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Supramolecular Ligands for the Extraction of Lanthanide and Actinide Ions

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Abstract

Interest in the isolation and recovery of lanthanide and actinide metals has gained recent attention due to their increasing use in everyday materials (e.g. batteries, screens, sensors) as well as their application in alternative energy production (e.g. nuclear power). However, the purification of these metals, both from recycled materials and raw sources, is daunting due to the similar chemical properties of these elements. This review focuses on the use of supramolecular, preorganized organic ligands as extraction agents in liquid-liquid extraction systems to achieve the separation and recovery of *f*-elements. For the purposes of this review, "supramolecular ligands" are those that append two or more chelating groups to a scaffold. The synthesis of each ligand is presented, along with selections of the extraction results from each compound. When appropriate, the extraction results of the supramolecular, preorganized ligands are compared with their monomeric, commercial counterparts.

I. Introduction

A. Importance of *f*-elements and improved separation methods. The quest for viable alternative energy options along with rapidly advancing technologies in medicine and materials have placed an increasing focus on *f*-element chemistry in recent years. Nuclear power is among the non-carbon producing alternative energy sources and has the potential to help meet worldwide electricity demand while also reducing carbon emissions that threaten the health of the global ecosystem.[1] Actinide (An) elements such as thorium, uranium, and plutonium are of particular relevance to the nuclear fuel cycle due to their inherent radioactive properties utilized within reactors.[2] The non-radioactive lanthanides of the *f*-element group appear in this process as decay products of the An radionuclides and are also well-documented for their unique optical and magnetic properties. Lanthanide (Ln) metals such as europium and terbium display brilliant luminescence under the appropriate conditions, making them useful for applications in advanced display screens,[3] sensors,[4] and bioassays.[5] The magnetic properties of other Ln ions, including gadolinium and neodymium, present opportunities for use in medical imaging agents,[6] computing,[7] and advanced motors (e.g., within electric and hybrid vehicles).[8]

In considering further reliance on nuclear power, one frequently cited drawback is the problem of storage and processing of the resultant waste products. Much of the nuclear waste already in storage from past efforts along with the byproducts of current nuclear power processes consist of *f*-element metal ions dissolved in acidic solutions. A major focus of spent fuel processing involves the extraction of the radioactive actinide metals from the less dangerous lanthanides.[9] Given the radioactivity of the Ans present in waste streams, these materials require special handling and storage conditions; but if efficiently isolated these isotopes could be recycled and used for further energy production. The presence of lanthanides in nuclear waste also complicates processing as these metal ions effectively absorb the neutrons used in the treatment of long-lived radionuclides by transmutation.[10] The efficient removal of Ln metals is therefore essential to improve upon current nuclear waste remediation technologies and render nuclear power more viable as an alternative energy source.

In addition to the impact on nuclear waste remediation, many of the lanthanides present in the waste streams can also be recycled and utilized in a variety of emerging applications. As noted above, many current and developing technologies rely on Ln metals, and the need for effective Ln separations is further driven by the growing desire to recycle materials utilizing Ln metals (e.g., permanent magnets and hybrid car batteries).[11, 12] There has also been an increased focus in recent years on developing improved methods for purification of Ln metals from raw sources (ground ores and minerals).[13] It is anticipated that such efforts would facilitate more efficient, environmentally friendly methods for isolation of these metals as well as open up new supply chains as their relevance in modern society increases. Considering the ever-growing emphasis on the search for efficient An and Ln chelators as well as alternative forms of energy, the design and implementation of improved separation strategies for the *f*-elements has clearly become an important goal of modern chemical research.

B. The liquid-liquid extraction approach to *f*-element separations.

Historically, separation strategies for An and Ln ions have been largely based on the liquid-liquid extraction approach, where the organic phase in a neutral organic solvent (e.g. kerosene).[9, 14] While other methods have been explored in recent years, including the use of ionic liquids as the organic phase in liquid-liquid extractions,[15-21] supercritical fluids,[22] solid phase techniques,[23, 24] and redox based processes,[25] traditional liquid-liquid extraction protocols have remained the "industry standard" due primarily to issues of scalability and compatibility with existing infrastructure. The concept of the liquid-liquid extraction protocol for *f*-element separations is similar to what is accomplished via a standard separatory funnel extraction procedure. In the extraction context, metal ions are initially dissolved in an aqueous solution (often nitric acid) that is stirred vigorously with an organic solvent. Instead of relying solely on the relative solubility of the metal ions in the organic versus aqueous phases to accomplish extraction by the organic solvent, as is typically done in a simple separatory funnel extraction, an additional chelating agent (often an organic, multidentate ligand) is added to the organic phase. This ligand is the key component in achieving successful metal ion extraction. During mixing of the two phases, the organic ligand transitions to the aqueous phase, binds the metal ion and creates a more hydrophobic metal-ligand complex. It is advantageous here to create complexes where the highly charged metal ion, along with its anions, are hidden in the hydrophobic cavity of the ligand(s). This metal-ligand complex is then extracted into the organic phase (Figure 1).

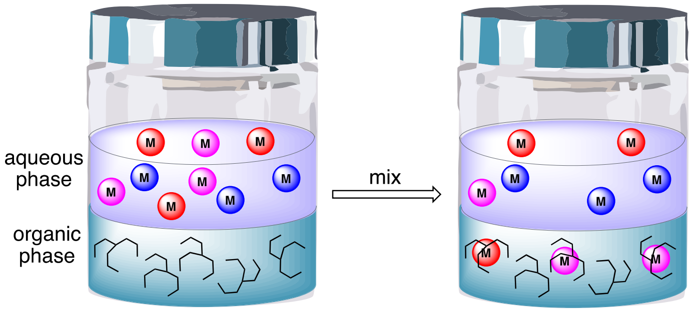


Figure 1. Schematic representation of liquid-liquid extraction process for *f*-element separations. The colored spheres represent metal ions, dissolved initially in an acidic aqueous phase. Upon mixing, the chelating agent, represented by a generic line-angle structure, binds and extracts the metal ions into the organic layer in the form of metal-ligand complex.

Given the nature of the liquid-liquid extraction process, there are clearly many variables that affect the overall separations process both in terms of overall metal extraction efficiency and regarding potential metal ion selectivity (e.g., preferential extraction of An versus Ln ions within a complex mixture). Since the metal is removed from the aqueous phase in the form of the intact complex, solubility of the metal-ligand chelate is important and variation of the organic extraction solvent can be a major factor. Mixing times, temperature, and relative concentrations of ligand and metal ion are all potential variables that may significantly influence metal extraction. However, central to this process remains the chelating agent itself, which is the focus of this review as detailed further below. Ligand design in the area of *f*-element extraction applications is guided by well-established coordination chemistry properties of these metals, leading to many classes of chelating agents with a variety of creative architectures. For example, choice of donor atoms has been examined particularly in separating An from Ln metals for nuclear waste remediation, as the softer An ions prefer soft, polarizable donor atoms (e.g., sulfur).[26] In attempts to achieve selective Ln extraction, challenges arise given the more uniform electrostatic nature of bonding versus An ions and most transition metals along with the relatively small size difference across the entire Ln series.[27] As a result, selective Ln/Ln extraction may be achieved by slight differences in cavity size promoted by a given ligand design along with changes in solvation and/or tertiary complexes formed by additional anion binding within the liquid-liquid extraction protocol. While many factors can come into play, the fundamental challenge remains the design of preorganized chelating ligands and supramolecular assemblies that are suitable for extracting the metal ion(s) of interest.

C. Current separation strategies

There are many different strategies currently being used to achieve the separation of *f*-elements from one another and from other metals. This review will focus on the use of preorganized, supramolecular organic ligands in the organic phase of the liquid-liquid extraction process. This work has been inspired by industrial processes such as PUREX (Plutonium Uranium Recovery by EXtraction),[28] TRUEX (TRansUranium EXtraction process),[29] and DIAMEX (DIAMide EXtraction process).[30] These processes involve the use of an organic ligand dissolved in a hydrocarbon solvent (usually dodecane or kerosene) to extract Ln and An ions out of a highly acidic (1-5 M) nitric acid solution.[9, 26, 31-36] Structures of the monomeric ligands used in these three processes are shown in Figure 2a. In solution, it has been shown that these ligands form complexes with Ln and An ions with 1:2, 1:3 or 1:4 metal-ligand stoichiometries. These complexes also include nitrate anions as well as one or more solvent molecules. The assembly of this multimeric complex is entropically costly as it requires that at least seven separate molecules assemble in solution to make one supramolecular complex (Figure 2b).

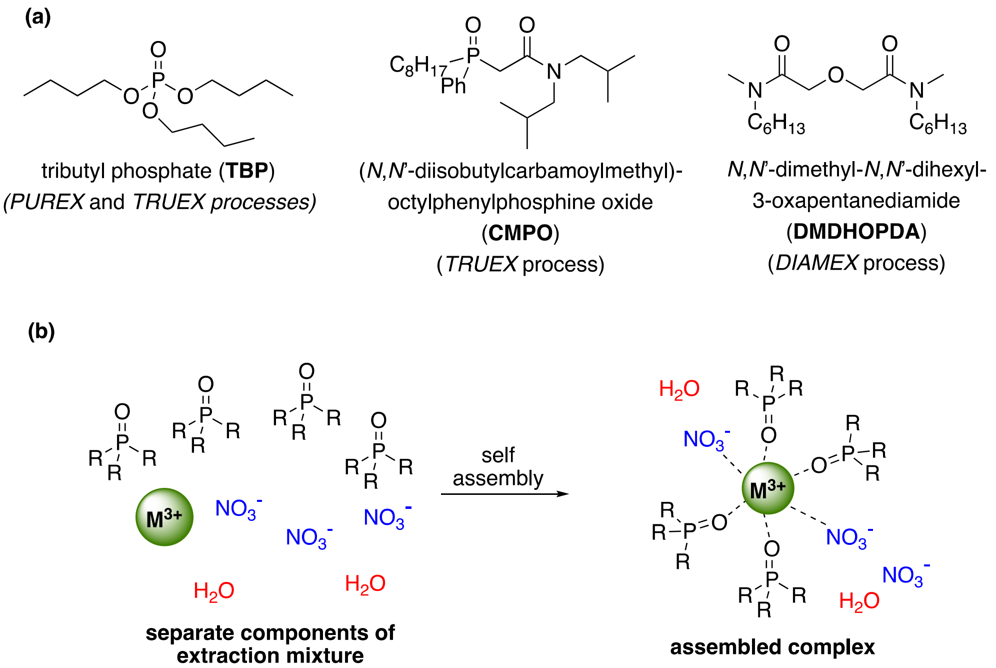


Figure 2. (a) Structures of organic ligands used in the PUREX, TRUEX and DIAMEX solvent extraction processes; (b) depiction of the assembly process that occurs during a liquid-liquid extraction protocol.

The authors of the work discussed in this review have attempted to pay a portion of this entropic cost through covalent bonds by appending the chelating groups shown above to multipodal scaffolds to produce chelating ligands of higher denticity. The hope is that these “preorganized supramolecular ligands” will be more efficient ligands for Ln and An ions (higher K_a) and will also be more selective for one specific Ln or An ion, or particular groups of ions, over others.

D. Some things to consider.

1. Scope of Review. We have written this review to include work targeted at Ln and An separations using liquid-liquid extraction techniques, where the organic phase includes a supramolecular ligand. The types of supramolecular ligands included in this review consist of two or more chelating groups tethered to one another using a scaffold. The ligands are organized by research group, and are presented more-or-less chronologically (with some overlap in the time frames between authors). This order of presentation was chosen to highlight the evolution of this application of ligand design for *f*-element chelation. We have not included here systems where monomeric organic ligands are used and form aggregates in solution, nor have we included systems that employ a solid support. The hope is that these ligands will demonstrate higher extraction efficiencies and better selectivities than their monomeric counterparts. In the process of liquid-liquid extraction the extracted species is often an ill-defined “supramolecular” aggregate that contains the ligand(s), metal, anion(s) and solvent molecule(s). Thus, the use of preorganized supramolecular organic ligands for metal extraction purposes is logical, and may help to pay the entropic costs involved in the formation of the extracted species as noted above. At the end of this review we highlight a couple of supramolecular systems that incorporate a Ln or An ion into the assembled structure where the extraction properties of the complex have also been studied.

Please also note that for many of the systems discussed below, the authors have characterized the metal-ligand complexes in both solution and the solid state using, for example, NMR, fluorescence, MS, and/or X-Ray crystallography. Since this review focuses on the design, synthesis and extraction properties of supramolecular ligands, we have included a minimal amount of other experimental data here. We refer the reader to the primary references for details regarding these other characterization experiments.

2. Extraction efficiency vs. distribution ratio vs. separation factor. There are three common ways to quantitatively describe the ability of an organic ligand to remove metal ions from aqueous solution. As a measure of effectiveness for each supramolecular ligand presented here, we will provide both a percent extraction (%E) and a distribution ratio (*D*) value. The definition of percent extraction (or "extraction efficiency") is the concentration of metal extracted into the organic layer divided by the total concentration of metal present in the experiment:

$$\%\mathrm{E} = [\mathrm{M}]_{\mathrm{org}}/[\mathrm{M}]_{\mathrm{total}}$$

Since these experiments begin with the metal dissolved in an aqueous solution, the larger the %E value the better the extractant.

