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Synthesis and extraction results of new halide terminated 2-alkyl-*p-tert*-butylcalix[4]arenes bearing phosphine oxides or ketones on the narrow rim

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Abstract:

The synthesis of lower rim tetraphosphorylated and tetraketone calix[4]arenes with haloalkyl groups tethered to a single methylene bridge and their utilization as extraction agents for rare earth elements are reported. Synthesis of these new functionalized calix[4]arene species has been achieved in good to modest yields, and extraction of nine lanthanide nitrates has been explored using these novel calix[4]arene species. The tetraphosphorylated calix[4]arenes show better lanthanide extraction efficiency than their ketone counterparts, especially for europium (III). These experiments demonstrate that inclusion of a substituent tethered to the methylene bridge does not significantly reduce the extraction efficiency of these new calix[4]arene ligands as compared to similar unsubstituted ligands in literature, making them important precursors in the development of functionalized stationary phases for separation of lanthanides. Development of similar CMPO-bearing narrow rims and new solid-phase extraction materials for the solid-liquid separation of lanthanides remains the subject of future work.

1. Introduction:

The rare earth elements (REEs), composed primarily of the fifteen lanthanides, find broad application in many modern devices, ranging from use as magnets in wind turbines, hard drives, and air conditioners to incorporation in hybrid car batteries.^{1,2} These elements have proven indispensable to the sustainable and green world approach prevalent in modern society.³ China has been a key player in REE production over the past several decades. Recent decisions to significantly reduce export quotas of these valuable minerals to ostensibly meet Chinese domestic requirements has resulted in increased tariffs and thereby an economic driving force to look for alternative sources of REEs.⁴ Isolation and purification of REEs from mineral deposits has always been a lengthy and laborious task for the mining industry. Separation techniques currently employed for this processing generate undesirably large quantities of waste due to the chemical treatments that are necessary to process the raw ore and subsequently separate individual REEs, contributing significantly to their cost.⁵ In addition to their production from raw ores, the idea of recovering REEs from stored nuclear waste is quite attractive. High-level nuclear wastes (HLWs), obtained as secondary waste after separation of uranium or plutonium

from a nuclear reactor's depleted fuel are composed of fission products including minor actinides like Am and Cm, as well as lanthanides including Nd, Gd, Eu, and Sm.^{6,7} The recovery of lanthanides at this stage of nuclear waste management will not only help meet lanthanide production requirements, but will also reduce the total quantity of waste requiring long term storage.⁷ Another potentially valuable source of lanthanides involves their recovery from outdated electronic devices and materials that have completed their functional lifetime. The effective utilization of each of these lanthanide sources requires improved methods and techniques that will in turn lead to better, cleaner, and more economical processes for the separation and isolation of REEs.¹

Over the past decade, much effort has been invested toward improving the separation of lanthanides.^{8,9} Primarily, research in this field has focused on liquid–liquid extraction (LLE) techniques employing coordinating solvents, ionic liquids, or multivalent coordinating ligands assembled on scaffolds such as calixarenes to separate these elements from other metals and earthly impurities.^{7,9} In general, many of the LLE studies previously disclosed have shown significantly improved extraction efficiencies compared to the currently employed industrial separation techniques.^{8,10-12} Despite these advances, these new methods still suffer from the general drawbacks affiliated with LLE, including high solvent and ligand cost and large quantities of chemical waste.

Calixarenes have been widely employed in extraction chemistry over the last two decades.^{7,13-15} These cyclic oligomers are readily produced via the condensation of t-butylphenol with formaldehyde under basic conditions.¹⁶ The cup-shaped macrocyclic structure of a calixarene provides sites for easy modification and functionalization on its upper and lower rims (Figure 1), making it attractive as a scaffold/platform for attachment of monovalent ligating units. The

incorporation of several monovalent ligating units to a single rigid calixarene core results in the formation of a multivalent ligand system. Calixarene-based ligands have proven to be useful for applications in the biomedical field, including ion and molecular recognition.¹³⁻¹⁵ They have also been used in metal recovery and waste treatment as highly selective and efficient extraction agents for alkali, transition, and heavy metals due to their ability to effectively chelate these metal ions strongly.^{7,17,18} Upper and lower rim-functionalized calixarenes have displayed excellent extraction efficiency in various LLE processes. In particular, calixarenes with amines, amides, esters, ketones, or phosphine oxides on the lower rims have proven to be very effective in the areas of ion recognition and LLE.^{10,19-21} Tailoring the groups present on the lower rim has led to successful extraction of alkaline, alkaline earth, or transition metals, and has also been successful in the extraction and separation of lanthanides and actinides from radioactive wastes.^{19,20,22,23} Despite their excellent extraction capabilities, calixarenes are often overlooked industrially due to the financial drawbacks inherent with LLE. For the separation of lanthanides, this is often a laborious, time-consuming process accompanied by difficulty in layer separation due to the formation of emulsions. Also, LLE is not a green process as large quantities of organic solvents are necessary, resulting in significant amounts of waste, subsequently requiring further treatment or disposal and thus increasing costs.⁵⁻⁷

Given the limitations of LLE, several investigators have explored the related solid phase extraction (SPE) approach.²⁴ SPE provides numerous advantages, including reduced volumes of organic solvents, capacity for large-scale separations, and automation of the extraction process, making it a much more economical and greener process. Functionalized calixarenes have been made heterogeneous by immobilization on solid supports, including silica and polymers such as polystyrene through reactions to covalently link their lower or upper rims to the solid support.²⁴⁻

