4-*tert*-Butylcalix[4]arene tetrahydroxamate chelators for the selective extraction of actinide ions: synthesis and preliminary metal ion extraction studies[1]

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Organic extractants capable of selective and efficient removal of actinides such as plutonium and americium from aqueous process waste streams are potentially useful in radioactive waste remediation. In this context, with the help of molecular modelling, the 4-*tert*-butylcalix[4]arene tetrahydroxamate chelators 1 and 2 have been identified as structures capable of achieving the selective solvent extraction of actinide(IV) ions from aqueous solutions. The syntheses of 1 and 2 from 4-*tert*-butylcalix[4]arene have been accomplished in moderate yields using short synthetic sequences. Some extraction studies have been performed using Th^{4+} (as a surrogate for Pu^{4+}), Fe^{3+}, UO_2^{2+} and Cu^{2+} to estimate the metal ion selectivity and extraction efficacy of these chelators. Our preliminary results show these ligands are capable of extracting thorium(IV) efficiently but that they may not be selective for its extraction in the presence of iron(III).

Introduction

A variety of separation technologies and processes are currently being explored for the remediation of high level and transuranic radioactive waste.[2] Actinides present in process waste streams must be removed to ultralow levels prior to their discharge in order to meet increasingly stringent regulatory limits. In connection with these efforts, there is an urgent need to develop cost effective and efficient chelating and extracting agents to selectively remove actinides such as plutonium and americium from waste streams as well as from contaminated soil and water.[3]

The ability to design chelators that have the requisite properties of selectivity and high binding constants for a particular metal ion requires a sophisticated and systematic approach that takes advantage of the nature and the specific coordination chemistry of the metal ion.[4] Because of their larger size, actinide ions typically have a higher coordination number (eight or more) and a somewhat flexible ligand geometry compared to most other metal ions. It is generally accepted that selective actinide complexation can be achieved by taking advantage of their larger coordination sphere relative to the smaller transition metals.[5,6] Another important factor in the design of actinide specific chelators is the degree of preorganization of the molecules' ligand groups. This preorganization is important in order to achieve favourable entropic changes as well as to provide optimal geometry for target metal ion complexation without introducing additional steric strain elsewhere in the molecule.[7]

The plutonium chelators being developed so far have targeted the 4+ oxidation state which is important both biologically[6] and environmentally.[8] Raymond and co-workers have exploited the similarity in the coordination chemistry of plutonium(IV) and iron(III) to develop a number of cyclic and acyclic chelators for the binding of plutonium, some of which are potentially useful for *in vivo* biodecorporation of this metal ion.[9] Since the plutonium(IV) ion is a hard Lewis acid, the preferred ligands that have been incorporated into these synthetic chelators have been catecholates, hydroxypyridinonates and hydroxamates.[10]

A number of reports have appeared on the properties and applications of calix[*n*]arenes, a unique class of molecules.[11] Calixarenes that are immobilized in the cone conformation present an ideal backbone for the introduction of various ligand groups onto the same face of the molecule. The use of calixarenes for the complexation of a variety of metal ions including some transition and f-block elements has been reported.[12] Shinkai and co-workers have developed some calixarene based uranophiles (having carboxylate groups appended to the lower rim) which exhibit remarkable selectivity for the uranyl (UO_2^{2+}) ion.[13] They have also synthesized similar *p*-tert-butylcalix[*n*]arene derivatives with hydroxamate groups and examined their ability to extract uranium and other transition metal ions from aqueous solution.[14] In general the calix[6]arene derivatives seem to be the more efficient extractants for the uranyl ions than their corresponding calix[4] analogues.

The coordination geometry of the uranyl ion[15] (planar penta- or hexa-coordinate) is, however, quite different from that of plutonium and other actinide(IV) ions (octadentate, square antiprism or dodecahedral). Very little work has been done on the design of calixarene based extractants for the tetra- and trivalent actinides. Recently, the synthesis of some calixarene derivatives having groups analogous to CMPO [octyl(phenyl)-*N*,*N*-diisobutylcarbamoylmethylphosphine oxide] appended to the upper rim, has been disclosed.[16] The authors found that these calixarene derivatives were better extractants for actinides such as Np, Pu and Am than CMPO itself. Another novel class of calixarene derivatives with phosphine oxide groups attached to the lower rim has been synthesized and shown to have high efficiency in the extraction of Th^{IV} and Pu^{IV} from simulated nuclear waste.[17]

The goal of our research programme is to develop organic chelators capable of specific binding/removal of actinides, such as plutonium(IV) from soils and process waste streams in the presence of more abundant and competing metal ions such as iron(III), aluminium(III), alkali and alkaline earth metal ions.[18] In this paper, we would like to disclose the preparation of some

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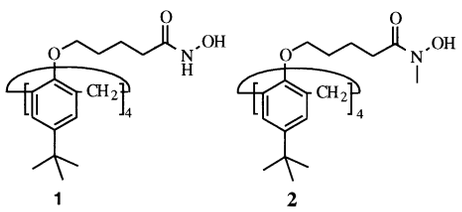
new calixarene-based hydroxamate extractants designed for the selective complexation of actinide(IV) ions and some details on their metal ion extraction properties.