Some authors prefer to report the extraction ability of their ligands using a "distribution ratio" (*D*). The definition of a distribution ratio is the concentration of metal in the organic layer divided by the concentration of metal in the aqueous layer at the end of the experiment:

$$D = [\mathrm{M}]_{\mathrm{org}}/[\mathrm{M}]_{\mathrm{aq}}$$

Since these experiments also begin with the metal dissolved in aqueous solution, the larger the number the better the extractant. Here, a distribution ratio value of 1 would mean that there is an equal distribution of metal between the organic and aqueous layers (corresponding to an extraction efficiency of 50%). Distribution ratios that are greater than one represent a situation where more metal was removed to the organic layer at the end of the experiment; those *D* values less than one mean that more metal was left behind in the aqueous layer.

Percent extraction and distribution ratio values can be easily converted using the equations shown below. For convenience, we have also included a brief table showing how %E and *D* values are related (Table 1) to help the reader interpret and compare any data that is presented.

$$\%E = [D/(D+1)] \times 100$$

$$D = \%E/(100-\%E)$$

Table 1. Relationship between selected percent extraction (%E) and distribution ratio (*D*) values.

%E	***D***
1	0.01
10	0.1
25	0.3
50	1.0
75	3.0
90	9.0
99	99

The final value used to describe the extraction characteristics of a ligand is the "separation factor" (SF). The separation factor compares the distribution ratios of one ligand for two different metals, and is often used as a measure of how selective a ligand is for one metal over another.

$$SF = (D_{M1})/(D_{M2})$$

Thus, a separation factor close to 1 indicates that the ligand equally extracts both metals from aqueous solution (not particularly selective). However, a large separation factor indicates that the ligand extracts metal #1 at much greater amounts than metal #2. For some applications, such as the recycling of batteries with two or more Ln metals present, it is more important for a ligand to be selective for one metal over another (large SF) rather than a quantitatively good extractant overall (large %E or *D*). For other applications, such as the removal of Ln ions from spent nuclear fuel, a good overall Ln extractant may be needed (%E and *D*) with less importance placed on the selectivity of that extractant for one Ln ion over another. In this case, the Ln/An separation factor would be more important.

3. Take caution when comparing numbers! It is difficult to compare the extraction results of each set of ligands to one another since, often times, the extraction experiments were conducted using different nitric acid concentrations, ligand concentrations, metal concentrations and organic solvents. Our advice is this: that while numbers within the same table of this review article can more-or-less be compared to one another, reader we encourage you to take caution when comparing numbers from one table to another as the experimental conditions can vary widely. Furthermore, we have presented here results looking at how the extraction behavior of the ligands has been influenced by structural variations. We have not focused our discussion on the influence that changes in ligand concentration, metal concentration, nitric acid concentration, and organic solvent had on the extraction process. The authors of the primary references cited here have done this, to varying degrees, and we encourage the reader to look to those papers for more details regarding these experiments and the effects of changes in extraction protocol.

4. A final note on synthesis. As part of this review we will also highlight the synthetic strategy developed by researchers to prepare each supramolecular ligand. Often times the synthesis of these complicated compounds is not trivial as it requires that high-yielding reactions occur at multiple sites, and it is worth highlighting the creative and elegant efforts of the synthetic chemists that carried out this work.

II. Supramolecular ligands used in liquid-liquid extraction of *f*-elements

As described above, we discuss in this review supramolecular ligands that use a scaffold to tether two or more chelating groups together. We also briefly discuss a few systems that incorporate a Ln or An ion into a larger supramolecular structure, but only those systems where the extraction properties have been studied. Selections of work that exploited tetrapyridylethylene diamines, triphenylmethanes, resorcinarenes and calixarenes as scaffolds has been reviewed recently by Verboom,[37, 38], Mori[39] and Odinets.[40] While many of the structures described in these papers fall under the umbrella of this review, they are not included here to avoid redundancies in the literature. For other examples of chelating, multidentate ligands we refer the reader to reviews that cover studies using pyridine rings,[35] triazinylpyridine rings,[33] phenanthrolines,[26] and other nitrogen-containing heterocycles.[26, 41]

A. *Calix[4]arenes by Böhmer and co-workers.*

Böhmer and co-workers have utilized the calixarene scaffold to present the CMPO group for the separation of Ln and An ions for over two decades. While calixarenes are conformationally flexible in solution, substitution of the aromatic rings with alkyl chains or bulky groups can act to rigidify the macrocyclic scaffold. Böhmer and co-workers have exploited this feature throughout their research to present a wide variety of groups that have been preorganized to recognize a Ln or An ion. Discussion of this entire body of work is outside the scope of this review,[42-58] and a portion of this work has been reviewed previously.[37] We have chosen to include here a series of compounds where the authors made small structural changes to the groups on either the upper- or lower-rim of the calixarene scaffold, and where these seemingly subtle changes had an effect on the extraction properties of the target ligand. In addition to the monomeric calix[4]arene based systems described below, Böhmer and co-workers have also attached these supramolecular ligands to solid supports[45, 59] and developed capsular systems in solution.[60]

1. Synthesis of calix[4]arene ligands substituted with CMPO groups at the wide rim. To prepare the parent CMPO-substituted calix[4]arenes studied by this group,[42] the authors began with the well-known *tert*-butylcalix[4]arene **1**.[61] The hydroxyl groups at the narrow rim were deprotonated with NaH and alkylated with a variety of R groups (Figure 3). The *tert*-butyl groups on the wide rim were then replaced with nitro groups under standard nitration conditions, which were subsequently reduced to amines using catalytic hydrogenation in the presence of Raney nickel to give calixarenes **2**. The amino groups were then acylated with the activated ester **3** to give the series of compounds **A**.

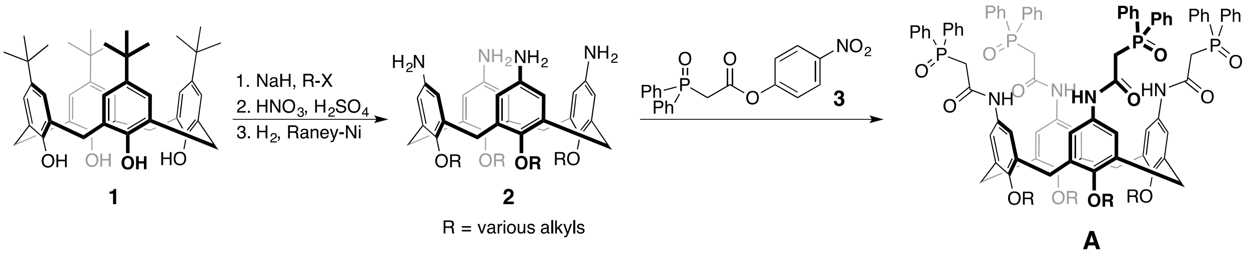


Figure 3. Synthetic approach to wide-rim CMPO-substituted calix[4]arenes.

Böhmer and co-workers also prepared two compounds where the CMPO groups were linked to the wide rim of a calix[4]arene scaffold via an adamantane ring.[49] The synthesis of these molecules begins with the *C*-alkylation of calix[4]arene **4** with 3-carboxy-1-adamantol in the presence of trifluoroacetic acid (Figure 4).[62] The hydroxyl groups on the calixarene ring were then alkylated under standard conditions, and the carboxylic acid groups were transformed to the corresponding acid chlorides with thionyl chloride. Here the synthesis diverges, and two different derivatives were prepared. To prepare the derivative **B1** where the CMPO group is directly attached to the adamantane ring, the authors transformed the acid chlorides into acyl azides, which in the presence of heat and acid underwent a smooth Curtius Rearrangement to give the tetraamine. For the derivative **B2** where there is one methylene unit between the adamantane ring and the CMPO group, the authors reacted the tetraacidchloride with ammonia to give the tetraamide, which was reduced to the tetraamine with lithium aluminum hydride. Both tetraamines were acylated with the *p*-nitrophenyl ester **3** (see Figure 3 for this structure) to give final compounds **B1** and **B2**.

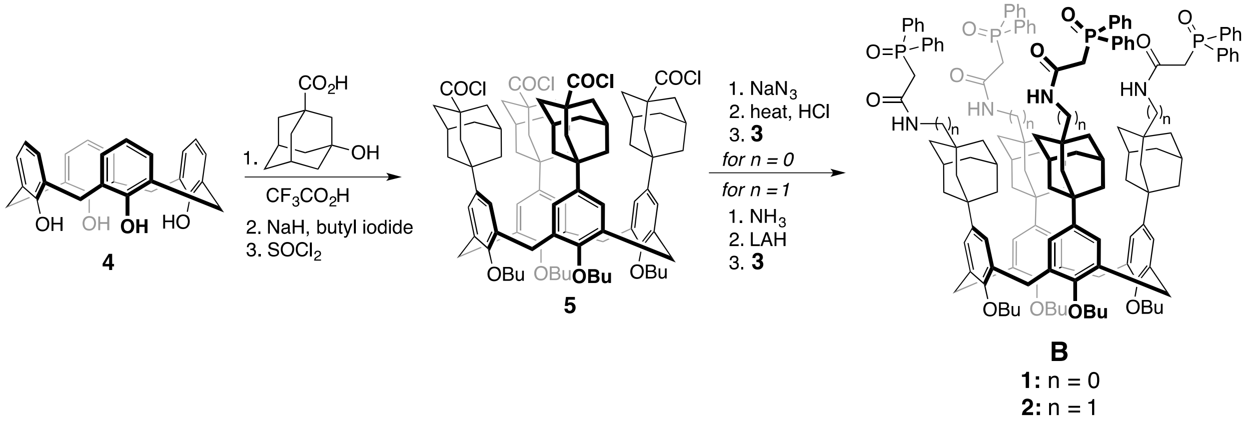


Figure 4. Synthesis of adamantyl-linked CMPO calixarene derivatives **B1** and **B2**.

An intriguing anionic derivative of compounds **B** that was reported in 2011 is shown in Figure 5. Here, the authors prepare calix[4]arenes with two CMPO groups and two cobalt bis(dicarbollide)$^{-1}$ anions ([(1,2-$C_2B_9H_{11}$)$_2$-3,3'-Co]$^{-1}$) on the wide rim (**C**).[56] The bis(dicarbollide) anion was chosen for its high level of both thermal and chemical stability, especially in acidic solutions. It was also proposed that the incorporation of two anions into the ligand structure would reduce the need to cotransport nitrate anions with the target Ln or An metal upon extraction. The synthesis of this derivative begins with the dinitro-dihydroxycalix[4]arene **6**, which was alkylated directly with the dicarbollide **7**. The nitro groups on the calix[4]arene were then reduced with hydrazine in the presence of Pd on alumina, and acylated with activated ester **3** to give the final substituted calix[4]arene **C**.

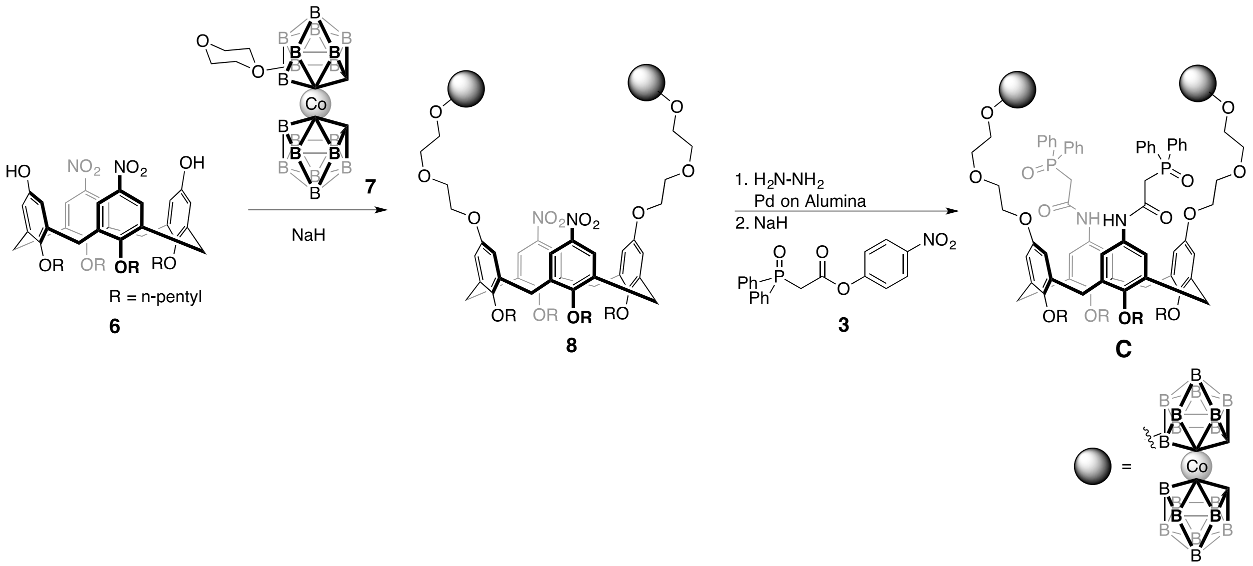


Figure 5. Synthesis of anionic bis(dicarbollide)-substituted calix[4]arene **C**.