²⁶ Unfortunately, attachment via the upper or lower rims has significantly reduced the ability of these ligands to effectively coordinate to metal centers, resulting in drastically reduced extraction efficiencies attributed to reduced flexibility in these molecules. In order to mitigate the detrimental effects resulting from covalent linkage to these solid supports, our group is investigating the methylene bridges on the calixarenes as the point of attachment. We believe that covalent attachment through these methylene units will have little or no effect on the conformational flexibility of the calixarene in the resultant material. Fantini demonstrated a simple one-pot synthetic route to selectively monofunctionalize a methylene bridge of calix[4]arenes.²⁷ In collaboration with Fantini, our group previously designed and demonstrated synthetic routes to 2-(ω -haloalkyl)-calix[4]arenes with 3-6 carbon spacer alkyl chains.²⁸ The longer five-carbon and six-carbon alkyl tethers are preferred as they will help to physically separate the functionalized calix[4]arene ligand from a solid support like silica upon which they will be immobilized in the future, thereby minimizing interactions between the ligand, an extracted metal ion and the surface of the solid support. Herein, we detail the incorporation of coordinating ligands such as phosphine oxides and ketones at the lower rim of the aforementioned 2-functionalized haloalkyl-calix[4]arenes. Furthermore, we report the utilization of these new molecules in LLE experiments involving lanthanide nitrate solutions as a means to investigate the effect of the long alkyl tail at the methylene bridge on extraction efficiencies of lower rim coordinating groups. These new ligands will be further modified at their halide terminated end and will ultimately be immobilized on solid supports through this modified end in our future efforts to produce improved materials for SPE of lanthanides.



Figure 1. Calix[4]arene: (i) flat line drawing with numbering, (ii) three dimensional perspective, and (iii) similarity to a basket.



(i) NaH, THF:DMF (9:1), CH₃I, Reflux 2 h;

(ii) n-BuLi, THF, Br(CH₂)_nCl, RT overnight, n=5 or 6

Scheme 1. Synthesis of 2-(ω -chloroalkyl)-tetramethoxy-*p*-tert-butylcalix[4]arenes.²⁸



Scheme 2. Synthesis of 2-(ω -chloroalkyl)-tetrahydroxy-*p*-tert-butylcalix[4]arenes.



Scheme 3. Synthesis of 2-(ω -chloroalkyl)-tetra-(diphenylphosphonylmethyl)-*p*-tert-butylcalix[4]arenes.



Scheme 4. Synthesis of 2-(ω-iodoalkyl)-tetra-(pivaloylmethyl)-*p*-tert-butylcalix[4]arenes.



%E using lower rim phosphine oxide calix[4]arene derivatives

Figure 2. Percent extraction (%*E*) for the lanthanide ions with ligands **5**, **6a** and **6b**; concentration of ligand ($C_L=2.5\times10^{-2}$ M) in dichloromethane, concentration of lanthanide nitrates ($C_{Ln}=1\times10^{-4}$ M) in 1 M HNO₃.

2. <u>Results and discussion</u>

2.1. Synthesis and characterization

Synthesis of 2-(ω -chloroalkyl)-tetramethoxy-*p*-tert-butylcalix[4]arenes **3a** and **3b** (Scheme 1) proceeded as reported by our group in 2009.²⁸ To extend that work, we sought to functionalize the narrow lower rim with suitable coordinating ligands for lanthanide ions, such as phosphine oxides or ketones. Ligands bearing oxygen donor atoms like phosphine oxides, phosphonates, amides, carboxylic acids, and ketones on the lower rims have been extensively investigated in extraction and separation of actinides and rare earth metals in the last two decades.⁷ As noted in previous studies, hydroxyl groups on the lower rims can be readily transformed to the desired phosphine oxide or keto groups.^{29,30} Thus, the tetramethoxy-calix[4]arenes **3a** and **3b** were first subjected to exhaustive demethylation using BBr₃ in CH₂Cl₂ overnight, followed by basic hydrolysis to yield the 2-(ω -chloroalkyl)-tetrahydroxy-*p*-tert-butylcalix[4]arenes 4a and 4b (Scheme 2). The ¹H NMR spectra of **4a** and **4b** each showed a resonance for the hydroxyl protons at δ 10.32 ppm, while the absence of a resonance for the methoxy protons indicated complete conversion. The NMR spectra (collected in CDCl₃) showed that 4a and 4b each adopt a full cone conformation in solution, due to the strong hydrogen bonding now present at the lower rim unlike the tetramethoxy derivatives **3a** and **3b**, which were fluxional in solution.²⁸ Furthermore strong broad peaks at ~ 3185 cm⁻¹ in the IR spectra also confirmed the presence of hydroxyl groups on the lower rim.

Simple Williamson etherification of **1** and **4** with $Ph_2P(O)CH_2OTs$ using NaH as the base in toluene yielded the crude tetraphosphorylated species **5**, **6a**, and **6b** in poor to moderate conversion after extended heating for 6 days (Scheme 3).²⁹ The incorporation of the bulky diphenylphosphine oxide groups at the lower rim resulting in a sluggish reaction. Examination of

the crude material by NMR showed the presence of partially phosphinylated species, but did not reveal any peaks attributable to side products as might be expected from an elimination reaction to form an alkene at the terminus of the alkyl tether. Silica column purification yielded pure 5, 6a, and 6b, each of which was identified using ¹H, ¹³C and ³¹P NMR spectroscopy in CDCl₃. The ¹H NMR spectra showed multiplets at 7.60–7.90 ppm and 7.10–7.40 ppm, corresponding to the lower rim diphenyl phosphine oxide moieties. The most notable resonances in the ¹³C NMR spectra were the methylene carbon resonances adjacent to the phosphorus atoms (-CH₂P(O)Ph₂), appearing as two doublets at 71.7 and 71.4 ppm with large ${}^{1}J_{PC}$ coupling constants (77.1 Hz). Additionally two doublets between 152 and 154 ppm were observed, corresponded to ${}^{3}J_{PC}$ coupling of the quarternary carbons (C-O-CH₂P). Two phosphorus resonances were observed in the ³¹P NMR spectra, consistent with the presence of two non-equivalent phosphorus atoms in these molecules. These results confirmed the cone conformation in solution for these molecules, which is maintained due to the steric bulk of the diphenyl phosphine oxide ligands now attached on the lower rims, making it impossible to fit through the calix[4]arene core and preventing conformational fluxionality. Additionally, the various NMR spectra verified the C_s symmetry of 6a and 6b resulting from the single methylene functionalized alkyl tether in those species. These reaction products were further confirmed by mass spectrometry with the observation of [M+H]⁺ peaks and IR spectroscopy, which showed a peak at 1197 cm⁻¹ corresponding to P=O vibrations.³¹

