 0.1 (5.17)	85.1 ± 0.1 (5.71)	94.2 ± 0.3 (16.24)	91.6 ± 0.3 (10.90)	80.4 ± 0.2 (4.10)
Ag^+						11.0 ± 0.2 (0.12)	11.0 ± 0.2 (0.12)	30.3 ± 0.7 (0.43)	39.6 ± 0.2 (0.66)		
Eu^{3+}						35.6 ± 0.1 (0.55)	13.5 ± 0.1 (0.16)	49.4 ± 0.1 (0.98)	68.6 ± 0.7 (2.18)	46.9 ± 1.3 (0.88)	14.7 ± 0.1 (0.17)

[a] Ref 9.

Table 3. D_M and Sr^{2+}/Na^+ Selectivity ($\alpha_{Sr/Na}$) for All Calixarenes Studied and DC18C6 (**3**) in NPHE ($C_L = 10^{-2}$ M)

	$M(NO_3)_n$ 5×10^{-4} M/HNO_3 1 M				$NaNO_3$ 4 M/HNO_3 1 M			
ligand	^{22}Na	^{85}Sr	^{137}Cs	D_{Sr}/D_{Na}	^{60}Co	^{85}Sr	^{137}Cs	^{152}Eu
$\mathbf{5_6}$	<0.001	0.13	<0.001	>130	<0.001	0.5	<0.001	<0.001
$\mathbf{7_6}$	<0.001	2.9	<0.001	>2900	<0.001	1.8	<0.001	<0.001
$\mathbf{9_6}$	<0.001	0.80	<0.001	>800	<0.001	1.09	<0.001	<0.001
$\mathbf{5_8}$	<0.001	20	<0.001	>20 000	<0.001	5	0.1	<0.001
$\mathbf{7_8}$	<0.001	6.5	<0.001	>6500	<0.001	2.2	0.28	<0.001
$\mathbf{8_8}$	<0.001	30	<0.001	>30 000	<0.001	0.34	0.14	<0.001
$\mathbf{9_8}$	<0.001	24	<0.001	>24 000	<0.001	3.8	0.27	<0.001
$\mathbf{1_8}$	*a*	*a*	*a*	n.a.[b]	<0.001	0.4	0.2	<0.001
$\mathbf{2_8}$	<0.001	8.3	0.01	>8300	<0.001	1.3	0.03	<0.001
DC18C6	0.006	0.28	0.03	47	*b*	*b*	*b*	*b*

[a] Formation of a precipitate occurs. [b] Not tested; n.a. = not applicable.

Extraction from Simulated Waste. Encouraged by the preliminary extraction data, we also tested these ligands under conditions which simulate the real radioactive waste treatment. Extractions of aqueous solutions containing sodium, cesium, or strontium nitrate at 5×10^{-4} M and HNO_3 at 1 M (single metal ion extractions) were performed using 10^{-2} M 2-nitrophenyl hexyl ether (NPHE) solutions of the ionophore. The distribution coefficients obtained are reported in Table 3. D_{Cs} values are very low for all calixarenes tested, even for those exhibiting high extraction of cesium picrate in dichloromethane (Table 2). It is noteworthy that, for all the tested calixarenes except $\mathbf{5_6}$, the strontium distribution coefficients are higher than those obtained with DC18C6.[20] They also show a high Sr^{2+}/Na^+ selectivity, thanks to a negligible sodium distribution coefficient D_{Na}, that could only be estimated to be <0.001.

Within the calix[6]arenes studied, $\mathbf{7_6}$ presents the highest affinity for strontium, while the other hexamers $\mathbf{5_6}$ and $\mathbf{9_6}$, bearing bulkier groups on the upper rim, display lower strontium distribution coefficients, probably because of their reduced conformational mobility. In general, octamers display higher D_{Sr} and $\alpha_{Sr/Na}$ than hexamers. Under these conditions, the increasing order of ligand efficiency and selectivity is $\mathbf{7_8} < \mathbf{2_8} < \mathbf{5_8} < \mathbf{9_8} < \mathbf{8_8}$. We also performed competitive extraction experiments, using water solutions of chemical composition closer to the real waste: the concentration of HNO_3 was kept at 1 M, and $NaNO_3$ was raised to 4 M, while Co, Sr, Cs, and Eu radionuclides were present only at trace level ($<10^{-6}$ M). The data obtained (Table 3) indicate that Co and Eu are not extracted significantly and Cs is extracted only by calix[8]arene amides. However, all tested calixarene amides can still extract strontium ion also under these highly competing conditions, with the increasing order of ligand efficiency being $\mathbf{2_8} < \mathbf{7_6} < \mathbf{7_8} < \mathbf{9_8} < \mathbf{5_8}$, confirming the higher efficiency of octamides compared with hexamides and *p*-alkoxy compared with *p*-H or *p*-*tert*-butyl derivatives. A plot of the distribution coefficient of strontium versus the nitric acid concentration in the aqueous phase (Figure 2) confirms the much higher efficiency of $\mathbf{9_8}$ in comparison with that of DC18C6 (**3**); D_{Sr} for DC18C6 never exceeds 1, whereas that for $\mathbf{9_8}$ reaches a maximum of 30 for nitric acid concentration between 2 and 4 M, which are those encountered in the real waste, notwithstanding the fact that DC18C6 was used at a concentration 10 times higher than $\mathbf{9_8}$.