2. Synthesis of calix[4]arene ligands substituted with CMPO groups at the narrow rim. The Böhmer group also developed a synthetic route to prepare supramolecular ligands with CMPO groups dangling from the narrow rim of a calix[4]arene (Figure 6). The synthesis began with the direct alkylation at the wide rim of unsubstituted calix[4]arene **4** with 1-hydroxyadamantane to give tetra-adamantyl calixarene **9**.[63] From here, the authors prepared three compounds with varying linker lengths between the CMPO and the calix[4]arene to explore the effect of linker length on ligand extraction ability (**D1-3**).[49, 55] Depending on the linker length, the calix[4]arene hydroxyl groups were alkylated either directly or via a series of steps to bear four phthalimide groups, which were removed under Gabriel conditions (hydrazine hydrate) to give the primary tetraamines **11**. These amines were acylated with the activated ester **3** to give the final ligands **D1-3**. In addition to these compounds, the authors also prepared three closely related ligands where the linker lengths between the calixarene and CMPO were different *within* the compound (**E1-3**). A final derivative included here is **F**[51] where two of the CMPO groups have been replaced with bis(dicarbollide) anions. The synthetic strategies developed to prepare these compounds are similar to that described for the preparation of **C** and **D**.

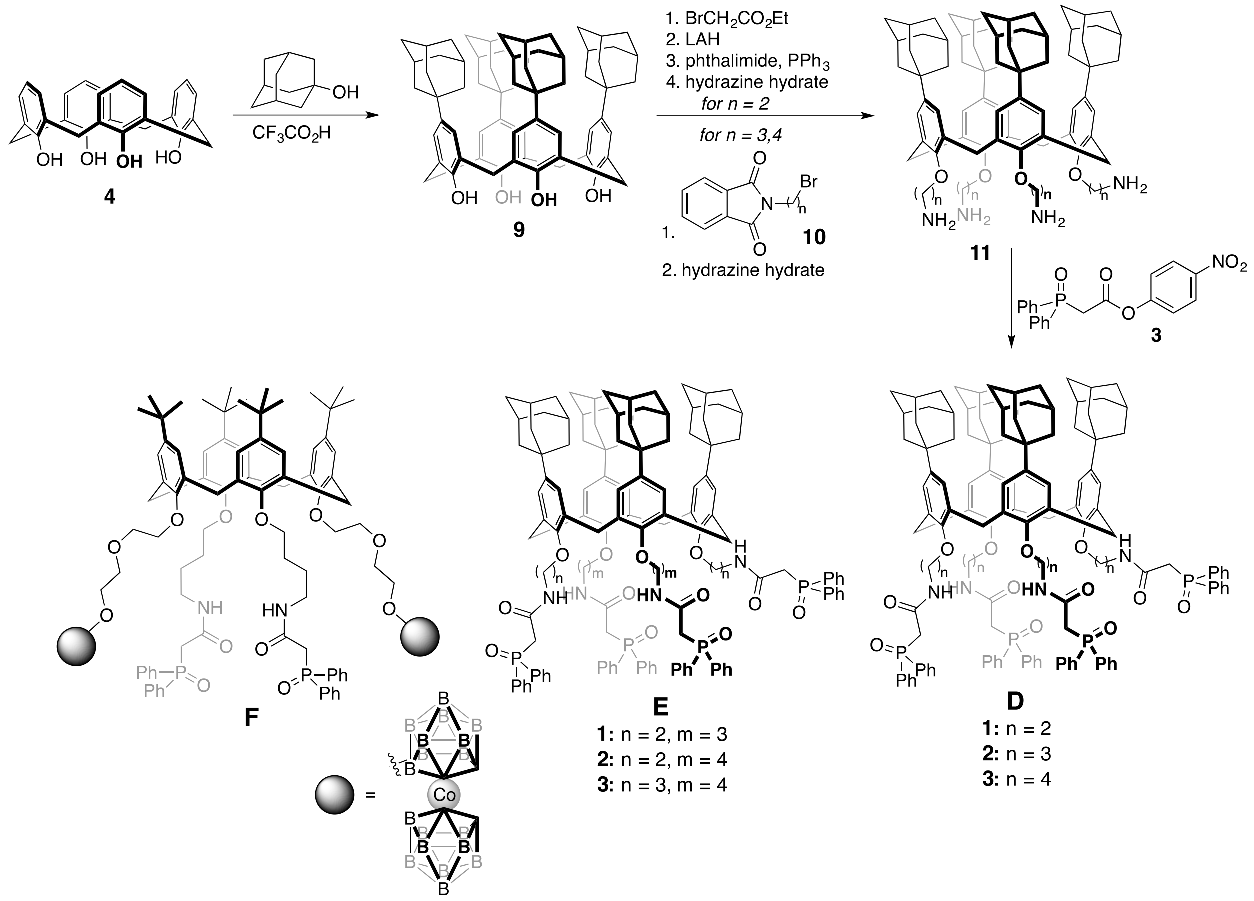


Figure 6. Synthesis of substituted calixarenes **D**, **E** and **F** bearing CMPO groups at the narrow rim.

3. Separation results with Böhmer's calix[4]arene ligands. The Ln/An separation problem addressed by Böhmer and co-workers is the need for more efficient ligands to treat nuclear waste. The authors chose to look at the extraction ability of their ligands for a selection of Ln and An ions, with special attention paid to how selective each ligand was for one metal versus another. Here, while specific percent extraction values are important (how *efficiently* does the ligand extract a metal?), what is just as important is the separation factor for each ligand (how *selectively* does the ligand extract a metal?).

The initial calix[4]arene-based ligand of this work, **A**, represents a series of eight compounds that present four CMPO units on the wide rim of a calix[4]arene, with straight chain and branched -R groups on the narrow rim.[42] The authors reported that the identity of the -R group had little effect on the extraction ability of the ligand; the results from a representative example (R = $C_{18}H_{37}$) are listed in Table 2. This specific calix[4]arene ligand extracted Th^{4+} with a %E of 63% (1×10^{-4} M ligand) and

Eu^{3+} with a %E of 68% ($1x10^{-3}$ M ligand; organic solvent = dichloromethane). These %E values correspond to distribution ratios (*D*) of 1.7 and 2.1. The authors also prepared linear analogues of **A**, and found the extraction ability of these oligomers, when present at a $1x10^{-3}$ M concentration, was markedly decreased compared to the parent cyclic compounds with %E values of 78% for Th^{4+} and <3% for Eu^{3+} ($D = 3.5$ and <0.03). This result suggests that the cyclic calix[4]arene scaffold pre-organizes CMPO groups in a reasonable geometry for the recognition of Ln and An ions.

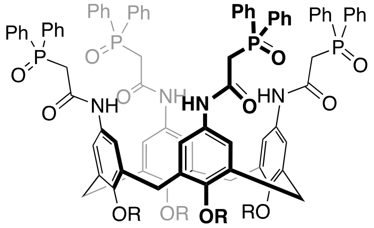
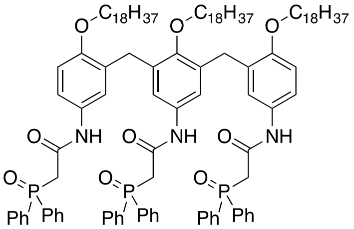
When CMPO groups were linked to the wide rim of a calix[4]arene via adamantyl groups (**B2**), the %E values for the extraction of Eu^{3+} from 3M nitric acid solutions decreased slightly to 55% compared to the 68% value obtained in 1M nitric acid for compound **A** (Table 2). The authors also found that the linker length between the adamantyl ring and the CMPO group had an effect on the extraction performance of this ligand, with the longer chain **B2** performing better than **B1**. Ligand **B1**, where the CMPO group was directly attached to the adamantyl linker, demonstrated %E values for Am^{3+} and Eu^{3+} of 21% and 16%, respectively out of 3M HNO_3 (ligand concentration = 5mM in CH_2Cl_2). Ligand **B2**, which has a methylene spacer between the adamantane ring and the CMPO group, extracted both Am^{3+} and Eu^{3+} under these same conditions with %E values of 96%. The authors attribute this difference in extraction ability to the hindered nature of the CMPO groups of ligand **B1** since they are directly attached to the bulky adamantane rings.

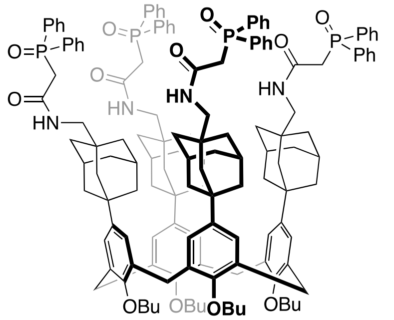
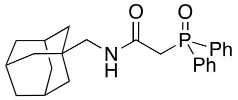
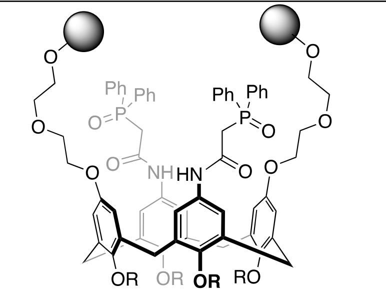
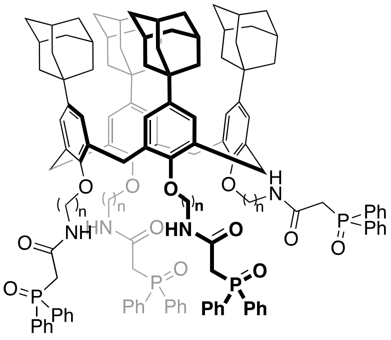
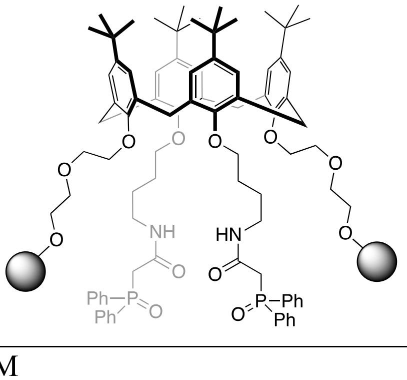
Interestingly, the authors prepared the monomeric version of **B2** (structure shown in Table 2) and determined its extraction ability in order to test if the preorganization provided by the calix[4]arene scaffold influenced the performance of the CMPO group. The monomeric **B2** demonstrates a decreased ability to extract both Eu^{3+} and Am^{3+} from nitric acid solutions with %E values of less than 1%, even at ligand concentrations that are more than an order of magnitude higher than the supramolecular **B2**.

Extraction results from the third wide rim substituted calix[4]arene discussed here, **C**, are also listed in Table 2.[56] The replacement of two CMPO groups with anionic cobalt (bis)carbollide rings resulted in a decrease in the extraction efficiency toward Eu^{3+} (note the change in organic solvent from CH_2Cl_2 to hexyl methyl ketone/hydrogentated tetrapropylene(HMK/TPH)). This result is intriguing since it had been proposed that the inclusion of anionic groups on the ligand would reduce the need to remove nitrate anions from aqueous solution, resulting in a more efficient extractant. The authors suggest that the attachment of the CMPO groups directly to the calix[4]arene aromatic rings, rather than via a flexible linker, may have hindered the ability for ligand **C** to effectively chelate and extract the Ln metal.

For the selection of narrow-rim substituted calix[4]arenes described in this review, selected extraction results are summarized in Table 2. For the series of compounds **D** and **E**,[49] where the wide rim is substituted with adamantyl groups and the narrow rim is substituted with CMPO groups linked via an ether chain, the derivative with the best extractant performance is compound **D3** with the longest linker between the CMPO and the calix[4]arene. This compound extracted Eu^{3+} and Am^{3+} from 1M HNO_3 with %E values of 47 and 58, respectively. As the linker lengths were sequentially decreased, the extraction efficiency of this ligand also decreased. The authors suggest that the greater flexibility of the chelating groups in ligand **D3** allowed for higher cooperative effects upon metal binding. An additional derivative of compound **D** that was prepared by the authors was **F**, where two of the CMPO groups were replaced with anionic cobalt bis(carbollide) rings.[51, 56] Here, the extraction of both Am^{3+} and Eu^{3+} from HMK/TPH (1:1) was nearly quantitative with %E values of >99% for derivative **F**, which has a CMPO linker length of four methylene units.[56] This result supports the authors' previous suggestions that the poor extraction ability of compound **C** was due to the lack of a flexible linker between the calix[4]arene and the CMPO group.

Table 2. Selected extraction results for ligands **A** through **F**. Unless otherwise stated - organic phase: $1x10^{-3}$ M ligand in CH_2Cl_2; aqueous phase: $1x10^{-4}$ M Ln or An nitrate in 1 M HNO_3 at room temperature. %E = extraction efficiency ($[metal]_{extracted}/[metal]_{total}$); D = distribution ratio $[M_{org}/M_{aq}]$; SF = separation factor (D_{M1}/D_{M2}).