Results and discussion

The primary tetrahydroxamic acid **1** and its secondary (*N*-methyl) analogue **2** were identified by us, using molecular modelling,[19] as potential structures for the specific chelation and extraction of tetravalent actinides such as plutonium(IV) from aqueous solutions. The rigid skeleton of these calixarene-based molecules offers a degree of preorganization of the ligand moieties with respect to actinide ion binding. However, it was important to identify the minimum chain length necessary to allow all four hydroxamate groups in a chelator such as **1** to simultaneously bind the plutonium(IV) cation without introducing steric strain in the calixarene backbone.



1 **2**

The CAChe™ molecular modelling system, version 3.1, was used in our modelling study.[20] The tetra-*tert*-butylcalix[4]arene unit was first constructed followed by construction of the tetrahydroxamato-plutonium(IV) subunit. These fragments were then allowed to assume a minimum energy conformation after which the calixarene and plutonium–hydroxamate units were connected by the appropriate length alkyl chain. The coordinates of the calixarene and plutonium were then fixed and the energies of the connecting chains were minimized. Following this step the plutonium–hydroxamate unit was unlocked and the energy of the structure was again minimized leaving the geometry of the calixarene moiety fixed. Finally, the calixarene unit was unlocked and the entire structure was allowed to assume a minimum energy conformation. The minimum energy structure of the **1**–Pu^{4+} complex and other structural analogues with pendant arms of different lengths were then compared against the structures of the tetra-*tert*-butylcalix[4]arene. When pendant arms shorter than five carbons were employed, deviations in the structures of the parent calixarene unit and the plutonium complex unit were observed. The deviations found for the two-carbon side chain were quite severe while those found for the four-carbon chain were much less pronounced. No structural deviations were observed between the calixarene unit in the free calix[4]arene and the calix[4]arene–Pu^{4+} complex when a five-carbon chain was used to anchor the ligands. The minimum energy structure for the **1**–Pu^{4+} complex obtained from these studies is shown in Fig. 1. The results for the **2**–Pu^{4+} complex were similar. Molecular modelling suggests

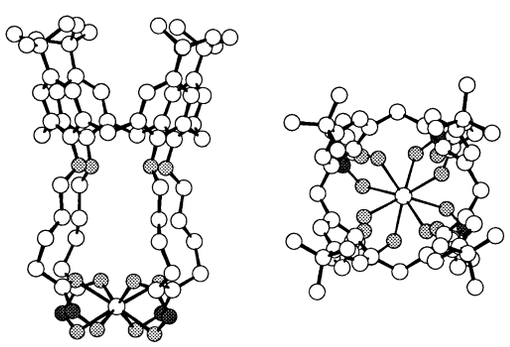
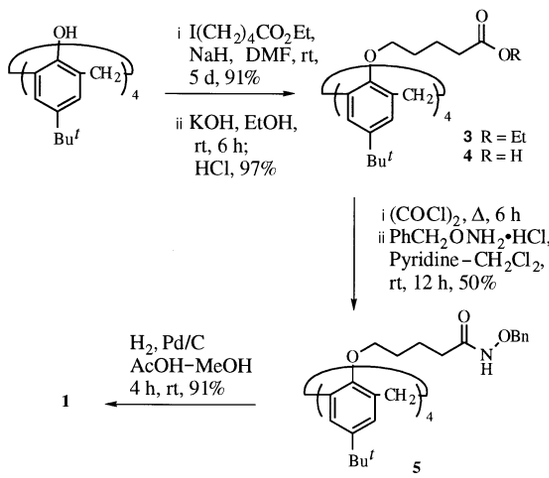


Fig. 1 Polar and equatorial views of the energy minimized **1**–Pu^{4+} model (hydrogens have been omitted for clarity)

that the four hydroxamate groups on these chelators can simultaneously bind an actinide(IV) ion in an appropriate eight-coordinate geometry resulting in the formation of a neutral organic soluble metal–ligand complex. The complex of **2** with an actinide(IV) ion would be expected to show superior organic solubility properties in comparison to those of **1**.

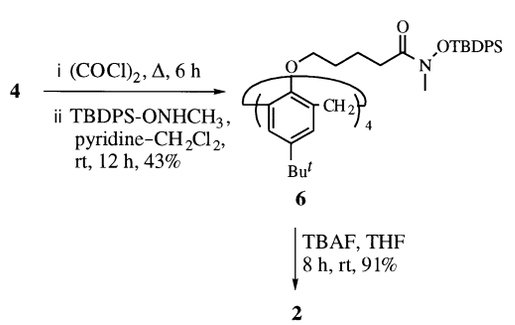
The synthesis of chelator **1** was achieved from commercially available *tert*-butylcalix[4]arene in four steps as shown in Scheme 1. Treatment of calix[4]arene with NaH, followed by