The tetraketone species **7**, **8a** and **8b** were synthesized by extended heating of **1** and **4** in dry acetone along with K_2CO_3 and 1-bromopinacolone for 6 days (Scheme 4).³⁰ KI was also added to the reaction mixture in order to increase the rate of the substitution reaction utilizing the Finkelstein effect. The resulting products were crystallized from ethanol to yield pure **8a** and **8b**

in modest yields. The identities of these compounds were confirmed by ¹H and ¹³C NMR spectroscopy with diagnostic resonances including the ¹³C peaks for the carbonyl carbon (C=O) and the methylene carbon adjacent to the carbonyl group ($-CH_2C(O)-$). As in the previous cases, these molecules also adopt a cone conformation in solution, as confirmed by the NMR spectroscopic data in CDCl₃. Mass spectrometry revealed the presence of an iodo-terminated tether instead of the expected chloro-terminated tether, as indicated by the higher mass [M+Na]⁺ peak observed for **8a** and **8b**, which was attributed to a simultaneous Finkelstein reaction taking place at the tether's end.²⁸ IR spectroscopy further confirmed the presence of the keto group bound to the lower rim with the characteristic C=O vibrations appearing at ~1720 cm⁻¹. All of the new molecules described herein are summarized in Table 1.

2.2. Liquid-liquid extraction of lanthanides

The LLE experiments carried out in this study are based on HSAB theory, wherein a hard acid, the trivalent lanthanide ion (Ln^{3+}) , is coordinated by dative interactions from a hard donor atom like oxygen in P=O or C=O groups present on the lower narrow rim of the calix[4]arene ligand.^{32,33} The extraction efficiency of these new phosphine oxide (6) and ketone (8) based calix[4]arene ligands toward nine lanthanide nitrates was studied and the results are summarized in Figures 2 and S1, respectively (see Supporting Information). These results were compared to a related previous study²⁰ and also provide the groundwork for the future development of these ligands for separation and isolation of lanthanides in heterogeneous systems. The data reported herein provides a direct comparison of the effect of the 2-position haloalkyl tail on the extraction ability of the lower rim substituted calix[4]arenes with coordinating phosphine oxide and ketone groups compared to the native unsubstituted calix[4]arenes.

Figure 2 shows the percent extraction (%E) results for the new lower rim phosphine oxide molecules 6a and 6b in the LLE of lanthanide nitrates in aqueous 1 M HNO₃ solution to the organic dichloromethane phase (CH_2Cl_2). The %E of these trivalent metal ions was also determined from experimental extraction data obtained using the native lower rim phosphine oxide molecule 5, which has been previously reported in the literature.²⁰ Figure 2 clearly demonstrates that Eu³⁺ is favored over other ions across the lanthanide series. In general, the percent extraction of Eu^{3+} with 5 is quite comparable to the reported value²⁰ (red bar in Figure 2), while it can be seen that ligands **6a** and **6b** show slightly reduced extraction efficiencies for Eu^{3+} compared with 5. The extraction efficiency of the ligands toward Eu^{3+} decreases in the order 5>6a>6b, showing that the calix[4] arenes with increasing number of carbon atoms in the haloalkyl tail experience a slight reduction in extraction efficiency. This order is maintained for all the lanthanide ions studied in this work. This decreased extraction efficiency of the alkyl tailed species compared to the unsubstituted species can be attributed to a number of factors: unfavorable spatial orientation of the four coordinating P=O groups on the lower rim due to the presence of the 2-position alkyl tail, hindering flexibility/mobility of the diphenyl phosphine oxide groups adjacent to the methylene bridge having the tail, and also the possibility of the highly flexible tail bending into the cavity made by the lower rim P=O ligands, thereby preventing the lanthanide ions from entering the lower cavity and reducing the coordinative interactions with the oxygen atoms. The order of extraction of these rare earth metal ions decreases as follows: $Eu^{3+}>Sm^{3+}>Gd^{3+}>Pr^{3+}>La^{3+}>Gd^{3+}>Dy^{3+}\geq Yb^{3+}>Nd^{3+}>Ce^{3+}$. A number of factors such as electronics, size of the metal ion, steric effects, and spatial orientation of coordinating groups of the ligands all working in tandem could impact the selectivity observed during extraction. As shown in Figure 2, as the size of the metal ion decreases from La^{3+} to Eu^{3+} ,

the extraction efficiency increases, with Ce^{3+} and Nd^{3+} being slight outliers. However, this trend reverses upon moving from Eu^{3+} to Yb^{3+} as the size of the metals continues to decrease. This data indicates that the cavity formed by the orientation of the four phosphine oxide groups on the lower rim provides the perfect size for Eu^{3+} coordination by the oxygen atoms of P=O. The reduced extraction efficiency moving away from Eu^{3+} in either direction shows that as the metal becomes larger or smaller, the ionic radius and cavity size mismatch reduces the utility of these ligands. Slight deviations from this trend with other metal ions highlight the fact that not just the size, but also the electronics of these metal ions, is important, with both working in tandem to determine the ability of each ligand to extract a certain metal ion. The high selectivity for Eu^{3+} observed with ligands **6a** and **6b**, as clearly demonstrated by the large difference in *D* values (Table 2) and lower extraction efficiency of these ligands toward other trivalent metal ions, can be developed as a useful technique in the separation of Eu^{3+} from mixtures of lanthanide ions in future work.

The same set of trivalent lanthanide ions was subjected to LLE using the ketone-functionalized lower rim calix[4]arene ligands **7**, **8a**, and **8b**. The results of these extractions are depicted in Figure S1 (see Supporting Information). The extraction efficiencies of ketone derivatives are in striking contrast to the results obtained for the phosphine oxide lower rims. Virtually no extraction occurred for the nine lanthanide ions tested (Table S1). The cavity size formed by the orientation of these carbonyl groups, governed by their bulky t-butyl groups, and the significantly reduced polarity of the C=O bonds compared to the P=O bonds in the phosphine oxide groups both contribute to the lack of effective extraction. Furthermore, no complex formation was observed when lanthanum nitrate or praseodymium nitrate hexahydrate was added to a methanol solution of **7** or **8a** and stirred at room temperature overnight, whereas complex

formation was seen with both **5** and 6a.³¹ From the results obtained, ketone derivatives have proven to be a poor choice as extracting agents for lanthanide ions.