Although compound $\mathbf{9_8}$ is very selective, its strontium distribution coefficient decreases by increasing the sodium nitrate concentration in the aqueous layer (Figure 3). Interest-

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[20] Dozol, J.-F. *Value Adding through Solvent Extraction*, Proceedings of International Solvent Extraction Conference, Melbourne, March 19–23, 1996; Shallcross, D. C., Paimin, R., Prvcic, L. M., Eds.; University of Melbourne, 1996; p 1333.

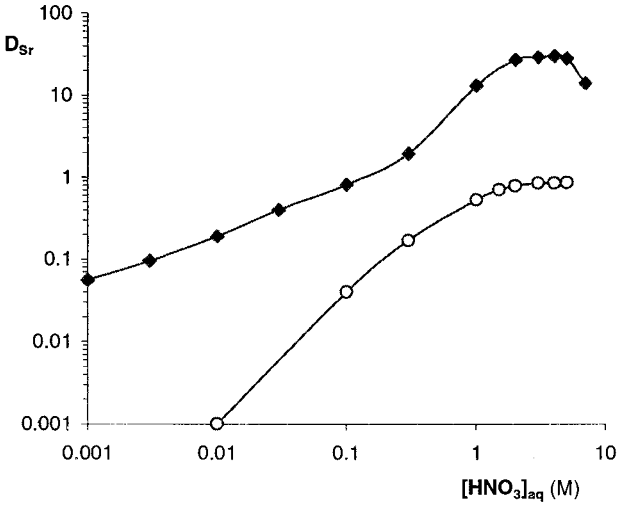

Figure 2. Strontium distribution coefficient in NPHE as a function of the nitric acid concentration in the aqueous layer for ligand **9**$_8$ (◆, c = 0.01 M) and DC18C6 **3** (○, c = 0.1 M).

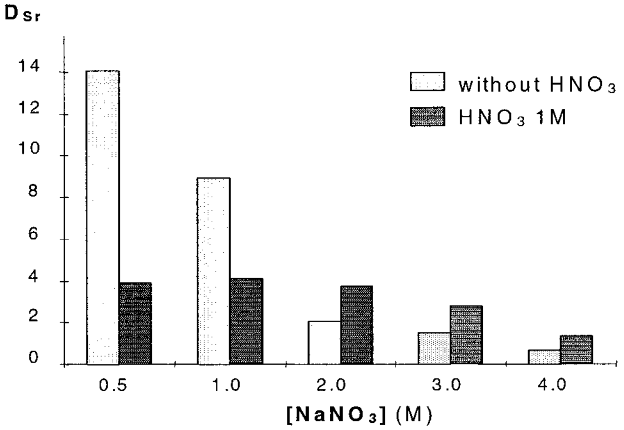

Figure 3. Strontium distribution coefficients as a function of increasing sodium concentration for ligand **9**$_8$.

ingly, at high $NaNO_3$ concentration (2−4 M), the strontium distribution coefficients are higher in the presence of 1 M HNO_3 (simulated nuclear waste conditions) than in its absence (Figure 3).