Ligand	**Structure**	**%E**	***D***	**SF**
wide rim				
A[42]		Th^{4+}: 63[a] Eu^{3+}: 68	Th^{4+}: 1.7 Eu^{3+}: 2.1	Th/Eu: 0.8
"linear" **A**[42]		Th^{4+}: 78 Eu^{3+}: <3	Th^{4+}: 3.5 Eu^{3+}: <0.03	Th/Eu: >110

B2[49]		Am^{3+}: 65^{b} Eu^{3+}: 55^{b}	Am^{3+}: 1.9 Eu^{3+}: 1.2	Am/Eu: 1.6
“monomer” **B2**[49]		Am^{3+}: <1^{c} Eu^{3+}: <11^{c}	Am^{3+}: <0.01 Eu^{3+}: <0.01	Am/Eu: ~1
C[56]		Eu^{3+}: 41^{d}	Eu^{3+}: 0.69	----
narrow rim				
D3[49] (n = 4)		Am^{3+}: 58 Eu^{3+}: 47	Am^{3+}: 1.4 Eu^{3+}: 0.9	Am/Eu: 1.6
F[56]		Am^{3+}: >99^{d} Eu^{3+}: >99^{d}	Am^{3+}: >100 Eu^{3+}: >100	Am/Eu: ~1

[a] [ligand] = 1x10^{-4} M

[b] [HNO$_3$] = 3M

[c] [ligand] = 4x10^{-2} M

[d] organic solvent = 1:1 hexyl methyl ketone/hydrogenated tetrapropylene (HMK/TPH)

B. Pyridine N-oxides, dibenzofurans and dibenzothiophenes by Paine and co-workers. The Paine group has exploited a variety of aromatic platforms to display chelating groups for Ln and An ions. While the synthesis of these compounds has been reported, along with their coordination chemistry with Ln and An ions, we will discuss here only those where the extraction chemistry has also been studied.

The scaffolds we chose to describe in this review are the pyridine-*N*-oxide, dibenzofuran, dibenzothiophene and diazepane ring systems. A unique feature of each of these scaffolds is that they serve a dual role of pre-organizing the chelating groups as well as providing a potential hard or soft donor to an incoming metal ion. Paine and co-workers have worked with these structures for over 30 years, with reports dating back to 1987. The beginnings of this work involved the decoration of pyridine rings with substituted phosphine oxide groups. These compounds have contained different -R groups on the phosphorus atom, such as phenyl rings,[64-67] alkyl chains,[68] cyclohexanes,[69] amides,[70] ethoxy and hydroxy groups,[71] trifluoromethyl-substituted benzenes[72] and pyrazole rings.[73] We will include here two of the initial compounds in this series, **G** ("NOPO") and **H** ("NOPOPO"), since some of their extraction properties toward *f*-elements have been reported and they are structurally related to the rest of the compounds discussed here.

1. Synthesis of pyridine N-oxide based compounds. In 1993 Paine and co-workers reported a synthetic scheme to achieve the mono- and di-substituted pyridine *N*-oxide compounds **G** and **H** (Figure 7).[67] The 2-methylchlorine derivative of pyridine (**12**) was substituted with potassium diphenylphosphine, and the phosphorus atom was oxidized with hydrogen peroxide to give the phosphine oxide **13**. When this oxidation is carried out at room temperature, the reaction conditions leave the pyridine nitrogen atom untouched. However, inclusion of acetic acid with hydrogen peroxide and heating to 60-65 ˚C results in formation of the pyridine *N*-oxide **G**. Application of these synthetic conditions to 2,6-di(methylchloro)pyridine results in formation of the bis-phosphine oxide **H**.

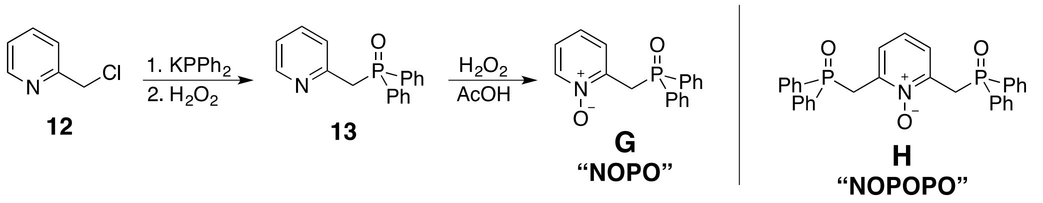


Figure 7. Synthesis of pyridine-*N*-oxide derivatives "NOPO" (**G**) and "NOPOPO" (**H**).

Paine and co-workers have also used the pyridine *N*-oxide platform to present one or two CMPO groups to a willing Ln or An ion (**I-O,** Figures 8 and 9). For compounds **I-L**, the CMPO group is attached to the aromatic scaffold via the central methylene carbon.[74] The synthesis of these chelators began with deprotonation of phosphine oxide **13** with *n*-BuLi followed by acylation with acid chloride **14** to give the CMPO intermediate **15**. Oxidation to the pyridine *N*-oxide **I** proceeds smoothly with either hydrogen peroxide in acetic acid or *m*-CPBA. This same route was used to prepare the di-substituted derivative **J**.[75] Compounds **K** and **L**, with one additional methylene unit between the pyridine ring and CMPO group, were prepared by attaching CMPO **16** directly onto 2-(chloromethyl)pyridine **12**, followed by pyridine *N*-oxide formation using H_2O_2 or *m*-CPBA.

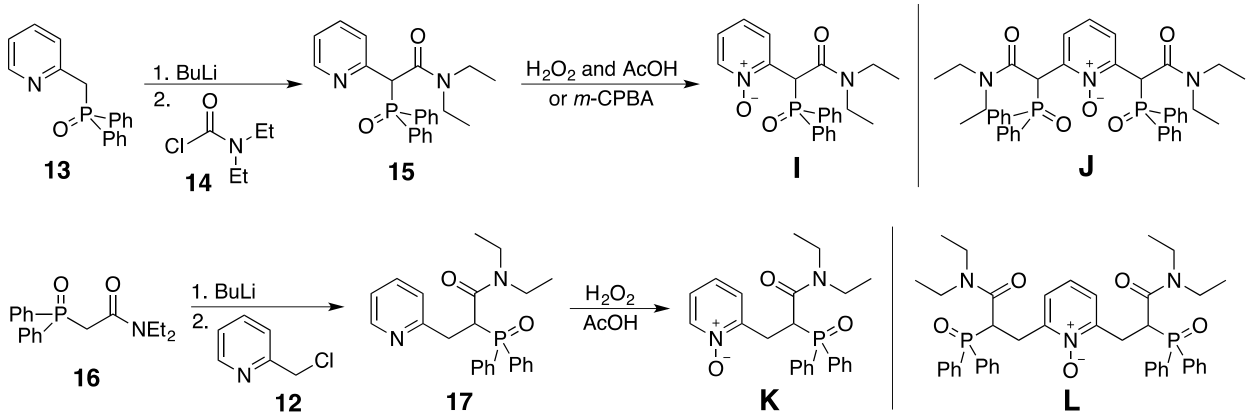


Figure 8. Synthesis of CMPO substituted pyridine-*N*-oxide derivatives **I**-**L**.

Compounds **M**-**O** also present CMPO groups on a pyridine scaffold, but for these derivatives the attachment site is through the CMPO amide nitrogen atom (Figure 9).[76] The synthesis of mono-substituted derivative **M** begins with the reaction of acid chloride **19** with 2-(aminomethyl)pyridine. Arbuzov chemistry with the resultant alkyl chloride followed by *N*-oxidation with *m*-CPBA produced the desired compound in good yield. The preparation of disubstituted CMPO derivative **N** and the mixed phosphine oxide-CMPO system **O** followed similar pathways. The Paine group has presented the synthesis and Ln coordination chemistry of other pyridine *N*-oxide platforms that are outside the scope of this review.[77]

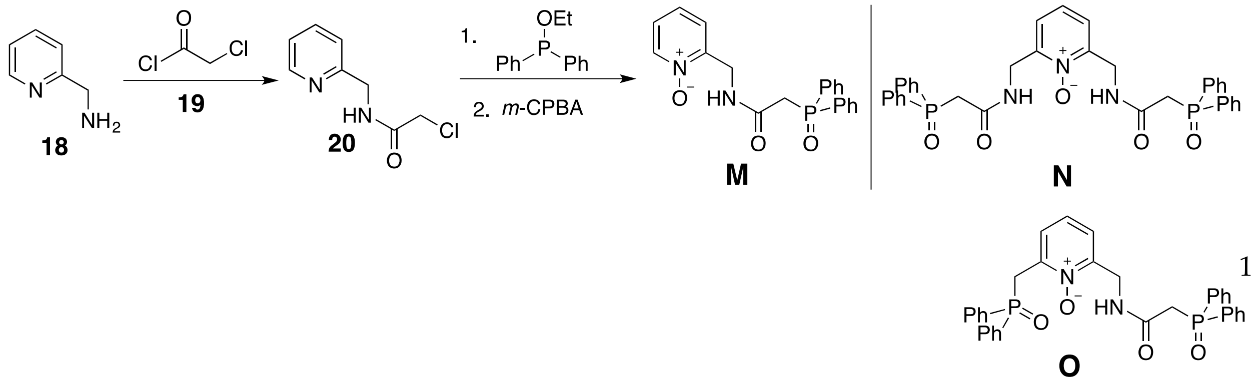


Figure 9. Synthesis of pyridine-*N*-oxide derivatives **M-O**.

2. Synthesis of dibenzofuran and dibenzothiophene derivatives P-V. These scaffolds were derivatized to present two phosphine oxide groups in complement to the oxygen, sulfur, or sulfone donor of the aromatic ring (Figure 10).[78, 79] Starting with either dibenzofuran **21** or dibenzothiophene **22**, the dichloromethyl derivatives **23** and **24** were prepared in three steps. Substitution of the chlorine atoms with Ph_2PO_2Et gave target compounds **P** and **Q**. For the sulfur containing compound **Q**, smooth oxidation to the sulfone **R** was achieved with *m*-CPBA. Alternatively, attachment of the diphenylphosphine oxide groups directly to the dibenzofuran scaffold was accomplished through a two-step lithium-halogen exchange reaction to give **S**. These same conditions were used to derivatize the dibenzothiophene scaffold, which was oxidized with *m*-CPBA to give sulfone **T**.

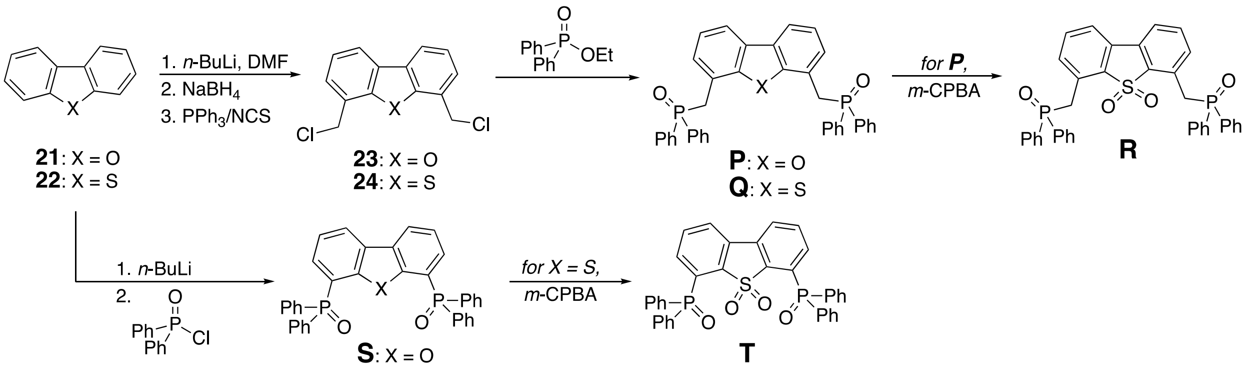


Figure 10. Synthesis of dibenzofuran and dibenzosulfone ligands **P-T**.

Paine and co-workers have also appended the CMPO group to a dibenzothiophene scaffold (Figure 11).[80] The synthesis of this compound was achieved in a similar manner to the chemistry described above, via chlorine substitution at the benzylic carbon of dichlorodibenzothiophenone **24** (**U**). The scaffold was further oxidized to the sulfone with *m*-CPBA in methylene chloride to give compound **V**. Note that compounds **U** and **V** were isolated as diastereomeric mixtures (*meso*/*rac* 29/71).

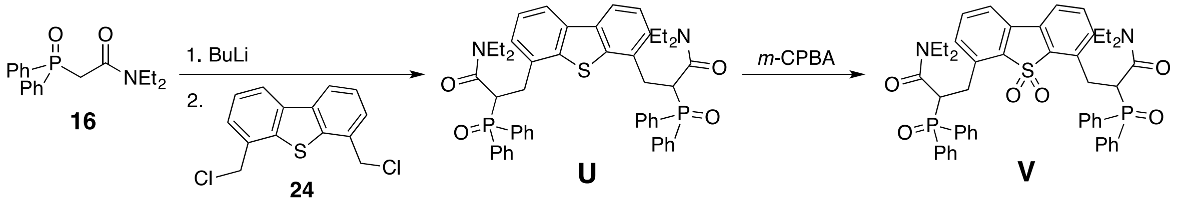


Figure 11. Synthesis of CMPO-substituted dibenzothiophene and dibenzosulfone ligands **U** and **V**.

3. Synthesis of 1,4-diazepane derivative W.[81] The most recent scaffold that has been used by the Paine group is the 1,4-diazacycloheptane ring (a.k.a. diazepane, Figure 12). This scaffold offers some rigidity for the presentation of chelating groups, as well as two secondary amines where chelating groups can be readily attached. In this work, the Paine group appended phosphine oxide groups to the nitrogen atoms of the diazepane ring via a 2,6-pyridine *N*-oxide linker using S_N2 chemistry.