In summary, the incorporation of a haloalkyl-tail on the 2-position of a calix[4]arene decreases its extraction ability slightly, but could prove to be a very useful tool in the separation of lanthanides once these tail-ends are immobilized on a solid support in the development of new heterogeneous materials. Overall, the phosphine oxide derivatives worked substantially better than the ketone derivatives and high selectivity for europium was achieved with the diphenyl phosphine oxide lower rims **6a** and **6b**.

3. Conclusion

New calix[4]arene ligands **4a** and **4b** were successfully synthesized and used as precursors to make functionalized calix[4]arene derivatives incorporating four phosphine oxides (**6a** and **6b**) or tert-butylketones (**8a** and **8b**) on their lower rims. Each of these molecules was fully characterized using NMR techniques, mass spectrometry, and IR spectroscopy. The new ligands (**6a**, **6b**, **8a** and **8b**) were then used in LLE studies with nine lanthanide nitrates. The phosphine oxide derivatives showed selectivity among the various lanthanides as well as excellent extraction efficiency for Eu³⁺. The phosphine oxide calix[4]arene derivatives with haloalkyl tails (**6a** and **6b**) showed slightly lower extraction efficiencies compared to the non-tail species **5**; however, all the phosphine oxide species are far better extracting agents than the ketone derivatives. These experiments thus demonstrated that the presence of an alkyl tail attached to the methylene bridge of a calix[4]arene does not significantly reduce its extraction efficiency compared to the unsubstituted analogues, making these functionalized calix[4]arenes useful precursors for the development of new heterogeneous supports unlike calix[4]arenes with substituents attached to the upper or lower rims, which display significantly reduced extraction

efficiencies. These new 2-position substituted calix[4]arenes with lower rim phosphine oxides will hence be further utilized in our group to develop new heterogeneous materials for the effective separation of lanthanides. Similarly the group plans to synthesize the CMPO analogues on the narrow rim of calix[4]arenes and immobilize them onto solid supports.

4. Experimental section

4.1. Materials and reagents

Compounds $1,^{34}$ 2, $3a,^{28}$ $3b,^{28}$ 5^{29} and 7^{30} were synthesized as previously reported. Schlenk and glove box techniques were used in the synthesis of compounds 4a, 4b, 6a, 6b, 8a and 8b. The following reagents were used as received from commercial suppliers: methanol, ethanol, dichloromethane, pentane, sodium carbonate, potassium carbonate, potassium iodide, methyl iodide, *n*-butyllithium (1.6 M in hexane), 1-bromo-5-chloropentane, 1-bromo-6-chlorohexane, boron tribromide (BBr₃), diphenylchlorophosphine, 1-bromopinacolone and silica gel (porosity: 60 Å, particle size: $40-63 \mu$ m). Sodium hydride (NaH) in mineral oil (60% by weight) was washed with pentane under N₂ atmosphere, placed under vacuum to remove solvents/volatiles after washing, and taken into the glove box to be stored for further use. Tetrahydrofuran was dried and purified by distillation from Na/benzophenone ketyl solution. Reaction solvents including dichloromethane and toluene were dried over 4 Å molecular sieves with an MBraun solvent purification system. Acetone for reaction was dried by stirring over dry calcium sulfate overnight and cannula filtered under nitrogen. Ph₂P(O)CH₂OTs was synthesized under ambient conditions as reported in literature.³⁵ All of the lanthanides tested (La³⁺, Ce³⁺, Pr³⁺, Nd³⁺, Sm³⁺, Eu³⁺, Gd³⁺, Dy³⁺, Yb³⁺) were used as nitrate salts and purchased from Strem Chemicals. The

spectrophotometric determination of lanthanides was carried out in the presence of Arsenazo (III) indicator.^{36,37}

4.2. Instruments and apparatus

A 400 MHz Varian or 600 MHz Inova NMR spectrometer was used to obtain the ¹H NMR and ¹³C NMR spectra at 399.9 MHz or 599.9 MHz and 100.6 MHz or 150.8 MHz, respectively, at ambient temperature. A Varian 400 MHz spectrometer was used to record ³¹P NMR data at 161.9 MHz at ambient temperature and referenced to 0.0 ppm externally using a 5% solution of H₃PO₄ in D₂O. The NMR spectra were acquired in CDCl₃ unless otherwise specified. NMR spectra of **2**, **3a** and **3b** made use of a 3:1 CDCl₃/CD₃CN solution containing NaI (1 g in 80 ml) as reported in our group's earlier work.^{27,28} The ¹H and ¹³C NMR shifts are reported relative to CHCl₃ (7.26 ppm) and CDCl₃ (77.3 ppm), respectively. High-resolution time-of-flight or quadrupole mass spectra were obtained from electrospray ionization carried out at the Mass Spectrometry Laboratory at the University of Illinois, Urbana, IL. Methanol was used to prepare the electrospray samples. A Thermo Scientific Evolution 300 UV–vis spectrophotometer was used to record the UV–vis spectra. IR spectra were recorded using a Perkin Elmer Spectrum 2 FT-IR spectrometer. Melting points of compounds were taken in a Uni-Melt capillary melting point apparatus.

4.3. General procedure for synthesis of 2-(ω-chloroalkyl)-tetrahydroxy-p-tertbutylcalix[4]arenes (**4a** and **4b**)

To a 250 ml Schlenk flask kept in an acetone-dry ice bath (-37 °C) containing **3** (1–10 g) dissolved in dry dichloromethane under nitrogen, 10 equivalents of boron tribromide (BBr₃) were added slowly using a syringe.³⁸ The pale yellow solution turned brown in color over the

period of addition of BBr₃. This reaction was allowed to stir for 2 h in the acetone-dry ice bath and further allowed to stir overnight for about 12 h at room temperature. The pale brown solution was then poured over ice and neutralized with sodium bicarbonate to give a pH of 7–8. The CH₂Cl₂ layer was washed twice with sodium bicarbonate solution, followed by two water washes. The collected aqueous layers were back extracted with CH₂Cl₂ and combined with the organic fraction. The organic fraction was then dried over MgSO₄, filtered and concentrated on a rotavap to yield an off-white solid.