Scheme 1

alkylation with ethyl 5-bromovalerate in a 10% solution of dimethylformamide (DMF) in tetrahydrofuran at reflux, gave the desired cone tetraester, **3**, in 41% yield. This alkylation was not stereoselective and was accompanied by the formation of almost equal amounts of the partial cone isomer, from which the desired product could be separated by careful column chromatography. It was subsequently found that the yield of the desired cone product, **3**, could be improved to 80–90% by performing this alkylation in DMF at room temperature for 5–7 d using ethyl 5-iodovalerate as the alkylating agent.[21] The tetraester was then saponified in alcoholic potassium hydroxide to give the tetracarboxylic acid **4** in 97% yield after acidification. Treatment of **4** with excess oxalyl chloride gave the corresponding acid chloride which was then used without purification in the following step. Reaction of the acid chloride with *O*-benzylhydroxylamine hydrochloride in pyridine–dichloromethane gave the tetraamide **5** in moderate yields after purification by column chromatography. Debenzylation of compound **5** using H_2–Pd/C in methanol gave the tetrahydroxamate chelator **1** in 91% yield.

The *N*-methyltetrahydroxamate **2** was also prepared from the carboxylic acid **4**. Once again, acid **4** was converted to the corresponding acid chloride with excess oxalyl chloride, and the crude product was used without purification in the next step. Treatment of the acid chloride with the *O*-*tert*-butyldiphenylsilyl protected *N*-methylhydroxylamine[18b] gave the tetraamide **6** in 43% yield after purification by column chromatography. The



Scheme 2

Table 1 Solvent extraction of Th^{4+} and Fe^{3+} by calixarenes **1**, **2** and **4** at various pH values

	% M^{n+} extracted by calixarene ligand[a]					
	Th^{4+}			Fe^{3+}		
pH initial	**1**	**2**	**4**	**1**	**2**	**4**
2	94.6	20.3	5.7	98.9	90.4	11.7
3	95.2	94.0	92.9	97.9	88.3	95.7
4[b]	100	100	98.0	—	—	—

[a] Equal volumes of the aqueous metal solution and ligand solution in chloroform were contacted for 2 h; $[Th^{4+}] = 0.18$ mmol dm^{-3} in 0.1 mol dm^{-3} NaCl, $[Fe^{3+}] = 0.17$ mmol dm^{-3} in 0.1 mol dm^{-3} NaCl, [**1**] = 0.90 mmol dm^{-3}, [**2**] = 0.86 mmol dm^{-3}, [**4**] = 0.95 mmol dm^{-3}. [b] Complete precipitation of the iron occurred prior to contacting the aqueous phase with the chloroform phase containing the extractant.

desired tetrahydroxamate **2** was then obtained in 91% yield by desilylation of **7** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF).

The ability of tetrahydroxamate chelators **1** and **2** as well as the corresponding tetracarboxylic acid **4** to extract some metal ions of interest from aqueous solution into chloroform has been examined.[14] Each of the calixarenes was tested for their ability to extract thorium(IV), iron(III), uranium(VI) and copper(II) into chloroform from aqueous solutions at various pH values. Thorium(IV) was chosen for this study because it is a known surrogate for plutonium(IV). The uranyl extraction properties of our chelators were also of practical interest.

In general, equal volumes of aqueous solution containing the metal ion of interest and chloroform containing a fivefold molar excess of one of the above ligands were contacted for about 2 h with gentle shaking. The initial pH of the aqueous solution was varied from 2 to 8 prior to contact with the ligand solution. Control studies clearly revealed that precipitation, presumably as metal hydroxides, occurred in the aqueous solutions of all metal ions studied above certain pH values. Significant amounts of precipitate were observed at pH 4 and above in the iron study, pH 5 in the thorium study and pH 8 in the uranium study. Data taken at pH values where large amounts of metal ion precipitate existed are not shown here. The percentage of metal extracted into the chloroform layer has been corrected to account for minor variations in the available metal ion concentration in the aqueous layer due to its precipitation.

The results of the thorium(IV) extraction studies are listed in Table 1. Compounds **1**, **2** and **4** appear to be capable of extracting >98% of the available thorium into chloroform at pH 4. However, the primary hydroxamate **1** was the most effective extractant at pH 2, removing greater than 90% of the thorium from the aqueous phase in comparison to *ca.* 20% for hydroxamate **2** and less than 6% for carboxylate **4**. Surprisingly, all three ligands, had comparable efficiency at pH 3 for the extraction of this metal ion.

The extraction ability of these chelators was also studied with iron(III), Table 1. The results of these studies are quite similar to those obtained with thorium(IV). At pH 2, the primary hydroxamic acid **1** was the most efficient extractant for this metal cation (99%), the secondary hydroxamic acid **2** was somewhat less efficient in its iron extraction efficiency (90%), while the tetracarboxylic acid **4** was found to be fairly inefficient in extracting the ferric ion (12%). However, at pH 3 the primary hydroxamic acid and the carboxylic acid appeared to extract iron with equal efficiency (98 and 96%, respectively) while the secondary hydroxamate appeared to be slightly less efficient (88%). Again it is surprising that the tetracarboxylic acid **4** appears to be as efficient as its hydroxamate analogues (**1** and **2**) at pH 3. At the present time, no explanation for this behaviour is evident. At pH 4 and above, the control experiments showed that most of the iron had precipitated from the aqueous solution and hence the extraction process could not be studied beyond this point. Preliminary results indicate that both **1** and **2** are capable of solubilizing hydrous ferric oxides; however, a more detailed investigation into this behaviour is necessary. In our studies, the primary hydroxamic acid **1** appears to be a superior extractant to the secondary hydroxamic acid **2** at low pH. This observation cannot be readily ascribed to pK_a effects as *N*-methylhydroxamic acids would be expected to have a pK_a slightly lower than their primary hydroxamic acid analogues (*e.g.* pK_a of acetohydroxamic acid = 9.02 and *N*-methylacetohydroxamic acid = 8.63).[22,23]