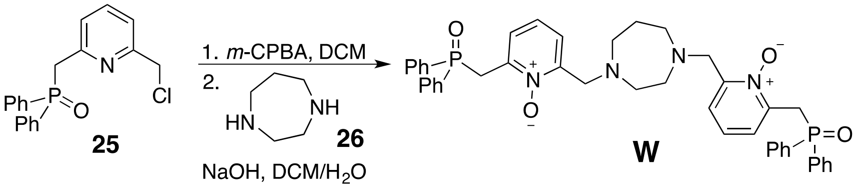
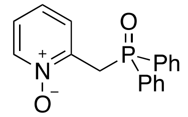
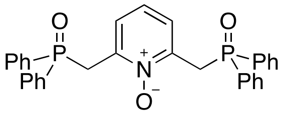
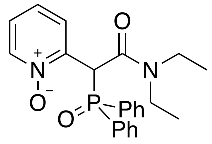
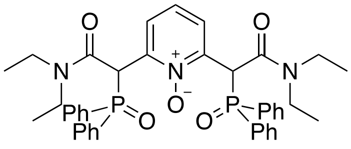
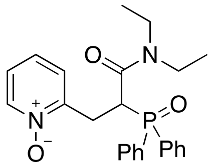
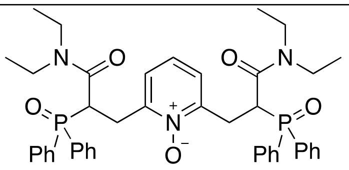
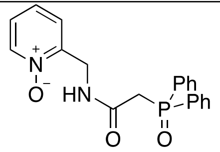
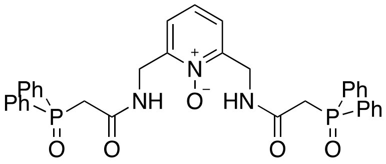
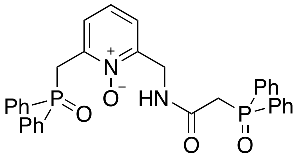
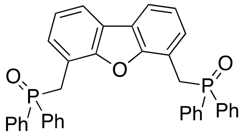


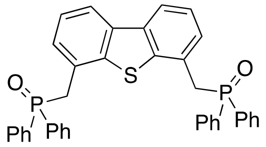
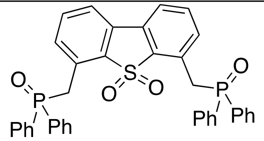
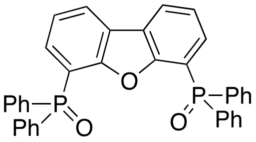
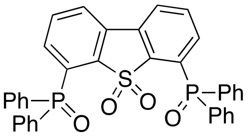
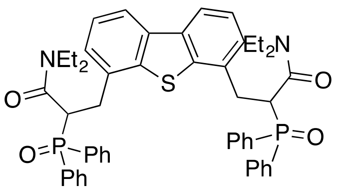
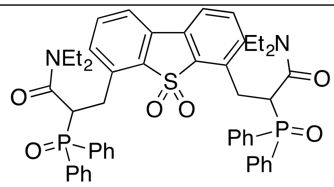
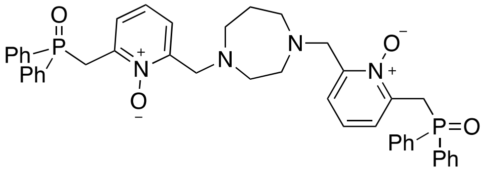
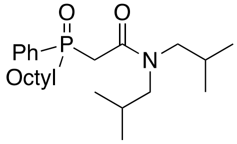
Figure 12. Synthesis of 1,4-diazepane derivative **W**.

4. Extraction results with ligands G-W. The Ln and An ion separation problem targeted by the Paine group has been the removal of actinide ions from spent nuclear fuel. Since the ^{241}Am isotope is responsible for a significant amount of the alpha radioactivity present in nuclear waste, ligands that can efficiently extract this ion out of acidic aqueous media are desirable. Characterizing the ability of ligands to discriminate between $^{241}Am^{3+}$ and Eu^{3+} is often used as a preliminary test to investigate the extraction potential for new compounds. For the compounds described in this section, liquid-liquid extraction studies were carried out with a variety of nitric acid concentrations and organic solvents. For ease of comparison, we tabulate here only the extraction results from experiments with 0.1 mM $Eu(NO_3)_3$ or trace ^{241}Am in 1M HNO_3 with 10 mM ligand in 1,2-dichlorethane.

Table 3. Selected extraction results for compounds **G-W**, with extraction conditions - aqueous phase: 0.1 mM $Eu(NO_3)_3$ or trace ^{241}Am in 1 M HNO_3; organic phase: 10 mM ligand in 1,2-dichloroethane; 1:1 ratio of organic to aqueous volume, and 25 °C. [a][82] 20 mM ligand in $CHCl_3$; [b][83] 1 mM ligand in 1,2-dichloroethane. %E = extraction efficiency ($[\text{metal}]_{\text{extracted}}/[\text{metal}]_{\text{total}}$); D = distribution ratio $[M_{org}/M_{aq}]$; SF = separation factor (D_{M1}/D_{M2}).
**Please note: the numbers in this table were generated by estimating the *D* values from graphical representations in the original publications. The %E and SF numbers were then calculated from these *D* values. Some error is inherent in each number in this table.

Ligand	**Structure**	**%E**	***D***	**SF (Am/Eu)**

G[67]		not reported	not reported	----
H[79]		Eu: 94[83][b] Am: 95[82][a]	Eu: 15[83][b] Am: 20[82][a]	1
I[74]		Eu: 2 Am: 9	Eu: 0.02 Am: 0.1	5
J[74]		Eu: 90 Am: 99	Eu: 9 Am: 90	10
K[74]		Eu: <1 Am: <1	Eu: 2x10^{-3} Am: 8x10^{-4}	0.4
L[74]		Eu: 7 Am: 17	Eu: 0.07 Am: 0.2	3
M[76]		Eu: <1 Am: <1	Eu: 2x10^{-4} Am: 6x10^{-5}	0.3
N[76]		not reported	not reported	----
O[76]		Eu: 33 Am: 17	Eu: 0.5 Am: 0.2	0.4
P[78]		Eu: <1 Am: <1	Eu: 0.001 Am: 0.001	~1

Q[79]		limited stability in HNO_3	limited stability in HNO_3	----
R[79]		Eu: <1 Am: <1	Eu: $7x10^{-4}$ Am: $5x10^{-4}$	0.7
S[78]		Eu: 3 Am: 2	Eu: 0.03 Am: 0.02	0.7
T[79]		Eu: 1 Am: 1	Eu: 0.01 Am: 0.01	~1
U[80] meso/rac 29/71		Eu: 5 Am: 17	Eu: 0.05 Am: 0.2	4
V[80] meso/rac 29/71		Eu: 7 Am: 8	Eu: 0.07 Am: 0.09	1
W[81]		Eu: 7 Am: 2	Eu: 0.07 Am: 0.02	0.4
CMPO[79]		Eu: 1 Am: 2	Eu: 0.01 Am: 0.02	2

For the extraction results summarized here (Table 3), bis-substituted compounds **J** and **H** show the highest levels of extraction of both Eu^{3+} and ^{241}Am from solutions of nitric acid. It seems the cavity created by a 2,6-disubsituted pyridine *N*-oxide is an appropriate size and shape for the recognition of *f*-elements. The increased extraction ability of **J** versus **H** could be due to the presence of a bidentate CMPO group versus a monodentate phosphine oxide. Ligand **J** also outcompetes the monomeric CMPO as an extractant for ^{241}Am and Eu^{3+} in terms of both extraction efficiency and selectivity, with an Am/Eu separation factor of 10.

Of this series of compounds, the poorest extractants out of 1M HNO_3 were **K, M** and **R**. As **K** and **M** are mono-substituted ligands, this result is not surprising. The relatively modest extraction ability of **R**, however, as the bis-substituted sulfone merits consideration. The authors proposed that the low extraction percentages for this compound may be due to the poor solubility of this particular metal-ligand complex in organic solvents, and/or the formation of only 1:1 metal-ligand complexes under the extraction conditions.[79] Since the ligand is the hydrophobic portion of the metal-ligand complex, complexes that contain a greater amount of exposed ligand should be more soluble in the organic phase and hence, will have a greater extraction ability.

C. Resorcin[4]arene and calix[4]arene ligands by Pellet-Rostaing and co-workers. Pellet-Rostaing and co-workers have exploited a variety of supramolecular approaches to address the selective extraction of lanthanide and actinide metals. We will discuss here those approaches that involved the use of resorcin[4]arene or calix[4]arene scaffolds. We direct the reader to other work by this group that involves the use of polymers,[84] surfactants[85] and ionic liquids.[86, 87] Pellet-Rostaing and co-workers have also investigated the use of simultaneous anion/cation recognition in the extraction of NaCl[88] and U(VI).[89]

1. Synthesis of resorcin[4]arene and calix[4]arene supramolecular ligands. Pellet-Rostaing and co-workers attached diglycolamide chelating groups to the upper rim of resorcin[4]arenes and the bottom rim of calix[4]arenes. For the resorcin[4]arene derivatives,[90, 91] the synthesis of the supramolecular scaffold follows well-trodden paths, beginning with the condensation of 2-methylresorcinol **27** with acetaldehyde in acid to give the macrocycle **28** (Figure 13). Cavitand formation was achieved by reaction of the phenol groups with dichloromethane, followed by benzylic bromination with NBS and substitution with sodium azide to give the tetraazide **30**. This azide was then reacted with three different alkynes in the presence of copper sulfate to give compounds **AA, BB** and **CC**. Compound **AA** displays four alkyl chains from the upper rim, while compounds **BB** and **CC** display diglycolamide groups with either *N*-octyl or -decyl chains.

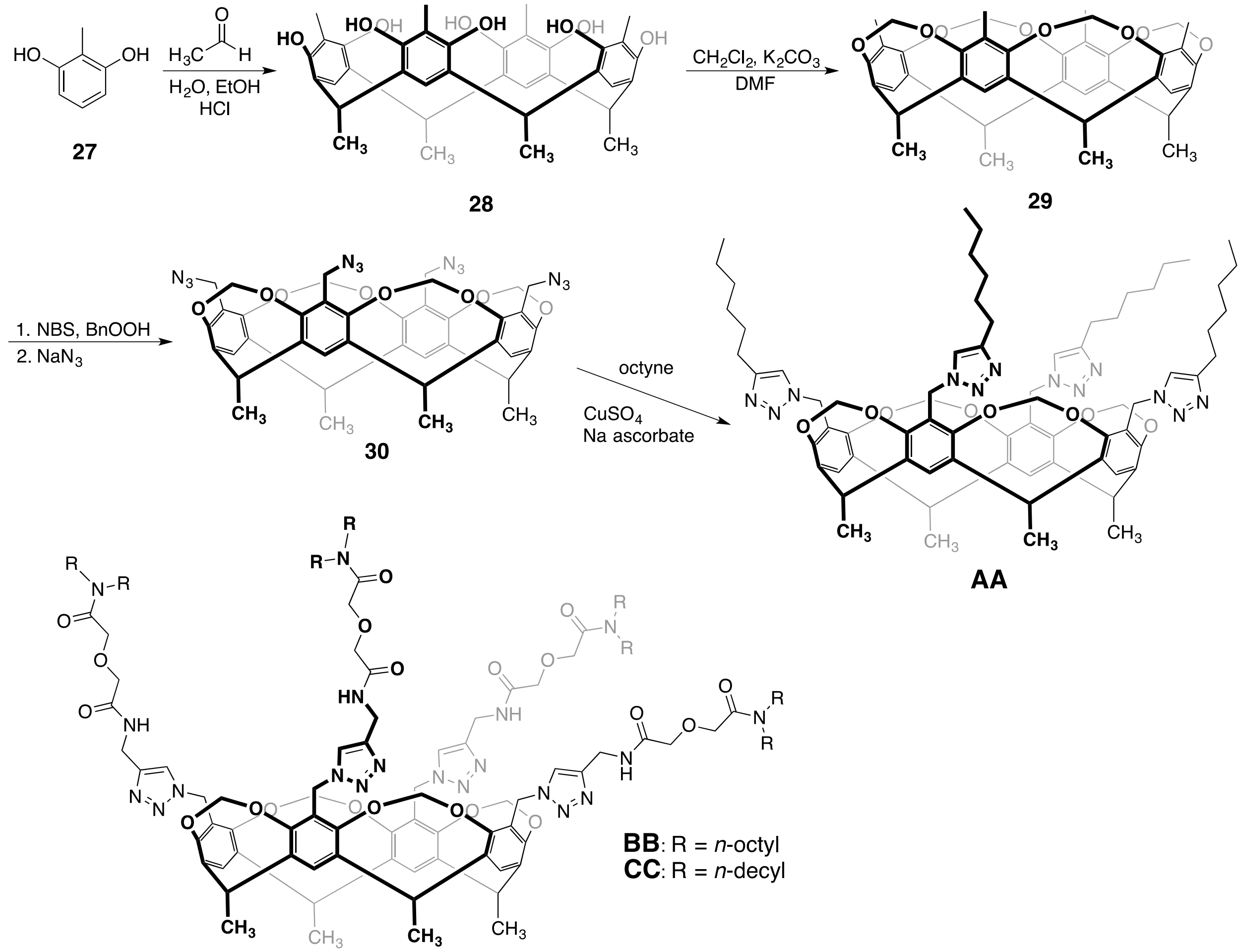


Figure 13. Synthesis of diglycolamide-substituted cavitands **AA-CC**.