4.3.1 2-(5-Chloropentyl)-tetrahydroxy-p-tert-butylcalix[4]arene (4a)³⁹

Reagents: **3a** (9.0 g, 11 mmol); BBr₃ (10.6 mL, 111 mmol); CH₂Cl₂ (120 mL). Yield: 7.6 g (91%); mp 214–218 °C; ¹H NMR (399.9 MHz, CDCl₃): δ 10.32 (s, 4H), 7.13 (d, 2H, ${}^{4}J_{HH}$ =2.0 Hz), 7.10 (d, 2H, ${}^{4}J_{HH}$ =2.0 Hz), 7.08 (d, 2H, ${}^{4}J_{HH}$ =2.0 Hz), 7.02 (d, 2H, ${}^{4}J_{HH}$ =2.0 Hz), 4.51 (t, 1H, ${}^{3}J_{HH}$ =7.6 Hz), 4.28 (d, 1H, ${}^{2}J_{HH}$ =14.0 Hz), 4.27 (d, 2H, ${}^{2}J_{HH}$ =14.0 Hz), 3.54 (t, 2H, ${}^{3}J_{HH}$ =7.2 Hz), 3.53 (d, 1H, ${}^{2}J_{HH}$ =14.0 Hz), 3.52 (d, 2H, ${}^{2}J_{HH}$ =14.0 Hz), 2.22 (q, 2H, ${}^{3}J_{HH}$ =7.2 Hz), 1.79 (quint, 2H, ${}^{3}J_{HH}$ =7.2 Hz), 1.54 (quint, 2H, ${}^{3}J_{HH}$ =7.2 Hz), 1.38 (m, 2H), 1.24 (s, 18H), 1.23 (s, 18H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃): δ 147.0, 146.9, 144.6, 144.5, 131.2, 128.0, 127.7, 127.5, 126.2, 126.1, 125.5, 121.9, 45.3, 35.8, 34.5, 34.3, 33.0, 32.9, 32.7, 32.4, 31.7, 27.5, 27.1; IR (cm⁻¹): 3189 (str, b, O–H), 2869 (m), 1483 (m), 1462 (m), 1395 (m), 1364 (w), 1202 (w), 1122 (w); ESI-HRMS calcd: C₄₉H₆₆ClO₄ [M+H]⁺: 753.4650, found: 753.4644.

4.3.2 2-(6-Chlorohexyl)-tetrahydroxy-p-tert-butylcalix[4]arene (4b)

Reagents: **3b** (10.0 g, 12.2 mmol); BBr₃ (11.6 mL, 122 mmol); CH₂Cl₂ (120 mL). Yield: 7.9 g (84%); m.p. 219–221 °C; ¹H NMR (599.9 MHz, CDCl₃): δ 10.32 (s, 4H), 7.15 (d, 2H, ⁴*J*_{HH}=2.4 Hz), 7.12 (d, 2H, ⁴*J*_{HH}=2.4 Hz), 7.10 (d, 2H, ⁴*J*_{HH}=2.4 Hz), 7.05 (d, 2H, ⁴*J*_{HH}=2.4 Hz), 4.53 (t,

1H, ${}^{3}J_{\text{HH}}$ =7.2 Hz), 4.31 (d, 1H, ${}^{2}J_{\text{HH}}$ =13.2 Hz), 4.29 (d, 2H, ${}^{2}J_{\text{HH}}$ =13.8 Hz), 3.56 (t, 2H, ${}^{3}J_{\text{HH}}$ =7.2 Hz), 3.56 (d, 1H, ${}^{2}J_{\text{HH}}$ =13.2 Hz), 3.54 (d, 2H, ${}^{2}J_{\text{HH}}$ =13.8 Hz), 2.23 (q, 2H, ${}^{3}J_{\text{HH}}$ =7.2 Hz), 1.80 (quint, 2H, ${}^{3}J_{\text{HH}}$ =7.2 Hz), 1.46 (m, 4H), 1.39 (m, 2H), 1.27 (s, 18H), 1.26 (s, 18H); ${}^{13}C{}^{1}H$ } NMR (100.6 MHz, CDCl₃): δ 147.0, 146.9, 144.6, 144.5, 131.3, 128.0, 127.8, 127.5, 126.2, 126.1, 125.5, 122.0, 45.3, 35.7, 34.5, 34.3, 33.0, 32.8, 32.3, 31.8, 31.7, 31.6, 29.0, 27.9, 27.0; IR (cm⁻¹): 3183 (str, b, O–H), 2867 (m), 1482 (m), 1463 (m), 1393 (w), 1362 (w), 1201 (w), 1121 (w); ESI-HRMS calcd: C₅₀H₆₈ClO₄ [M+H]⁺: 767.4806, found: 767.4796.

4.4. General procedure for synthesis of 2-(ω-chloroalkyl)-tetra-(diphenylphosphonylmethyl)-ptert-butylcalix[4]arenes (**6a** and **6b**)

Syntheses of compounds **6a** and **6b** were carried out similarly to the published synthesis of tetra-(diphenylphosphonylmethyl)-*p*-tert-butylcalix[4]arene **5**.²⁹ In a 250 ml flask under nitrogen, a suspension of **4a** or **4b** (1–8 g) and NaH (6 equivalents) in dry toluene was refluxed for 6 h. After cooling to ambient temperature, $Ph_2P(O)CH_2OTs$, synthesized as given in the literature, was added to the suspension and refluxed for 6 days. Water (10 ml) was added to the browncolored reaction mixture under nitrogen to quench any unreacted NaH at the end of the sixth day. The organic toluene layer was then washed twice with water, dried over MgSO₄, filtered, and the toluene was removed under reduced pressure on a rotavap to yield a brown crystalline powder. Purification using silica column flash chromatography (pentane:ethyl acetate:methanol; 8:1.5:0.5) gave a fine crystalline white solid after concentration of the isolated pure column fraction, which was monitored by thin layer chromatography (TLC).