Complexation Studies in the Solid State and in Solution. To have information on the structure and stability of strontium complexes of our new ligands, we undertook a systematic X-ray, ESI-MS, and UV−vis investigation. The X-ray crystal structures of the strontium complexes of hexamide **1**$_6$ and octamides **1**$_8$ and **7**$_8$, which have been published elsewhere,[10] show a remarkable difference between the hexameric and octameric ligands. The hexamide **1**$_6$ forms a 1:1 complex with Sr^{2+} cation, whereas the octamides **1**$_8$ and **7**$_8$ give rise to 2:1 (metal to ligand) complexes. Moreover, in the hexamide complex, the strontium ion is completely encapsulated in the polar region of the ligand and is coordinated only through oxygen donor atoms of the calixarene ligand, while in the octamides **1**$_8$ and **7**$_8$ there is room also for one chloride and two acetic acid moieties to coordinate the metal ion. Particularly interesting is the structure of the strontium complex of **7**$_8$ (Figure 4), because it clarifies the role of the *p*-alkoxy groups in cation binding. Although these groups could, in principle, participate in complexation, the X-ray crystal structure shows that this is not the case with ligand **7**$_8$.

None of the oxygen atoms of the methoxy groups is coordinated to the strontium ions, thus indicating that the high efficiency of this ligand, as well as that of the other *p*-alkoxycalix[8]arene amides, is due not to the additional coordination of the alkoxy groups but rather to their electron-donating effect, which enhances the donor properties of the phenolic oxygen atoms bearing the amide groups.

Table 4. Stability Constants (log $\beta_{xyz} \pm \sigma_{N-1}$) of Ca^{2+} and Sr^{2+} Complexes of Calix[8]arene Amides **1**$_8$, **2**$_8$, **5**$_8$, and **7**$_8$ in Methanol Obtained by Competition with PAN (T = 25 °C, I = 0.01 M in Et_4NClO_4)

cations	*xyz*[a]	**1**$_8$	**2**$_8$	**5**$_8$	**7**$_8$
Ca^{2+}	110	5.75 ± 0.08	5.06 ± 0.06	6.0 ± 0.2	4.3 ± 0.2
	210	12.0 ± 0.1	9.4 ± 0.2	11.5 ± 0.5	
Sr^{2+}	110	5.6 ± 0.3	5.8 ± 0.6	6.4 ± 0.1	6.0 ± 0.1
	111	12.0 ± 0.7	12.3 ± 0.2	11.72 ± 0.06	11.2 ± 0.1
	210	10.1 ± 0.4	11.0 ± 0.1	10.91 ± 0.05	10.4 ± 0.4

[a] *xyz* = M/L/PAN.

Interesting information on the structure of the complexes in solution was obtained by dissolving the crystals of the strontium complexes of **1**$_6$, **1**$_8$, and **7**$_8$ in methanol (10^{-5} M) and analyzing them by ESI (+) mass spectrometry. The strontium complex of **1**$_6$ shows the base peak belonging to the $[L + Sr + Pic]^+$ species and a peak, with a much lower intensity (5%), for the $[L + Sr]^{2+}$ species. There is no evidence for the formation of the dinuclear species in this case. On the contrary, the spectrum of the strontium complex of **7**$_8$ (Figure 5) shows, beside mononuclear species $[L + Sr]^{2+}$ as base peak, several dinuclear complexes. The most important ones are the $[L + 2Sr + 2AcOH]^{4+}$ and $[L + 2Sr + 4AcOH]^{4+}$, with the latter being a complex with four acetic acid units, as observed in the solid state.

Preliminary studies aimed at evaluating the stability of alkali and alkaline earth complexes of calix[8]arene amides **1**$_8$ and **2**$_8$ in methanol, using direct spectrophotometric titrations, showed very weak complexation (log $\beta_{11} \le 2$) of alkali metal ions and very strong complexation (log $\beta_{11} \ge 5$) of Ca^{2+}, Sr^{2+}, and Ba^{2+}. The low values of log β_{11} for the silver complexes of **1**$_8$ and **2**$_8$ (respectively, 3.25 ± 0.01 and 3.0 ± 0.4) as well as the low solubility of the ligands in methanol prevented the use of Ag^+ as auxiliary cation in competitive potentiometric measurements. For all these reasons, the complexation of alkaline earth metal ions by the most selective calix[8]arene amides (**5**$_8$, **7**$_8$, **1**$_8$, and **2**$_8$) was studied by competitive spectrophotometry with 1-(2-pyridylazo)-2-naphthol (PAN). The results show the formation of both 1:1 and 2:1 (M/L) complexes for all ligands studied with Ca^{2+} and Sr^{2+}, except for ligand **7**$_8$ with Ca^{2+} (Table 4). With Sr^{2+}, the presence of mixed species (1:1:1) involving the PAN molecule significantly improved the fit but did not affect the overall stability constant β_{210}. These results are in full agreement with the X-ray crystal structure determination and ESI-MS studies (vide supra) which show the formation of dinuclear complexes for ligand **1**$_8$ or **7**$_8$ and Sr^{2+}. With Ba^{2+}, no complexation data could be established accurately because of the too low stability constants of its complex with PAN (log β = 3.9); however, a lower limit (log $\beta \ge 6.5$) could be established.