This group also decorated the bottom rim of *t*-butylcalix[4]arene[61] **1** with diglycolamide groups[92] as well as an azacrown ether ring[89] (Figure 14). For compound **DD**, the diglycolamide groups were appended to the calix[4]arene scaffold following a similar methodology to that described above for the cavitand derivatives. The calix[4]arene-crown ether hybrid compounds **EE** and **FF** were prepared via selective alkylation of two phenol groups on the lower rim of *t*-butylcalix[4]arene **1** to give the diester **33**. This compound was then condensed with diethyleneamine **34** to form a crown ether-like macrocycle. The remaining free amine on this ring was then alkylated with either *n*-octyl or ethylhexyliodide to give compounds **EE** and **FF**.

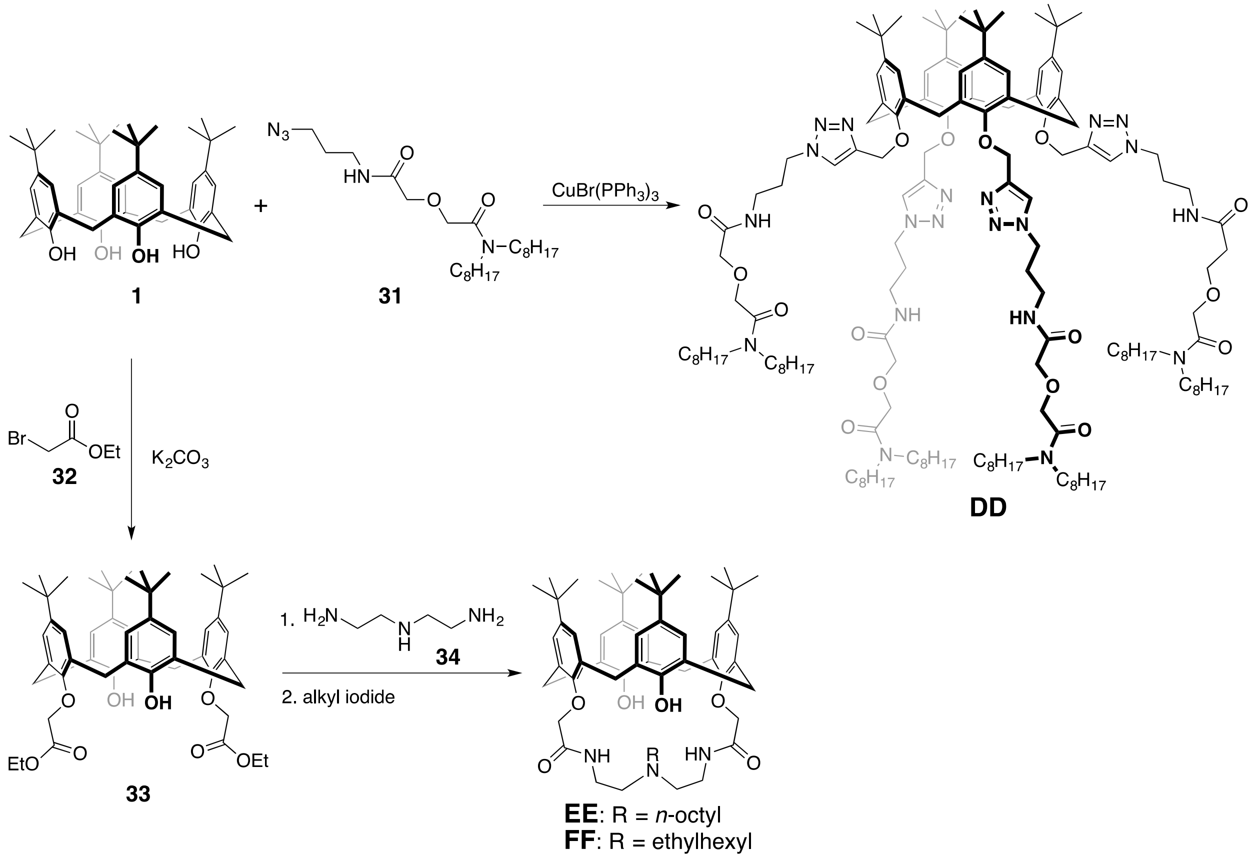


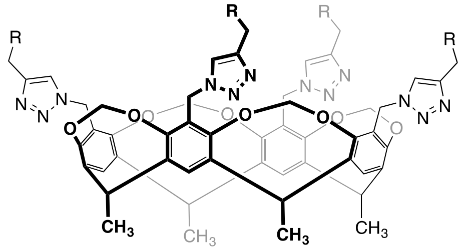
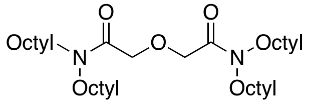
Figure 14. Synthesis of calix[4]arene based ligands **DD**-**FF**.

2. Separation results with Pellet-Rostaing's cavitand and calixarene based ligands.

A selection of results from the initial extraction experiments with the diglycolamide decorated resorcinarenes **BB**[90] and **CC**[91] are shown in Table 4. Both systems were able to extract Ln(III) ions out of acidic media, with an increase in %E as the ionic radius of the metal decreased. The authors investigated a variety of ligand concentrations in a toluene/iso-octanol organic solvent mixture, as well as nitric acid concentrations ranging from 1-5 M. In general, extraction efficiencies increased as both the ligand and nitric acid concentrations increased.

To probe the system further, two control experiments were carried out. First, the extraction ability of free diglycolamide (TODGA) was also determined under the same experimental conditions as that of **CC** (Table 4). This monomeric ligand showed relatively poor ability to extract the series of Ln(III) ions tested by the authors, with %E values of less than one. This result suggests that the preorganization provided by appending these chelating groups to the supramolecular scaffold may be responsible for the improved extraction ability of ligands **BB** and **CC** relative to free TODGA. The authors also tested the ability of the resorcin[4]arene scaffold substituted with non-chelating octyl chains (**AA**), to extract Ln(III) ions. This compound showed no extraction ability for the seven Ln(III) ions tested, even when this ligand was present in the organic layer at four times the concentration of the metal in the aqueous layer.[91] This result suggests that neither the resorcin[4]arene nor the triazole rings are responsible for the extraction of Ln(III) ions in these experiments.

Table 4. Selected extraction results for cavitand-based ligands **AA-CC**. Organic phase: 1 mM ligand/toluene-iso-octanol (90/10 v/v); aqueous phase: 1 mM $Ln(NO_3)_3$ in 5M HNO_3. [a] 4 mM ligand and 4 mM $Ln(NO_3)_3$. %E = extraction efficiency ($[metal]_{extracted}/[metal]_{total}$); *D* = distribution ratio [M_{org}/M_{aq}]; SF = separation factor (D_{M1}/D_{M2}).
**Please note: the numbers in this table were generated by estimating the *D* values from graphical representations in the original publications. The %E and SF numbers were then calculated from these *D* values. Some error is inherent in each number in this table.

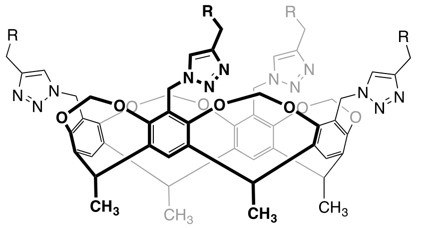
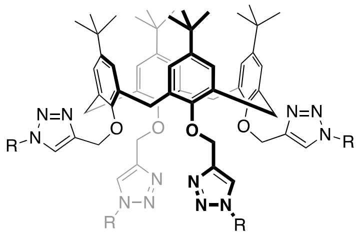
Ligand	Structure	%E	*D*	SF
AA[91] R = C_5H_{11}		0	0	----
BB[90] R = octyl subs. diglycolamide		La: 1 Eu: 15 Yb: 77	La: 0.01 Eu: 0.17 Yb: 3.40	Eu/La: 15 Yb/Eu: 20 Yb/La: 300
CC[a][91] R = decyl subs. diglycolamide		Ce: 0 Gd: 67 Yb: 95	Ce: 0 Gd: 2 Yb: 20	Yb/Gd: 10
TODGA[a][91]		Ce: 0 Gd: 0 Yb: 44	Ce: 0 Gd: 0 Yb: 0.8	----

To address the problem of recycling Ln ions from permanent magnets, Pettet-Rostaing and co-workers then determined the extraction ability of ligands **BB** and **CC** toward the four common metals present in permanent magnets: Fe, B, Nd and Dy.[91] For a solution containing equimolar amounts of each metal (6 mM) in 5 M nitric acid, solutions of 6 mM ligand in toluene/10% octanol retained the ability to selectively extract the smaller Dy(III) over Nd(III) while leaving virtually all of the Fe and B metals in the aqueous layer. Ligand **CC** was able to extract approximately 96% of Dy(III) from this solution, along with only 36% of Nd(III). Compound **BB** performed comparably to this, with extraction percentages of 87% for Dy(III) and 9% Nd(III). An interesting thing to consider with these results, as the authors point out, is that although **CC** boasts better extraction efficiencies for Dy(III) and Nd(III), **BB** demonstrates better selectivity for these ions with a higher Dy/Nd separation factor of 68 (versus 38).

The ability of ligands **BB** and **DD** to operate as part of an ionic liquid extraction solvent was also investigated.[92] Both of these ligands present the same chelating moiety to Ln(III) ions, with **BB** using the upper rim of a resorcin[4]arene and **DD** using the lower rim of a calix[4]arene as the supramolecular scaffold. The ionic liquid employed for these experiments was *N*-octyl-*N*-ethylpiperidiniumbis(trifluoromethylsulfonyl)imide ([EOPip]NTf_2), and 10% 1-octanol (v/v) was included to enhance solubilization of the organic ligands and to help prevent the formation of a third phase. Table 5 shows the extraction results from this set of experiments, which were performed on three Ln ions, La, Eu and Yb, that were chosen to span the row. Once again, these experiments demonstrate that these ligands extract the smaller Ln ion Yb(III) with a higher efficiency than the larger Ln ion La(III). Out of 1 M HNO_3, Yb(III) is extracted with a %E of 99 with **BB**, and a %E of >99 with **DD**. When compared to %E values for La(III) extraction of 5 and 3, respectively, these ligands display Yb/La separation factors (SF) of ~1100 and ~5500. Under these conditions, as the concentration of nitric acid is increased in these experiments, the authors observed a slight decrease in extraction ability.

The extraction ability and selectivity of this organic ligand-ionic liquid system was also tested against a simulated magnet leaching sample containing Nd, Dy, Fe and B.[92] Both ligands demonstrated significant selectivity for the extraction of Dy(III) over Nd(III) with Dy/Nd separation factors of 167 (**BB**) and 94 (**DD**). Neither system extracted appreciable amounts of Fe or B from the aqueous solution.

Table 5. Selected extraction results for diglycolamide containing ligands **BB** and **DD**. Organic phase: 2 mM ligand in [EOPip]NTf_2)/1-octanol (9:1 v/v); aqueous phase: 2 mM $Ln(NO_3)_3$ in 1M HNO_3. %E = extraction efficiency ($[\text{metal}]_{\text{extracted}}/[\text{metal}]_{\text{total}}$); *D* = distribution ratio [M_{org}/M_{aq}]; SF = separation factor (D_{M1}/D_{M2}).
**Please note: the numbers in this table were generated by estimating the *D* values from graphical representations in the original publications. The %E and SF numbers were then calculated from these *D* values. Some error is inherent in each number in this table.

Ligand	Structure	%E	*D*	SF
BB[92] R = octyl subs. diglycolamide		La: 6 Eu: 94 Yb: 99	La: 0.06 Eu: 15 Yb: 100	Yb/Eu: 7 Yb/La: 1600 Eu/La: 250
DD[92] R = octyl subs. diglycolamide		La: 3 Eu: 92 Yb: >99	La: 0.03 Eu: 11 Yb: 200	Yb/Eu: 18 Yb/La: 6700 Eu/La: 370

The final two compounds discussed here, **EE** and **FF**, were studied as extractants for the uranyl ion.[89] These structures are somewhat unique in that they have sites for binding both the uranyl cation and its counteranions. This work was carried out to address the isolation and purification of U(VI) from uranium deposits, which may contain other metals such as Mo(VI), Zr(IV), Ti(IV), La(III), Ce(III) and Fe(III) as contaminants. An intriguing aspect of these ligands is that while the authors incorporate a focused area of hard oxygen donors for chelation of the U(VI) metal cation, they also built in a positively charged ammonium center that is well poised to bind to the sulfate anions. Two variations of this parent structure were explored; one with an octyl chain (**EE**) and one with an ethylhexyl chain (**FF**) on the amine nitrogen.

For these two ligands, the compound bearing the branched alkyl chain (**FF**) extracts UO_2^{2+} with a %E of 94 out of 0.1 M H_2SO_4, versus 87 %E with **EE** (extraction conditions were: 20 mM ligand in 83:17 dodecane/octanol with 25 ppm (~5×10^{-5} M) metal). When compared to the six other metals tested, the extraction of Mo(VI) was the closest to uranyl with %E values of 84 (**FF**) and 74 (**EE**). The selectivity of these ligands was demonstrated further as the %E values for the extraction of the remaining five metals were all less than 38%.