4.4.1 2-(5-Chloropentyl)-tetra-(diphenylphosphonylmethyl)-p-tert-butylcalix[4]arene (6a)

Reagents: 4a (4.1 g, 5.4 mmol); NaH (0.81 g, 33 mmol); Ph₂P(O)CH₂OTs (10.4 g, 27.2 mmol); toluene (160 mL). Yield: 2.7 g (31%); mp >250 °C; ¹H NMR (399.9 MHz, CDCl₃): δ 7.85–7.68 and 7.35–7.19 (m, 40H, PPh₂), 6.50 (d, 2H, ${}^{4}J_{HH}$ =2.4 Hz), 6.41 (d, 2H, ${}^{4}J_{HH}$ =2.4 Hz), 6.32 (d, 2H, ${}^{4}J_{HH}$ =2.4 Hz), 6.28 (d, 2H, ${}^{4}J_{HH}$ =2.4 Hz), 5.35 (d, 2H, ${}^{2}J_{HH}$ =15.2 Hz), 5.19 (t, 1H, ${}^{3}J_{HH}$ =7.2 Hz), 5.17 (s, 4H), 5.15 (d, 2H, ${}^{2}J_{HH}$ =15.2 Hz), 4.87 (d, 2H, ${}^{2}J_{HH}$ =13.2 Hz), 4.85 (d, 1H, $^{2}J_{\text{HH}}$ =13.0 Hz), 3.50 (t, 2H, $^{3}J_{\text{HH}}$ =6.8 Hz), 2.79 (d, 2H, $^{2}J_{\text{HH}}$ =13.2 Hz), 2.58 (d, 1H, $^{2}J_{\text{HH}}$ =13.0 Hz), 1.87 (m, 2H), 1.79 (quint, 2H, ³J_{HH}=6.8 Hz), 1.54 (m, 4H), 0.95 (s, 18H), 0.92 (s, 18H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃): δ 153.3 (d, ³J_{PC}=4.0 Hz, quaternary C–O), 152.9 (d, ³*J*_{PC}=4.0 Hz, quaternary C–O), 145.0, 144.9, 136.8, 133.8, 133.6, 133.5, 132.6, 132.4, 132.3 (d, ${}^{1}J_{PC}$ =95.8 Hz, quaternary Ar), 131.4 (d, ${}^{3}J_{PC}$ =10.8 Hz, Ar), 131.3 (d, ${}^{2}J_{PC}$ =9.1 Hz, Ar), 131.2 (d, ${}^{4}J_{PC}$ =3.3 Hz, Ar), 128.6 (d, ${}^{4}J_{PC}$ =5.4 Hz, Ar), 128.5 (d, ${}^{2}J_{PC}$ =7.7 Hz, Ar), 128.4 (d, ${}^{3}J_{PC}$ =11.2 Hz, Ar), 124.9, 124.8, 121.7, 71.7 (d, ¹J_{PC}=77.1 Hz, -CH₂P(O)Ph₂), 71.3 (d, ¹J_{PC}=77.1 Hz, - $CH_2P(O)Ph_2$, 45.5, 36.8, 33.9, 33.8, 33.0, 32.9, 32.2, 31.5, 31.4, 27.9, 27.8; ³¹P{¹H} NMR (161.9 MHz, CDCl₃): δ 26.8, 26.0; IR (cm⁻¹): 2986 (m), 1592 (w), 1479 (m), 1362 (w), 1197 (m, P=O), 1120 (m), 1102 (w); ESI-HRMS calcd: $C_{101}H_{110}ClO_8P_4$ [M+H]⁺: 1609.6840, found: 1609.6755.

4.4.2 2-(6-Chlorohexyl)-tetra-(diphenylphosphonylmethyl)-p-tert-butylcalix[4]arene (6b)

Reagents: **4b** (4.5 g, 5.9 mmol); NaH (0.84 g, 35 mmol); Ph₂P(O)CH₂OTs (11.3 g, 29.3 mmol); toluene (160 mL). Yield: 2.3 g (24%); mp >250 °C; ¹H NMR (399.9 MHz, CDCl₃): δ 7.86–7.69 and 7.37–7.22 (m, 40H, PPh₂), 6.51 (d, 2H, ⁴J_{HH}=2.4 Hz), 6.42 (d, 2H, ⁴J_{HH}=2.4 Hz), 6.32 (d, 2H, ⁴J_{HH}=2.4 Hz), 6.29 (d, 2H, ⁴J_{HH}=2.4 Hz), 5.36 (d, 2H, ²J_{HH}=15.2 Hz), 5.19 (t, 1H, ³J_{HH}=6.8 Hz), 5.18 (s, 4H), 5.14 (d, 2H, ²J_{HH}=15.2 Hz), 4.88 (d, 2H, ²J_{HH}=13.2 Hz), 4.86 (d, 1H,