The Sr^{2+} stability constant increases exactly in the same order as that already found in extraction, that is, **1**$_8$ < **2**$_8$ < **7**$_8$ < **5**$_8$. This trend highlights the importance of the donor effect of the *p*-alkoxy groups at the upper rim. The stability constants of the 1:1 complexes between Ca^{2+} and Sr^{2+} cations and octamides in methanol are much lower than those estimated for the corresponding calix[4]arene tetramide **1**$_4$ (log $\beta \ge 9$)[6c] and comparable with those found for DC18C6.[21] However, both these ligands bind sodium ion in methanol much stronger (log

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[21] Buschmann H. J. *Chem. Ber.* **1985**, *118*, 2746.

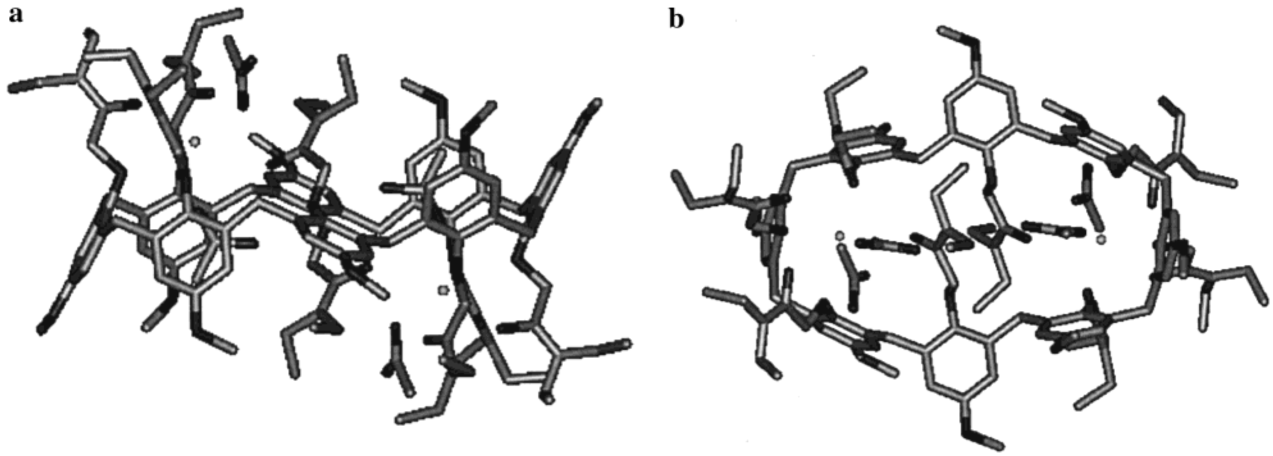

Figure 4. Lateral (a) and apical (b) view of the X-ray crystal structure of the strontium picrate complex of **7₈** (only coordinated acetic acid molecules are shown).

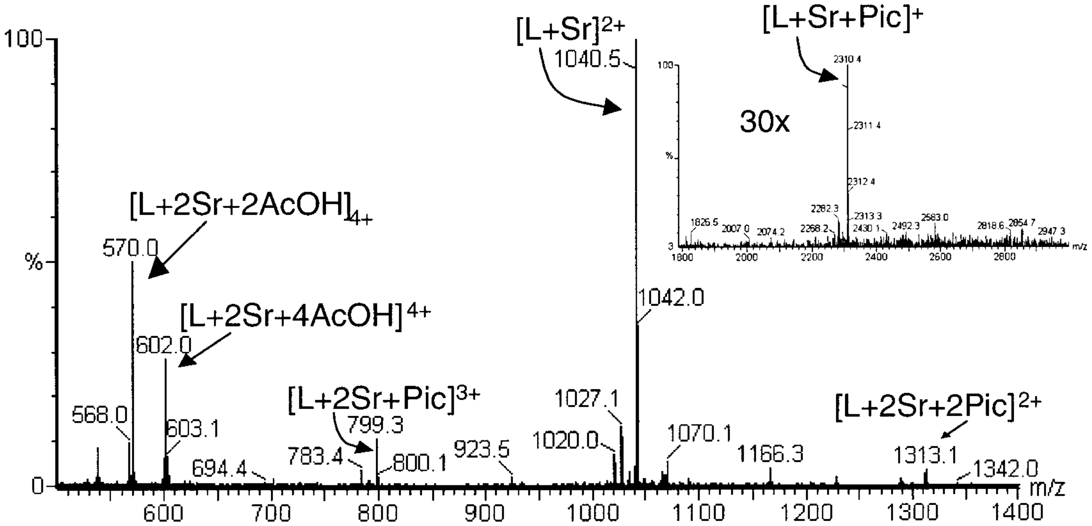

Figure 5. ESI(+)-MS of the strontium picrate complex of ligand **7₈** in methanol solution.