D. Tri-NOx ligands by Schelter and co-workers. The rare earth separation problem targeted by the Schelter group has been the recycling of Ln ions from materials such as magnets, batteries and wind turbine generators. The initial result reported for the Schelter ligand system involved the separation of neodymium (Nd) and dysprosium (Dy) as they are two of the Ln components that are found in sintered neodymium magnets (a.k.a. "neomagnets").[11, 93-95] Isolating these two metals from discarded magnets is one approach to increasing the supply stream of Nd and Dy, which have both been categorized as "critical materials" by the U.S. Dept. of Energy.[96]

1. Synthesis of H_3Tri-NOx. This efficient synthesis began with the reaction of 2-bromobenzylbromide **35** with aqueous ammonia to give the trialkylamine **36** (Figure 15).[97] A halogen exchange reaction with *n*-butyllithium followed by exposure to 2-methyl-2-nitrosopropane dimer resulted in formation of the protonated H_3Tri-NOx ligand **GG**.[98] In more recent work, Schelter and co-workers tuned the reactivity of this ligand by incorporating methoxy groups into each of the aromatic rings following a similar synthetic strategy (**HH**, "H_3Tri-NOx^{OMe}").[99] These ligands, once deprotonated with a strong base, present three hard, anionic oxygen donors and one relatively soft nitrogen donor to a prospective Ln ion. The tripodal amine motif pre-organizes these four donors into a cavity that is appropriate for the recognition of Ln and An ions.

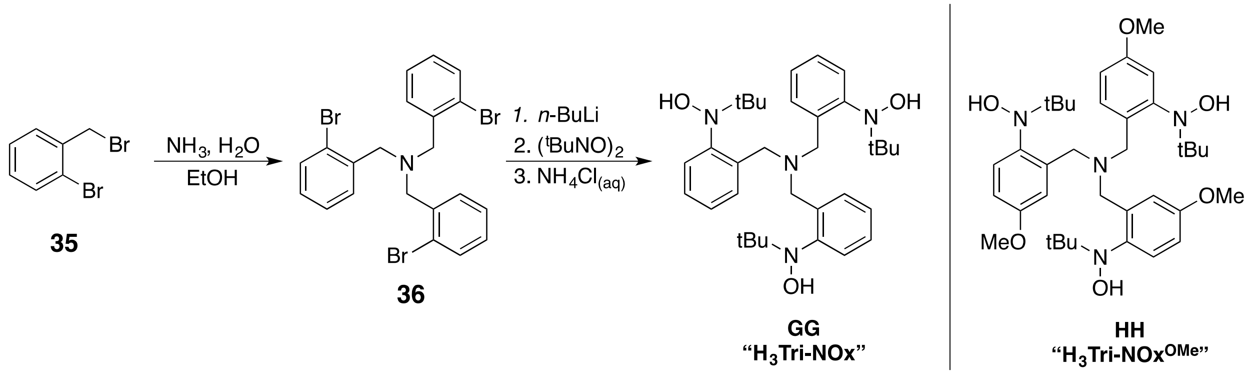


Figure 15. Synthesis of tripodal TriNOx ligands **GG** and **HH**.

2. Separation results with GG** and **HH. To determine the extraction ability of the original TriNOx ligand **GG**, the authors exposed equal amounts of Nd(OTf)$_3$ and Dy(OTf)$_3$ to the H_3TriNOx ligand in the presence of K[N(SiMe$_3$)$_2$]. This mixture was then extracted with a minimal amount of benzene, leaving a solid phase and a liquid organic phase. The amount of Nd^{3+} and Dy^{3+} ion present in both phases was quantified by inductively coupled plasma optical emission spectroscopy (ICP-OES).

Remarkably, after one round of extraction the ratio of Dy to Nd in the solid phase was 94.5 to 5.4, and in the liquid phase was 4.6 to 95.4. This represents a separation factor $S_{Nd/Dy}$ of 303.[99] This performance compares favorably with commercial processes using alkyl-substituted phosphoric acids that exhibit a Nd/Dy separation factor of 41.5.[100] Further studies by the Schelter group investigated the ability to control the extraction properties of this ligand via redox chemistry,[101] as well as the effect of the organic solvent.[102]

Separation work with the second generation TriNOx^{OMe} ligand **HH** used a similar extraction strategy to that described in the previous paragraph, where a solid consisting of equimolar amounts of Nd- and Dy(TriNOx^{OMe}) was exposed to an organic solvent, and the amount of each Ln ion was quantified in both the solid and liquid phases. For this ligand, a comparable Nd/Dy separation factor of 299 was obtained when the starting TriNOx^{OMe} mixture was extracted with benzene. However, the difference in the performance of these two ligands arose when the organic solvent was changed from benzene to toluene. While the original TriNOx **GG** ligand presented a Nd/Dy separation factor of only 30 from toluene, the second generation TriNOx^{OMe} **HH** ligand's separation factor held at 254.

So the question is: why do these two seemingly similar ligands have such different extraction properties? Please remember that the extracted species in such experiments is most likely not a simple monomeric Ln-ligand complex, but a highly solvated, multimeric species. Schelter and co-workers investigated the structures of these Ln-ligand complexes in both solution (via ^{1}H NMR) and in the solid state (X-ray crystallography). It turns out that both ligands form 1:1 and 1:2 metal-ligand complexes, and an equilibrium exists between these two species in solution. [102] In C_6D_6, the parent TriNOx ligand **GG** formed primarily dimeric Ln-ligand complexes for the first half of the row (Ln = La to Eu), while mostly monomeric complexes were seen for the second half of the row (Ln = Tb to Lu, Y). This work was extended and separation experiments were carried out between early and late-row lanthanides. In general, the TriNOx ligand showed the best separation factors for pairs of Ln ions that had the greatest difference in ionic radii.

For the second-generation ligand TriNOx^{OMe} **HH**, the authors showed that the electron donating ability of the methoxy groups caused pyramidalization of the nitrogen atoms of the hydroxylamine groups, resulting in a slight change to the cavity size and shape of the ligand. This slight structural change of the ligand altered the solution Ln-monomer/Ln-dimer equilibrium, resulting in a larger amount of Ln-dimer present in solution. Since the Ln-dimer is more soluble in organic solvents, this all culminated in the Nd-TriNOx^{OMe} dimer being extracted at a higher level into toluene than the original Nd-TriNOx system. This study yet again drives the point home that the molecular recognition of Ln and An ions in the extraction process can be quite sensitive to small electronic and structural changes in the ligands, and we encourage researchers in this field to design systems that can be tuned to investigate the effect of these changes.

E. Pillar[5]arenes by Lihua Yuan and Wen Feng. Yuan, Feng and co-workers have exploited the pillar[5]arene scaffold to utilize phosphine oxides, CMPO groups and diglycolamide chelating groups. These ligands present 10 functional groups to a target lanthanide or actinide ion, and have demonstrated the ability to act as efficient extraction agents. The separation problem that these research groups chose to approach was the separation of Ln ions (i.e. Eu^{3+}) from An ions (i.e. Am^{3+}) in the treatment of spent nuclear fuel. These research groups have also used the calixarene[103] and oligaramide[104] scaffolds to prepare extractants.

1. Synthesis of substituted pillar[5]arenes. First reported in 2008 by Ogoshi and co-workers,[105] the pillar[5]arene scaffold resembles the calix[5]arene macrocycle except that the linkage between aromatic rings occurs at the 2 and 5 positions (Figure 16). The structural result is that while calixarenes have a vase-like shape, pillar[5]arenes present functional groups at both rims in a nearly parallel orientation. The synthesis of this elegant structure is accomplished in one step by condensing the 1,4-disubstitutedbenzene **37** with paraformaldehyde in the presence of BF_3-etherate to give the cyclic pentamer **38**.

The series of dibromo- compounds **38** were then subjected to nucleophilic substitution with sodium azide, followed by reduction with catalytic hydrogenation to give the decaamines **39**.[106] These were acylated with diglycolamide groups bearing an activated ester to give the deca-amides **II**.[107] Yuan and co-workers prepared pillar[5]arenes bearing CMPO groups (**JJ**) using a similar synthetic strategy,[108] and they also appended phosphine oxides (**LL**) using Arbuzov chemistry.[109-112]

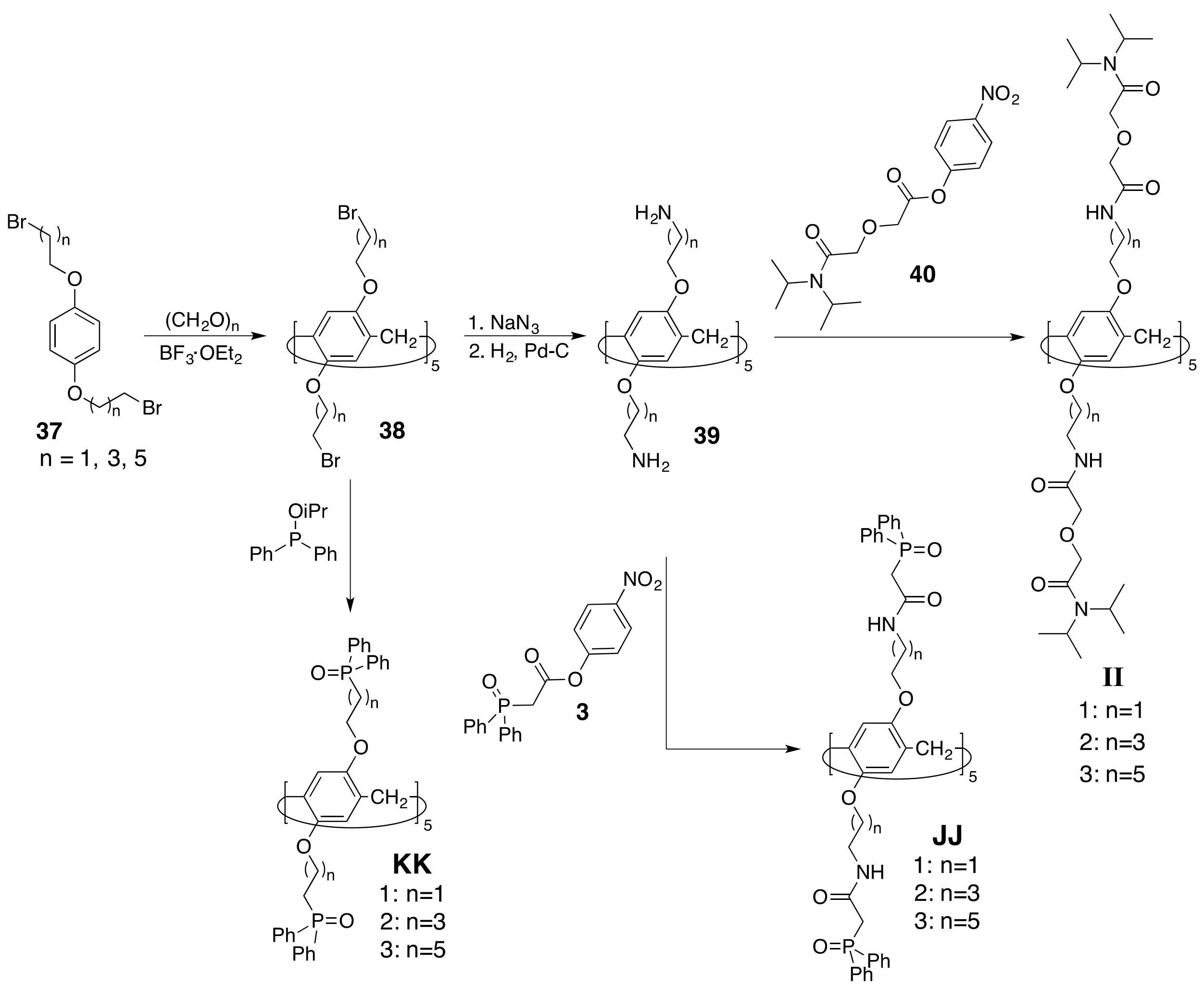


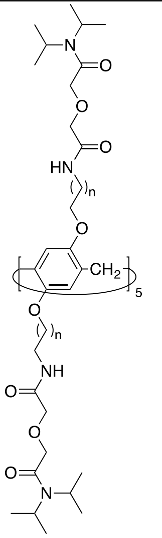
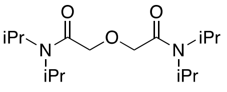
Figure 16. Synthesis of pillar[5]arene compounds **II, JJ** and **KK**.

2. Separation and extraction properties of substituted pillar[5]arenes.

For the series of deca-diglycolamide compounds **II**, the derivative with the greatest extraction ability for both Eu^{3+} and Am^{3+} was **II-2** with %E values of >99% and 95% for Eu^{3+} and Am^{3+}, respectively (organic phase = 1 mM ligand in 1-octanol; aqueous phase = 10^{-5} M Ln or An nitrate in 1M HNO_3).[107] This series of compounds all show greater extraction ability than the monomeric digylcolamide TiPrDGA (Table 6), which exhibits %E values less than 50% for both metals. However, while the supramolecular ligands **II** were better extractants for these metals, they were less selective for one metal over the other with Am/Eu separation factors ranging from 8.31 to 3.71 compared to an Am/Eu separation factor of 52 for the monomer TiPrDGA. The authors also investigated the influence of nitric acid concentration on extraction ability (0.1 - 4 M HNO_3) and found that, in general, both the extraction ability and selectivity of each ligand decreased with increasing acid concentration. The exception to this being that at very low levels of acid (0.1 M), the extraction ability of the ligands (*D*) was quite low but the extraction selectivity (SF) was the highest for each ligand.