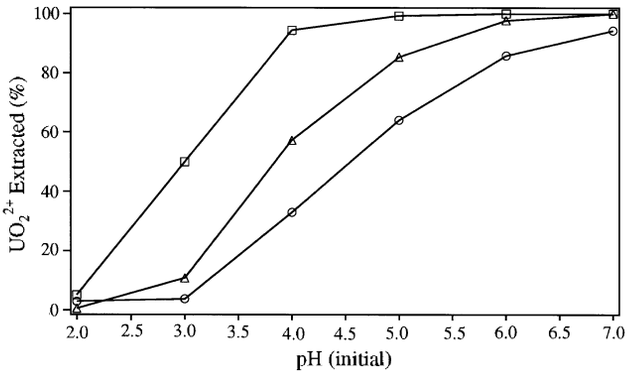


Fig. 2 pH dependence for UO_2^{2+} extraction from aqueous phase (5 ml) into chloroform (5 ml) at 25 °C; $[UO_2^{2+}] = 0.19$ mmol dm^{-3} in 0.1 mol dm^{-3} NaCl; [**1**(□)] = 0.90 mmol dm^{-3}, [**2**(△)] = 0.86 mmol dm^{-3}, [**4**(○)] = 0.95 mmol dm^{-3}

The uranyl extraction ability of calixarenes **1**, **2** and **4** was also studied (Fig. 2). From literature precedents,[13] it was expected that both hydroxamates **1** and **2** and the carboxylic acid **4** should be satisfactory extractants for the uranyl ion. The results of our extraction studies of these calixarenes with UO_2^{2+} indicate that the tetracarboxylic acid is somewhat less efficient than the hydroxamic acid analogues in removing uranium from acidic aqueous solutions. At pH 4, the primary hydroxamic acid **1** appears to be the most efficient extractant for uranium, removing 94% of the uranyl ion from the aqueous phase. The secondary hydroxamic acid **2** was somewhat less efficient than **1** in extracting uranium. At pH 4, 57% of the available uranium was extracted by **2**, while at pH 5 greater than 85% of the uranium was extracted. The tetracarboxylate **4** was generally less effective than its hydroxamate analogues, particularly at the lower pH values; nonetheless, this chelator was able to remove 94% of the available uranium from the aqueous phase at pH 7. Interestingly, at pH 2 none of the ligands are effective for the extraction of uranium into chloroform from the aqueous phase. At pH 3, only the primary hydroxamic acid **1** showed a significant ability for removing uranium from the aqueous phase (50% of the uranium was extracted).

The ability of these chelators to extract a divalent cation, namely the cupric ion, has also been examined (Fig. 3). The Lewis acidity of copper(II) is more comparable to the UO_2^{2+} ion than to thorium(IV) or iron(III). As in the uranium study, hydroxamate **1** was more efficient (96%) than the secondary hydroxamate **2** (73%) for the extraction of copper at pH 4 while the carboxylate extracted less than 6%. In fact the carboxylic acid **4** shows very little ability to extract copper(II) into chloroform between pH 2–6.

A competitive metal ion extraction study was also performed to determine the potential of calixarenes **1**, **2** and **4** for the selective extraction of thorium(IV) in the presence of the ferric ion. In this study, an aqueous solution at pH 2 containing equimolar quantities of Th^{4+} and Fe^{3+} was contacted with a slight molar excess of each of these ligands in chloroform. All three chelators appear to selectively extract the ferric ion (83, 98 and 49%, respectively for **1**, **2** and **4**) over thorium(IV) (24, 3 and 3%, respectively). The primary hydroxamic acid **1** was found to extract more thorium than the other calixarenes although it was

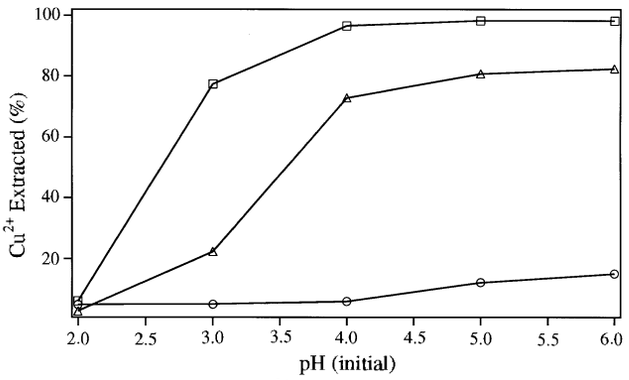


Fig. 3 pH dependence for Cu^{2+} extraction from aqueous phase (5 ml) into chloroform (5 ml) at 25 °C; $[Cu^{2+}] = 0.19$ mmol dm^{-3} in 0.1 mol dm^{-3} NaCl; [**1**(□)] = 0.90 mmol dm^{-3}, [**2**(△)] = 0.86 mmol dm^{-3}, [**4**(○)] = 0.95 mmol dm^{-3}