$\beta = 7.9$ for $\mathbf{1_4}$[6c] and log $\beta = 4.27$ for DC18C6[21]) than our new octamide ligands (log $\beta \leq 2$), which explains the higher Sr^{2+}/Na^+ selectivity found for the octamide ligands compared with other strontium selective ligands. No quantitative data is available for the binding of hexamide ligands with divalent metal ions in homogeneous conditions, but from the previously reported[9] and present results based on extraction data, it appears that Sr^{2+}/Na^+ selectivity of hexamides is intermediate between that of the tetramides and octamides (tetra < hexa < octa). This selectivity order is a consequence of a general trend found in neutral ionophores having the same binding sites, where the divalent/monovalent selectivity for metal ions of similar size and hardness increases with the number of binding groups and the flexibility of the ligand.[22] Moreover, the Sr^{2+}/Na^+ selectivity is also enhanced by the ability of the new octamide ligands to form 2:1 (cation/ligand) complexes with alkaline earth metal ions. We tried also to evaluate if there was any cooperative effect determining the interaction factor (IF $= 4K_{21}/K_{11}$, where $K_{21} = \beta_{21}/K_{11}$)[23] between the two binding sites in the case of calcium complexes where such analysis is not complicated by the simultaneous presence of mixed (1:1:1) species involving PAN. Evidence for such a cooperative effect was only obtained for the calcium complex of octamide $\mathbf{1_8}$ for which an interaction factor IF = 12.6 was calculated. For the calcium complexes of $\mathbf{2_8}$ and $\mathbf{5_8}$, the calculated IF was close to 1, which indicates statistical binding. We are currently investigating this phenomenon in order to better explain the different behavior of $\mathbf{1_8}$ compared with $\mathbf{2_8}$ and $\mathbf{5_8}$.

Conclusions

A new series of highly efficient and selective calix[6]- and calix[8]arene amide ionophores which show very promising results in the ^{90}Sr removal from radioactive waste was synthesized. Among these, calix[8]arene octamides show the highest efficiency in the complexation of alkaline earth metal ions and a remarkable selectivity for Ba^{2+} and Sr^{2+} over alkali metal ions. Octamides ($\mathbf{5_8}$, $\mathbf{7_8}$−$\mathbf{9_8}$) bearing alkoxy groups at the upper rim are more efficient and selective than octamides $\mathbf{1_8}$ and $\mathbf{2_8}$ derived, respectively, from *p-tert*-butyl and *p*-H calixarenes. Calixarenes **12** bearing amide groups at the upper rim and methoxy at the lower rim have been also prepared and show no binding ability. We have studied the extraction behavior of these new ligands in a variety of conditions, including solutions which simulate the real radioactive waste, and determined the stability constants toward alkali and alkaline earth metal ions in homogeneous methanol solutions. All data confirm that the

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[22] Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.

[23] Schneider, H.-J.; Yatsimirsky, A. In *Principles and methods in Supramolecular Chemistry*; John Wiley & Sons: Chichester, 2000, p 151.

new octamide ligands $\mathbf{5_8}$, $\mathbf{7_8}$−$\mathbf{9_8}$ form weak complexes with alkali metal ions but much stronger complexes with divalent metal ions and are the most efficient and selective neutral strontium extractants known so far. Solution studies performed by ESI-MS and competitive spectrophotometry together with solid-state X-ray crystallography give clear evidence for the formation of 2:1 (metal/ligand) complexes with strontium ion, which further explains the divalent/monovalent selectivity found for all octamide ligands. Evidence for a positive cooperative effect between the two metal ion binding sites was obtained in the case of the Ca^{2+} complex of octamide $\mathbf{1_8}$.

Acknowledgment. This work was financially supported by EU (F14WCT96 0022 Project) and by M.U.R.S.T. ("Supramolecular Devices" Project). We also thank the Centro di Misure of the University of Parma for NMR and mass facilities.

JA016597F