² $J_{\rm HH}$ =13.2 Hz), 3.52 (t, 2H, ³ $J_{\rm HH}$ =6.4 Hz), 2.78 (d, 2H, ² $J_{\rm HH}$ =13.2 Hz), 2.60 (d, 1H, ² $J_{\rm HH}$ =13.2 Hz), 1.87 (m, 2H), 1.74 (quint, 2H, ³ $J_{\rm HH}$ =6.4 Hz), 1.57 (m, 2H), 1.43 (m, 4H), 0.95 (s, 18H), 0.93 (s, 18H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃): δ153.4 (d, ³ $J_{\rm PC}$ =4.0 Hz, quaternary *C*-O), 153.0 (d, ³ $J_{\rm PC}$ =4.0 Hz, quaternary *C*-O), 145.1, 145.0, 137.0, 133.9, 133.8, 133.5, 132.7, 132.5, 132.4 (d, ¹ $J_{\rm PC}$ =95.8 Hz, quaternary Ar), 131.5 (d, ³ $J_{\rm PC}$ =11.2 Hz, Ar), 131.4 (d, ² $J_{\rm PC}$ =9.1 Hz, Ar), 131.3 (d, ⁴ $J_{\rm PC}$ =5.3 Hz, Ar), 128.7 (d, ³ $J_{\rm PC}$ =10.8 Hz, Ar), 128.6 (d, ² $J_{\rm PC}$ =7.4 Hz, Ar), 128.5 (d, ⁴ $J_{\rm PC}$ =5.4 Hz, Ar), 125.0, 124.9, 121.9, 71.7 (d, ¹ $J_{\rm PC}$ =77.1 Hz, -*C*H₂P(O)Ph₂), 71.4 (d, ¹ $J_{\rm PC}$ =77.1 Hz, -*C*H₂P(O)Ph₂), 45.6, 36.9, 34.9, 34.0, 33.9, 33.1, 33.0, 32.3, 31.6, 31.5, 30.1, 28.7, 27.3; ³¹P{¹H} NMR (161.9 MHz, CDCl₃): δ26.9, 26.1; IR (cm⁻¹): 2986 (m), 2868 (m), 1592 (m), 1479 (m), 1362 (w), 1197 (m, P=O), 1120 (m), 1104 (w); ESI-HRMS calcd: C₁₀₂H₁₁₂ClO₈P₄ [M+H]⁺: 1623.6996, found: 1623.6973.

4.5. General procedure for the synthesis of 2-(ω-iodoalkyl)-tetra-(pivaloylmethyl)-p-tertbutylcalix[4]arenes (**8a** and **8b**)

Compounds **8a** and **8b** were synthesized in a similar manner to that described for **7**.³⁰ A suspension of **4a** or **4b** and potassium carbonate (12 equivalents) in dry acetone was refluxed for 6 h under nitrogen. To this suspension, 1-bromopinacolone (6 equivalents) along with potassium iodide (6 equivalents) was added and refluxed for 6 days. The reaction mixture was poured into ice water and extracted with CH_2Cl_2 . This CH_2Cl_2 layer was washed with 3% H_2SO_4 (50 ml) solution followed by two portions of water (40 ml). The CH_2Cl_2 layer was dried over MgSO₄, filtered, and concentrated using a rotavap to yield a yellow-colored crude solid. This solid was then crystallized from cold ethanol in a freezer overnight. The resulting solid was washed with cold ethanol to yield a fine off-white crystalline solid.

4.5.1 2-(5-Iodopentyl)-tetra-(pivaloylmethyl)-p-tert-butylcalix[4]arene (8a)

Reagents: **4a** (5.0 g, 6.7 mmol); K₂CO₃ (11.0 g, 79.6 mmol); 1-bromopinacolone (3.6 ml, 27 mmol); KI (4.5 g, 27 mmol); acetone (120 mL). Yield: 1.9 g (24%); mp 218–224 °C; ¹H NMR (399.9 MHz, CDCl₃): δ 6.99–6.54 (m, 8H), 5.38 (t, 1H, ³J_{HH}=6.6 Hz), 5.24 (d, 2H, ²J_{HH}=13.0 Hz), 5.21 (d, 2H, ²J_{HH}=13.0 Hz), 5.18 (d, 2H, ²J_{HH}=13.2 Hz), 5.15 (d, 2H, ²J_{HH}=13.2 Hz), 4.95 (d, 2H, ²J_{HH}=12.4 Hz), 4.89 (d, 1H, ²J_{HH}=13.0 Hz), 3.17 (d, 2H, ²J_{HH}=12.4 Hz), 3.16 (t, 2H, ³J_{HH}=7.2 Hz), 3.15 (d, 1H, ²J_{HH}=13.0 Hz), 1.96 (q, 2H, ³J_{HH}=6.6 Hz), 1.82 (quint, 2H, ³J_{HH}=6.6 Hz), 1.47 (m, 4H), 1.21 (s, 18H), 1.18 (s, 18H), 1.07 (s, 18H), 1.06 (s, 18H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃): δ 211.7, 211.2, 153.7, 153.2, 144.7, 144.6, 136.7, 133.9, 133.8, 133.7, 125.4, 125.3, 124.9, 122.0, 75.2, 74.7, 42.8, 36.1, 34.7, 34.1, 34.0, 33.9, 33.7, 32.2, 32.1, 31.7, 31.6, 31.3, 27.4, 26.7, 26.6, 26.5; IR (cm⁻¹): 2986 (m), 1720 (m, C=O), 1602 (m), 1480 (m), 1368 (m), 1123 (w), 1046 (w), 991 (w); ESI-HRMS calcd: C₇₃H₁₀₅INaO₈ [M+Na]⁺: 1259.6752, found: 1259.6743.

4.5.2 2-(6-Iodohexyl)-tetra-(pivaloylmethyl)-p-tert-butylcalix[4]arene (8b)

Reagents: **4b** (7.7 g, 10 mmol); K₂CO₃ (16.6 g, 120 mmol); 1-bromopinacolone (5.5 ml, 41 mmol); KI (6.8 g, 41 mmol); acetone (160 mL). Yield: 3.0 g (24%); mp 219–227 °C; ¹H NMR (399.9 MHz, CDCl₃): δ 7.01–6.55 (m, 8H), 5.36 (t, 1H, ³*J*_{HH}=6.8 Hz), 5.26 (d, 2H, ²*J*_{HH}=13.2 Hz), 5.24 (d, 2H, ²*J*_{HH}=13.2 Hz), 5.22 (d, 2H, ²*J*_{HH}=12.8 Hz), 5.21 (d, 2H, ²*J*_{HH}=12.8 Hz), 4.97 (d, 2H, ²*J*_{HH}=12.0 Hz), 4.91 (d, 1H, ²*J*_{HH}=12.0 Hz), 3.18 (d, 2H, ²*J*_{HH}=12.0 Hz), 3.17 (t, 2H, ³*J*_{HH}=7.2 Hz), 3.17 (d, 1H, ²*J*_{HH}=12.0 Hz), 1.97 (q, 2H, ³*J*_{HH}=6.8 Hz), 1.81 (quint, 2H, ³*J*_{HH}=6.8 Hz), 1.41 (m, 6H), 1.23 (s, 18H), 1.20 (s, 18H), 1.08 (s, 18H), 1.07 (s, 18H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃): 211.7, 211.2, 153.7, 153.2, 144.6, 144.5, 136.7, 133.8, 133.7,

133.6 (quaternary aromatic carbons), 125.4, 125.3, 124.9, 122.0, 75.2, 74.7, 42.9, 36.2, 34.9, 34.2, 34.0, 33.7, 33.6, 32.2, 32.1, 31.7, 31.6, 30.8, 29.3, 28.4, 26.7, 26.6, 26.5; IR (cm⁻¹): 2967 (m), 2686 (m), 1721 (m, C=O), 1600 (m), 1479 (m), 1364 (m), 1123 (w), 1044 (w), 989 (w); ESI-HRMS calcd: C₇₄H₁₀₇INaO₈ [M+Na]⁺: 1273.6908, found: 1273.6896.