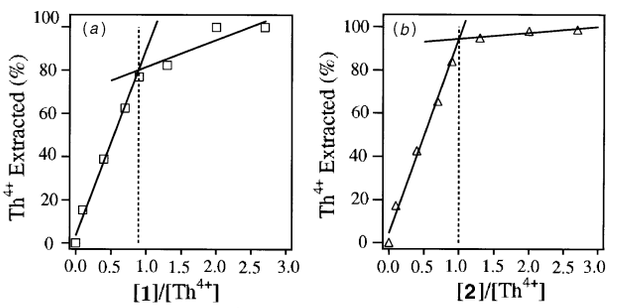


Fig. 4 Extraction of Th^{4+} using various ratios of **1** (*a*) and **2** (*b*) to Th^{4+} at (*a*) pH = 2, □; (*b*) pH = 3, △; $[Th^{4+}] = 0.90$ mmol dm^{-3}

still selective for iron over thorium. Surprisingly, the secondary hydroxamic acid **2** was found to be almost completely selective for the extraction of iron over thorium.

The results of the competitive extraction studies with thorium and iron, although somewhat disappointing, can be justified. Hydroxamic acids are expected to coordinate with iron and thorium (metals of comparable Lewis acidity) in a similar manner. In order to form a strong neutral, tetrahydroxamato complex with thorium in the extraction process, both **1** and **2** must lose four protons, one from each of the ligand moieties. Given that the pK_a values of hydroxamic acids are usually in the range of 8–10,[24] it is possible that chelators **1** and **2** are not fully coordinated to thorium at low pH values. On the other hand, only three of the hydroxamate groups of **1** and **2** need to participate in the coordination of the ferric ion to give a neutral species.[25] One may expect these chelators to preferentially extract thorium over iron at more alkaline pH values, but the precipitation of these metal ions under those conditions, precludes a reliable study.

It was also of some interest to determine the stoichiometry of the extracted species. It may be possible for these calixarenes to extract the metal ions, particularly, thorium(IV), as either 1:1 or 2:1 ligand–metal species. In order to address this issue, the molar ratio of chelator **1** or **2** to thorium was varied and the amount of the metal ion that was extracted into the chloroform phase determined (Fig. 4). A small molar excess of both **1** and **2** were required for the thorium to be completely extracted from the aqueous phase. These results are consistent with the extraction of a 1:1 metal–ligand complex by calixarenes **1** and **2**.

In conclusion, the cone calixarene extractants **1**, **2** and **4** can be readily prepared using short synthetic sequences. Our metal ion extraction studies show that the primary hydroxamate **1** is the most efficient extractant in this group and shows promise for the extraction of actinide ions from acidic waste solutions. However, by increasing the pH, efficient extraction of any of the metal ions described in this study can be achieved by these three ligands. The results also indicate that selective extraction of thorium or iron in the presence of uranyl and copper should be possible by use of hydroxamate ligand **1**, by taking advantage of the pH in the extraction process. However, it appears that our goal of achieving the selective extraction of thorium over iron may be difficult to achieve using these ligand systems.

Currently, the extraction of radioactive metal ions such as americium(III) and plutonium(IV) by this class of extractants is under investigation. Also, more in depth extraction studies are in progress to understand the extraction process including the nature and stoichiometry of the extracted species for both the hydroxamate and the carboxylate ligands. Hopefully, these studies will result in a better understanding of the metal ion extraction properties of this class of extractants and will allow the preparation of other more effective analogues of these chelators. The synthesis of water soluble analogues of these calixarene chelators may also be necessary to gain a more detailed understanding of the coordination properties of these new chelators.

Experimental

Synthesis

General procedures. IR spectra were recorded on a Perkin-Elmer 283B Spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Gemini-200 Spectrometer unless otherwise noted and ^{13}C NMR spectra were recorded at 100 MHz using a Varian Unity 400 spectrometer. NMR spectra were obtained in $CDCl_3$ with signals recorded downfield from an internal $SiMe_4$ reference. *J* Values are in Hz. Analytical and preparative TLC were performed on silica $60/F_{254}$ plastic or glass backed plates (E. M. Science). Column chromatography was done on silica gel (Merck 230–400 mesh) or neutral aluminium oxide (Aldrich 150 mesh, Brockmann I) as indicated. All solvents were HPLC grade and were obtained from Fisher Scientific or from VWR Scientific. Elemental analyses were performed by Desert Analytics, Tucson, Arizona. Reagents were obtained from Aldrich Chemical Company and were used without further purification unless otherwise indicated.

25,26,27,28-Tetrakis(4-ethoxycarbonylbutoxy)-*p*-*tert*-butylcalix[4]arene‡ (3). To a suspension of sodium hydride (50% in oil, 1.08 g, 27 mmol) in 10% DMF–THF (55 ml), calix[4]arene (2.00 g, 3.08 mmol) was added and the mixture stirred at room temp. Once the evolution of hydrogen ceased, a solution of ethyl 5-bromovalerate (8.56 g, 3.08 mmol) in THF (20 ml) was added over a period of 15 min. The reaction mixture was then refluxed for 6 h. The reaction mixture was allowed to cool to room temp. and the excess NaH was carefully decomposed by the addition of ethanol. The mixture was then diluted with water (100 ml) and extracted with chloroform (2 × 100 ml). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Unreacted ethyl-5-bromovalerate was removed by bulb-to-bulb distillation under vacuum (60 °C, 1 mmHg). The residual pale-yellow oil was purified by column chromatography on silica gel using a 85:15 hexane–ethyl acetate solvent mixture as the eluent. The cone product **3** (1.47 g, 41%) was isolated as a semi-solid. The partial cone product (1.43 g) could also be isolated from the reaction. Found: C, 74.5; H, 9.3. Calc. for $C_{72}H_{104}O_{12}$: C, 74.45; H, 9.0%; ν_{max}/cm^{-1} (neat) 1733 (CO); δ_H(200 MHz; $CDCl_3$) 1.08 (36 H, s, Bu^t), 1.26 (12 H, t, *J* 7.2, CH_2CH_3), 1.65–1.83 (8 H, m, $COCH_2CH_2$), 1.94–2.10 (8 H, m, OCH_2CH_2), 2.40 (8 H, t, *J* 7.4, CH_2CO_2Et), 3.14 (4 H, d, *J* 12.5, $PhCH_2Ph$), 3.87 (8 H, t, *J* 7.4, OCH_2), 4.14 (8 H, q, *J* 7.2, CH_2CH_3), 4.35 (4 H, d, *J* 12.5, $PhCH_2Ph$), 6.77 (8 H, s, Ph); δ_C(100 MHz; $CDCl_3$) 14.27, 21.66, 29.77, 31.55, 31.47, 33.84, 34.28, 60.21, 74.67, 125.00, 133.73, 144.42, 153.42, 175.37.

‡ IUPAC name: [1²,3²,5²,7²-tetra-*tert*-butyl-1⁵,3⁵,5⁵,7⁵-tetrakis(4-ethoxycarbonylbutoxy-1,3,5,7(1,3)-tetrabenzenacyclooctaphane; names for related compounds can be constructed similarly.

An improved procedure for the preparation of tetraester **3** is as follows: to a suspension of sodium hydride (60% in oil, 0.308 g, 7.7 mmol) in DMF (20 ml), calix[4]arene (1.00 g, 1.54 mmol) was added and the mixture stirred at room temp. Once the evolution of hydrogen ceased, ethyl 5-iodovalerate (6.30 g, 24.6 mmol) was added and the mixture stirred at room temp. for 5 d. The reaction mixture was then diluted with water (20 ml) and extracted with diethyl ether (2 × 75 ml). The combined organic extract was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified as described above to give the cone product **3** (1.54 g, 90.5%).

25,26,27,28-Tetrakis(4-carboxybutoxy)-*p*-*tert*-butylcalix-[4]arene (4). A solution of KOH (0.255 g, 3.87 mmol) in 95% ethanol (20 ml) was added to the calixarene tetraester **3** (1.00 g, 0.862 mmol) and the reaction mixture was stirred at room temp. After 6 h, the reaction mixture was diluted with water (10 ml), acidified with 2 mol dm^{-3} HCl and extracted with $CHCl_3$ (2 × 50 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo* to give the tetraacid **4** (0.875 g, 97%) as a white solid. The product could be recrystallized from 80% acetone–water: mp 242–243 °C; Found: C, 73.0; H, 8.4. Calc. for $C_{64}H_{88}O_{12}$: C, 73.25; H, 8.45%; ν_{max}/cm^{-1} (KBr) 1710 (CO); δ_H(200 MHz; $CDCl_3$) 1.10 (36 H, s, Bu^t), 1.7–1.9 (8 H, m, $COCH_2CH_2$), 2.0–2.2 (8 H, m, OCH_2CH_2), 2.51 (8 H, t, *J* 7.5, CH_2CO_2H), 3.15 (4 H, d, *J* 12.5, $PhCH_2Ph$), 3.88 (8 H, t, *J* 7.5, OCH_2), 4.38 (4 H, d, *J* 12.5, $PhCH_2Ph$), 6.78 (8 H, s, Ph); δ_C(100 MHz; $CDCl_3$) 21.31, 29.92, 31.04, 31.45, 33.84, 34.14, 75, 124.98, 133.65, 144.43, 153.57, 180.33.