4.6. Liquid-liquid extraction of lanthanide nitrates

Simple LLE (Eq. 1) was performed with the aqueous phase comprised of lanthanide nitrate (10^{-4} M) in HNO₃ (1 M) and the organic phase composed of calix[4]arene ligands **5**,²⁰ **6a**, **6b**, **7**, **8a** or **8b** in dichloromethane (2.5×10^{-2} M). A one milliliter aliquot of each phase was stirred in a stoppered vial at RT for 12 h. The two phases were allowed to separate over 2 h.

$$Calix_{(org)} + Ln(NO_3)_{3(aq)} \xleftarrow{} [Calix][Ln(NO_3)_3]_{(org)}$$
$$[M]_{(aq)} \qquad [M]_{(org)} \qquad (1)$$

UV–vis spectrophotometry with the Arsenazo III indicator was used to determine the percentage extraction (%*E*), with absorbance measured at 655 nm.^{20,37} With the much higher concentration of Arsenazo III than that of the metal ion, we assume complete complexation. The extraction percentages (%*E*) were calculated using the formula:

$$\%E = 100 \times \frac{[A^1 - A]}{[A^1 - A^0]} \tag{2}$$

where A^0 is the absorbance of Arsenazo III solution without cation, A^1 is the concentration of Arsenazo III solution with a known concentration of cation before extraction, and A is the

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concentration remaining after extraction.^{37,40} The ratio of concentration of metal ion in organic phase to concentration of metal ion in aqueous phase gives the distribution ratio (D), represented in Eq. (3). D characterizes the extractability of these ligands. If %E is stated as Eq. (4), distribution coefficients (D) can be calculated as shown in Eq. (5):

$$D = \frac{[M]_{org}}{[M]_{aq}}$$
(3)
%E = 100 × $\frac{[M]_{org}}{[M]_{org} + [M]_{aq}} = 100 × \frac{D}{1+D}$ (4)
$$D = \frac{\% E}{[100 - \% E]}$$
(5)

Table 1. Summary of new ligands.



Compound	L	Х	Isolated yield (%)	m.p. (°C)
4 a	Н	$-(CH_2)_5Cl$	91	214–218
4b	Н	$-(CH_2)_6Cl$	84	219-221
6a	$-P(O)Ph_2$	$-(CH_2)_5Cl$	31	>250
6b	$-P(O)Ph_2$	$-(CH_2)_6Cl$	24	>250
8a	$-C(O)C(CH_3)_3$	$-(CH_2)_5I$	23	218-224
8b	$-C(O)C(CH_3)_3$	-(CH ₂) ₆ I	24	219–227

Table 2. Distribution coefficients (*D*) for the extraction of lanthanides by phosphine oxidecalix[4]arenes^a from an aqueous phase ($C_{Ln}=1\times10^{-4}$ M, 1 M HNO₃).

Ligand	La ³⁺	Ce ³⁺	Pr^{3+}	Nd ³⁺	Sm ³⁺	Eu ³⁺	Gd^{3+}	Dy ³⁺	Yb ³⁺
5	0.40	0.17	0.46	0.18	0.46	2.09	0.35	0.23	0.22
						$(4.00)^{D}$			
6a	0.20	0.15	0.21	0.15	0.36	1.26	0.27	0.20	0.16
6b	0.16	0.13	0.17	0.13	0.32	0.96	0.27	0.18	0.12

^aFor all phosphine oxide-calix[4]arenes, $(C_L=2.5\times10^{-2} \text{ M})$ in dichloromethane. ^bRef. 20.

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TOC Synopsis:

New 2-substituted haloalkyl tetraphosphorylated and tetraketone calix[4]arenes were synthesized and used to understand the effect on extraction of lanthanide ions in comparison to known literature. With distinct selectivity for europium and differential affinity for metals across the lanthanide series, these new ligands should prove to be useful precursors for the development of solid phase extraction materials.

TOC Graphical abstract



Captions

Scheme 1. Synthesis of 2-(ω -chloroalkyl)-tetramethoxy-*p*-tert-butylcalix[4]arenes.²⁸

Scheme 2. Synthesis of 2-(ω-chloroalkyl)-tetrahydroxy-*p*-tert-butylcalix[4]arenes.

Scheme 3. Synthesis of 2-(ω-chloroalkyl)-tetra-(diphenylphosphonylmethyl)-*p*-tertbutylcalix[4]arenes.

Scheme 4. Synthesis of 2-(ω-iodoalkyl)-tetra-(pivaloylmethyl)-*p*-tert-butylcalix[4]arenes.

Figure 1. Calix[4]arene: (i) flat line drawing with numbering, (ii) three dimensional perspective, and (iii) similarity to a basket.

Figure 2. Percent extraction (%*E*) for the lanthanide ions with ligands **5**, **6a** and **6b**; concentration of ligand ($C_L=2.5\times10^{-2}$ M) in dichloromethane, concentration of lanthanide nitrates ($C_{Ln}=1\times10^{-4}$ M) in 1 M HNO₃.

Table 1. Summary of new ligands.

Table 2. Distribution coefficients (*D*) for the extraction of lanthanides by phosphine oxidecalix[4]arenes^a from an aqueous phase ($C_{Ln}=1\times10^{-4}$ M, 1 M HNO₃).