25,26,27,28-Tetrakis(4-*N*-benzyloxycarbamoylbutoxy)-*p*-*tert*-butylcalix[4]arene (5). The tetraacid **4** (0.598 g, 0.571 mmol) was refluxed with excess oxalyl chloride (2.5 ml) for 6 h. The reaction mixture was cooled to room temp. and the excess oxalyl chloride removed *in vacuo* to give the acid chloride (0.640 g) which was used without purification.

Pyridine (10 ml) was added to a solution of *O*-benzylhydroxylamine hydrochloride (0.636 g, 3.9 mmol) in CH_2Cl_2 (20 ml) over 10 min at 0 °C and the mixture was stirred for 0.5 h. A solution of the tetraacid chloride (0.636 g, 0.56 mmol) in CH_2Cl_2 (5 ml) was added and the reaction mixture was stirred at room temp. for 12 h. The reaction mixtutre was then diluted with CH_2Cl_2 (30 ml) and washed with 2 mol dm^{-3} HCl (2 × 20 ml) and water (3 × 30 ml). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (alumina, 10% methanol–chloroform) to give the tetraamide **5** (0.425 g, 50%) as a white solid: mp 182 °C; Found: C, 75.1; H, 8.1; N, 3.8. Calc. for $C_{92}H_{116}N_4O_{12}$: C, 75.2; H, 7.95; N, 3.8%; ν_{max}/cm^{-1} (KBr) 1652 (CO); δ_H(200 MHz; $CDCl_3$) 1.08 (36 H, s, Bu^t), 1.61–1.78 (8 H, m, $COCH_2CH_2$), 1.93–2.08 (8 H, m, OCH_2CH_2), 2.19 (8 H, unresolved t, CH_2CO), 3.09 (4 H, d, *J* 16, $PhCH_2Ph$), 3.78 (8 H, unresolved t, OCH_2), 4.30 (4 H, d, *J* 16, $PhCH_2Ph$), 4.82 (8 H, s, OCH_2Ph), 6.76 (8 H, s, Ph), 7.30–7.50 (20 H, m, Ph), 10.25 (4 H, s, NH); δ_C(100 MHz; $CDCl_3$) 22.43, 30.01, 30.87, 31.43, 33.10, 34.01, 74.98, 78.04, 124.97, 128.43, 129.13, 133.67, 135.41, 144.50, 153.22.

25,26,27,28-Tetrakis(*N*-hydroxycarbamoylbutoxy)-*p*-*tert*-butylcalix[4]arene (1). To a solution of the amide **5** (0.156 g, 0.100 mmol) in 33% acetic acid in methanol (15 ml) was added 5% Pd/C (25 mg) and the reaction was stirred under hydrogen at room temp. After 4 h, the catalyst was filtered off and solvent removed *in vacuo* to give the tetrahydroxamic acid **1** (0.110 g, 91%) as a white solid: mp 276 °C (decomp.); Found: C, 69.6; H, 8.2; N, 4.7. Calc. for $C_{64}H_{92}N_4O_{12}$: C, 69.3; H, 8.4; N, 5.0%; ν_{max}/cm^{-1} (KBr) 1652 (CO); δ_H(200 MHz; $CDCl_3$) 1.05 (36 H, s, Bu^t), 1.63–1.78 (8 H, m, $COCH_2CH_2$), 1.97–2.103 (8 H, m, OCH_2CH_2), 2.23–2.39 (8 H, m, CH_2CO), 3.09 (4 H, d, *J* 15, $PhCH_2Ph$), 3.72–3.88 (8 H, m, OCH_2), 4.32 (4 H, d, *J* 15, $PhCH_2Ph$), 6.9 (8 H, br s, Ph); δ_C(100 MHz; $CDCl_3$) 22.52, 30.22, 31.53, 32.52, 33.16, 33.87, 35.90, 75.07, 125.04, 133.74, 144.48, 153.52, 172.21.

25,26,27,28-Tetrakis [4-*N*-methyl-*O*-(diphenyl-*tert*-butylsilyl-oxy)carbamoylbutoxy]-*p*-*tert*-butylcalix[4]arene (6). The tetra-acid **4** (0.215 g, 0.205 mmol) was refluxed with excess oxalyl chloride (2.5 ml) for 6 h. The reaction mixture was cooled to room temp. and the excess oxalyl chloride removed *in vacuo* to give the corresponding acid chloride (0.230 g) which was used without purification.

To a solution of pyridine (1 ml) and *N*-methyl-*O*-(*tert*-butyldiphenylsilyl)hydroxylamine[18b] (0.467 g, 1.6 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added a solution of the crude acid chloride in CH_2Cl_2 (5 ml) over 5 min and the reaction mixture was stirred at room temp. After 12 h, the reaction mixture was washed with water (10 ml), dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (alumina, 10% ethyl acetate–hexane) to give the tetraamide **6** (0.185 g, 42.9%) as a white solid: mp 59 °C; Found: C, 73.6; H, 8.0; N, 2.5. Calc. for $C_{132}H_{172}O_{12}Si_4N_4 \cdot 2H_2O$: C, 73.6; H, 8.2; N, 2.6; ν_{max}/cm^{-1} (KBr) 1670 (CO); δ_H(200 MHz; $CDCl_3$) 1.11 (36 H, s, Bu^t), 1.08 (36 H, s, $SiBu^t$), 1.35–1.50 (8 H, m, $COCH_2CH_2$), 1.70–1.88 (8 H, m, OCH_2CH_2), 2.20 (8 H, t, *J* 7.5, CH_2CO), 3.10 (4 H, d, *J* 14, $PhCH_2Ph$), 3.10 (12 H, s, NCH_3), 3.72 (8 H, t, *J* 7.5, OCH_2), 4.31 (4 H, d, *J* 14, $PhCH_2Ph$), 6.80 (8 H, s, Ph), 7.26–7.46 (24 H, m, Ph), 7.68 (16 H, d, *J* 5.0, Ph); δ_C(100 MHz; $CDCl_3$) 19.62, 153.89, 21.14, 27.39, 29.76, 31.73, 31.88, 33.07, 34.21, 74.95, 125.23, 128.08, 130.72, 132.14, 134.13, 136.37, 144.55, 153.89.

25,26,27,28-Tetrakis(4-*N*-hydroxy-*N*-methylcarbamoyl-butoxy)-*p*-*tert*-butylcalix[4]arene (2). Tetrabutylammonium fluoride (1.6 ml, 1.6 mmol) was added to a solution of **6** (0.680 g, 0.300 mmol) in THF (10 ml) and the reaction was stirred at room temp. After 8 h the reaction mixture was diluted with water (20 ml) and extracted with $CHCl_3$ (2 × 30 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was recrystallized from methanol–water to give the hydroxamic acid **2** (0.350 g, 91%): mp 238 °C; Found: C, 69.1; H, 8.4; N, 4.6. Calc. for $C_{68}H_{100}O_{12}N_4 \cdot H_2O$: C, 69.0; H, 8.7; N, 4.7%; ν_{max}/cm^{-1} (KBr) 1616 (CO); δ_H(200 MHz; $CDCl_3$) 1.07 (36 H, app t, Bu^t), 1.57–1.73 (8 H, m, $COCH_2CH_2$), 2.02–2.18 (8 H, m, OCH_2CH_2), 2.62 (8 H, unresolved t, CH_2CO), 3.10 (4 H, d, *J* 14, $PhCH_2Ph$), 3.25 (12 H, s, NCH_3), 3.82 (8 H, unresolved t, OCH_2), 4.38 (4 H, d, *J* 14, $PhCH_2Ph$), 6.77 (8 H, app t, Ph). The splitting of the aromatic and *tert*-butyl signals is presumably due to H-bonding; δ_C(100 MHz; $CDCl_3$) 21.40, 30.59, 31.11, 31.23, 31.42, 31.58, 32.62, 34.02, 35.90, 74.70, 124.95, 133.72, 144.44, 153.54, 174.4.

Solvent extraction studies

Stock solutions of the metal ions were prepared from $Th(NO_3)_4 \cdot 10H_2O$, $UO_2(NO_3)_2 \cdot 6H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$ and $Cu(NO_3)_2 \cdot 6H_2O$. All metal salts were reagent grade or better. The final concentrations of the Th^{4+}, UO_2^{2+}, Fe^{3+} and Cu^{2+} ion solutions were determined by either ICP analysis or colorimetric titration with arsenazo(III) against NIST traceable standards. Stock solutions of the calixarenes (1000 ppm) were prepared from pure samples of **1**, **2** and **4** and were dissolved in $CHCl_3$ to give solutions of 0.90, 0.86 and 0.95 mmol dm^{-3}, respectively. All the experiments were conducted in a 0.1 mol dm^{-3} sodium chloride solution to maintain constant ionic strength.

Typically, the evaluation of the extraction ability of these calixarenes were performed at room temp. as follows: dilute sodium hydroxide was added dropwise to the solution of the target metal ion (greater than 200 ml total volume) until the desired pH (2–8) was reached. An aliquot of the resulting metal ion solution (4 ml) was then transferred to a 16 × 150 mm screw-cap vial. An equal volume aliquot of the individual calixarene solution was added to the vial and the resulting biphasic mixture was then gently mixed for 2 h using a test-tube shaker (Labquake, model C4115). The concentration of the metal ion remaining in the aqueous phase was then measured by ICP analysis or by complexometric titration with arsenazo(III).

Control experiments were also performed to correct for the amount of metal ion lost *via* precipitation at the pH of interest. The pH of the metal ion solution was adjusted to the desired pH (2–8) and the resulting solution was mixed with an equal volume of chloroform for 2 h. Then, the amount of metal ion remaining in the aqueous phase was determined. The amount of metal ion extracted into the chloroform phase was then the difference between its initial concentration in the aqueous phase as determined in the control study and its concentration after contacting the aqueous phase with the calixarene in chloroform.

Acknowledgements

This work was supported by the Waste-Management Education and Research Consortium of New Mexico and the Efficient Separations and Processing Crosscutting Program of the United States Department of Energy. Dr Hollie Jacobs of NMSU is thanked for helpful discussions.

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Paper 6/07354I
Received 28*th October* 1996
Accepted 7*th January* 1997