The authors also investigated the extraction ability of compounds **II** when an ionic liquid was used as the organic solvent.[113, 114] In this case the ionic liquid, C_8mimNTf$_2$, acted as both a solvent for and a guest of the pillar[5]arene macrocycle. Under similar extraction conditions to those described above, (ligand concentration = 5.0 x 10^{-4} M), the authors observed higher distribution ratios for the extraction of both Eu^{3+} and Am^{3+} out of 1 M HNO_3 (Table 6). The extraction selectivity of these ligands also increased in the ionic liquid, with Am/Eu separation factors ranging from 0.8 to 0.5 (versus 0.12-0.29 out of 1-octanol). Under these conditions the authors also quantified the extraction ability of **II** for Pu^{4+}, Cs^+, Sr^{2+}, UO_2^{2+} and PuO_2^{2+} and found that the ligands were selective for Am^{3+} and Pu^{4+} over the other cations.

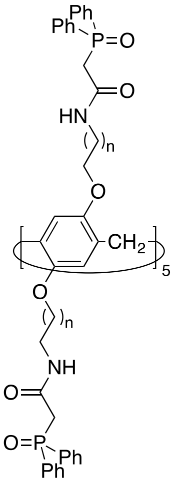
Table 6. Selected extraction results for diglycolamide containing ligands **II** and TiPrDGA. Organic phase: 5.0 x 10^{-4} M ligand in 1-octanol or C_8mimNTf$_2$; aqueous phase: 1M HNO_3. %E = extraction efficiency ([metal]$_{\text{extracted}}$/[metal]$_{\text{total}}$); *D* = distribution ratio [M_{org}/M_{aq}]; SF = separation factor (D_{M1}/D_{M2}).

Ligand	**Structure**	**%E**	***D***	**SF**
organic solvent		1-octanol (C_8mimNTf$_2$)	1-octanol (C_8mimNTf$_2$)	1-octanol (C_8mimNTf$_2$)
II-1[113] n = 1		Eu: 93 (>99) Am: 60 (>99)	Eu: 12.4 (865) Am: 1.5 (728)	Am/Eu: 0.12 (0.8)
II-2[113] n = 3		Eu: 98 (>99) Am: 91 (>99)	Eu: 63 (1731) Am: 9.6 (1164)	Am/Eu: 0.15 (0.7)
II-3[113] n = 5		Eu: 98 (>99) Am: 94 (>99)	Eu: 52 (7803) Am: 15 (4098)	Am/Eu: 0.29 (0.5)
TiPrDGA[107]		Eu: 34[a] Am: 1[a]	Eu: 0.52[a] Am: 0.01[a]	Eu/Am: 52.0[a]

^{a}ligand concentration = 10 mM

For the series of CMPO-decorated pillar[5]arenes **JJ**, the authors also investigated their ability to extract Eu^{3+} and Am^{3+} from aqueous nitric acid.[108] The organic solvent system used for these studies was a 95:5 (v/v) mixture of *m*-nitro(trifluoromethyl)benzene (*m*-NTFB) and *n*-octanol. The extraction abilities of these ligands were similar to the diglycolamide-substituted series **II**, with the best overall extractant being **JJ-3** having the longest tether between the scaffold and chelating CMPO (Table 7). The selectivity of this ligand is also significant with an Am/Eu separation factor of 13.0, which is much higher than the diglycolamide derivatives. This is not too surprising since the CMPO group is well known for its affinity for actinide cations. When the ionic liquid $C_8mimNTf_2$ was used as the organic solvent, the extraction efficiency of all three ligands for Am^{3+} increased significantly, although the selectivity for Am^{3+} vs. Eu^{3+} suffered as separation factors for all three ligands were close to one.[115] In separate work, the authors also showed that these ligands were efficient extractants for the Th^{4+} cation out of nitric acid, with %E values ranging from 97 for **JJ-1** to >99 for **JJ-3** (1 M HNO_3, organic solvent = $C_8mimNTf_2$).[116]

Table 7. Selected extraction results for CMPO containing ligands **JJ**. Organic phase: 1 mM ligand in *m*-NTFB/*n*-octanol (95:5); aqueous phase: 1M HNO_3. %E = extraction efficiency ($[metal]_{extracted}/[metal]_{total}$); D = distribution ratio [M_{org}/M_{aq}]; SF = separation factor (D_{M1}/D_{M2}).

Ligand	Structure	%E	*D*	SF (Am/Eu)
JJ-1[108] n = 1		Eu: 82 Am: 90	Eu: 4.54 Am: 8.69	1.91
JJ-2[108] n = 3		Eu: 86 Am: 91	Eu: 6.17 Am: 10.7	1.73
JJ-3[108] n = 5		Eu: 93 Am: 99	Eu: 13.1 Am: 171	13.0

For the series of phosphine oxide substituted ligands **KK**, the authors found that the extraction properties of these compounds were well suited for the separation of the uranyl ion

(UO_2^{2+}) from other metals.[109, 112] The authors investigated a variety of organic solvents ranging from dichloromethane to ionic liquids, and this selectivity held under a variety of conditions.[110, 111]

F. Use of tripodal amines by Biros, Werner and Odinets. The Biros, Werner and Odinets groups have used three different tris-amine compounds as scaffolds to present three CMPO groups to Ln and An ions. Given the preferred 3:1, ligand to metal ratio for An coordination in solution with monopodal CMPO,[29] the use of tripodal scaffolds to anchor three chelating groups for *f*-element binding and extraction may prove advantageous. This approach has been utilized by Scott and co-workers with a triphenoxymethane platform leading to unique An selective extraction results.[117] The interests of the Biros, Werner and Odinets groups involve the extraction of An ions from spent nuclear fuel mixtures and the selective extraction of Ln ions as is needed for isolation and recycling applications.

1. Synthesis of tripodal CMPO ligands. In 2012 Odinets and co-workers reported the synthesis of a tripodal CMPO ligand that employed the commercially available tris-(2-aminoethyl)amine (TREN, **41**, Figure 17a) as the scaffold, and hydrophobic phenyl rings on the CMPO phosphine oxide. The synthesis of this multidentate ligand was accomplished via straightforward amide coupling with acid chloride **42** to give compound **LL**,[118] while Biros and Werner later prepared this compound using the activated ester strategy developed by Böhmer.[119] Biros and Werner also prepared the more hydrophilic derivative **MM** using direct nucleophilic acyl substitution of the ester **43** with the TREN tris-amine.[120] In this compound, the groups on the CMPO phosphine oxide were ethyl esters. In further efforts to utilize preorganized CMPO ligands with robust, multipodal scaffolds, Biros and Werner have employed both the tris-(2-aminopropyl)amine (TRPN, **44**) and the tris-methylaminophosphine oxide (**46**)[121] scaffolds. Following similar synthetic strategies to those described above, tripodal ligands **NN**[119] and **OO**[122] were prepared that contain ethyl ester or phenyl rings on the CMPO phosphine oxide, respectively (Figure 17b and c).

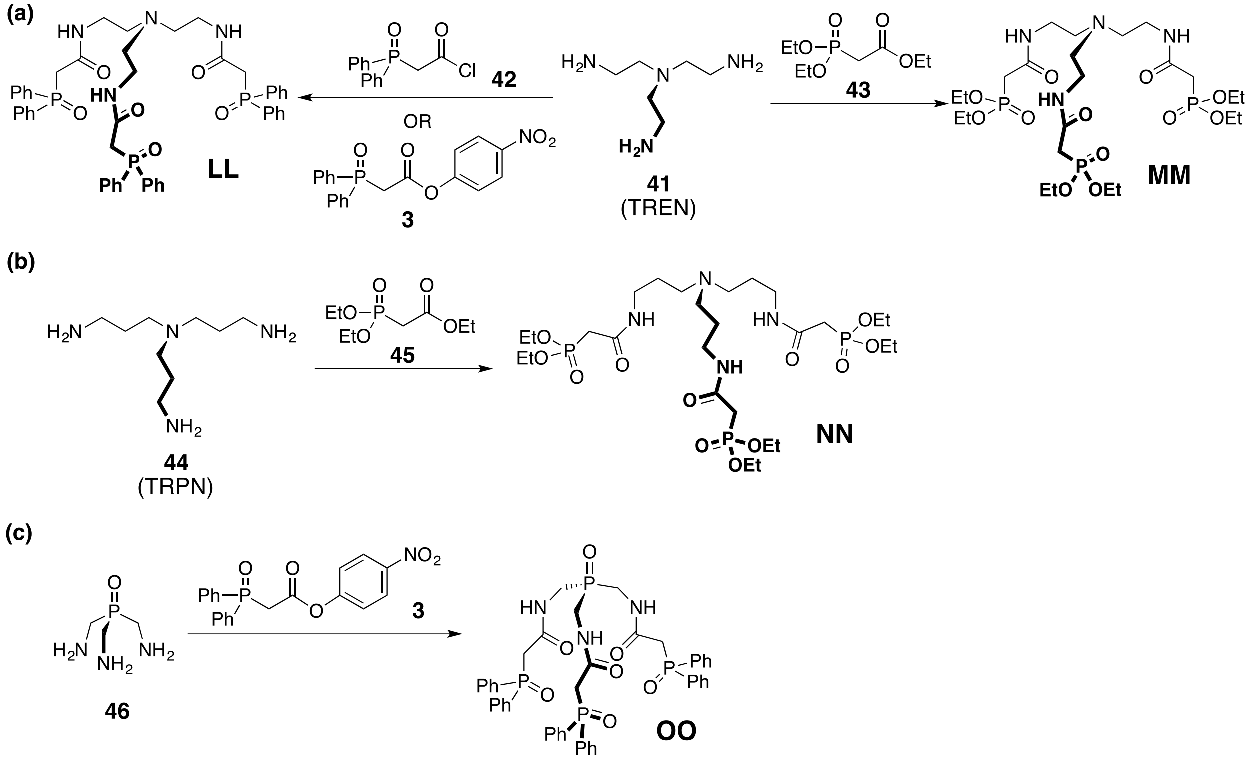


Figure 17. Synthesis of a series of tripodal ligands, **LL-OO**, that present CMPO groups.

2. Separation results with tripodal CMPO ligands. Selected extraction results for tripodal ligands **LL-OO** are shown in Table 8. Odinets and co-workers determined the extraction ability of ligand **LL** in 1,2-dichloroethane for Ln and An metals out of aqueous solutions with varying concentrations of of nitric acid, ammonium nitrate, and the ionic liquid [bmim][Tf_2N].[118] To be consistent with the rest of this review, we will focus here on the extraction results from 1M nitric acid. Furthermore, these research groups characterized the extraction abilities of their ligands for many Ln ions along with the An ions Th^{4+} and UO_2^{2+}. Summarizing all of these results is outside the scope of this review, but we present here extraction data for selected metal ions.

The phenyl substituted tripodal CMPO ligand **LL** was studied by both the Odinets and Biros and Werner groups, however the experiments were performed under different conditions. For extraction experiments out of 1 M HNO_3 (0.01 mM metal, 10 mM ligand in 1,2-dichloroethane) Odinets and co-workers observed that ligand **LL** had a preference for the light Ln ions La-Tb, and boasted percent extraction values ranging from 80% (La^{3+}) to 50% (Tb^{3+}) for these ions.[118] The extraction behavior was influenced by the concentration of nitric acid, with maximum extraction efficiencies for these metals observed at 3M HNO_3. When the extraction conditions were set at 1 mM ligand in

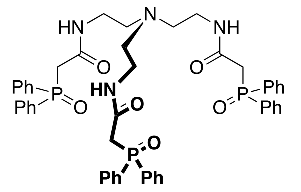
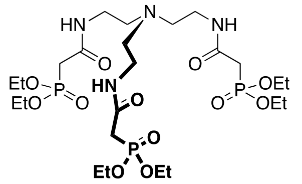
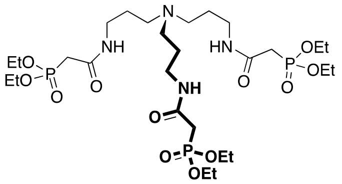
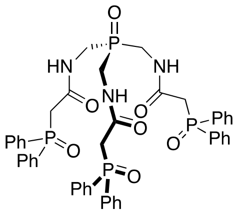
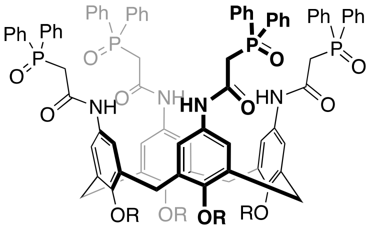
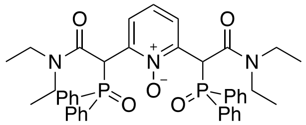
CH_2Cl_2 with 0.1 mM metal in 1 M HNO_3, extraction efficiencies dropped sharply to mostly only single digit values, with a modest preference for those elements in the middle of the Ln row (Gd, Tb) and Lu.[119]

Biros and Werner also studied the extraction efficiencies of the structurally related tripodal CMPO ligands **MM**-**OO**. The first alteration was to incorporate hydrophilic ethyl esters onto the CMPO groups in place of the phenyl rings (ligand **MM**).[119, 120] The major change observed in the extraction properties of this ligand was that the extraction efficiency for Tb^{3+} increased from 11% to 18%, while the values for all other Ln ions dropped significantly or remained same. The next largest percent extraction value with ligand **MM** was 9% (Ho^{3+}), with the reported values for Gd^{3+} and Dy^{3+} (the neighboring metals of Tb^{3+}) at 1% and 5%, respectively. When both the size and flexibility of the scaffold was increased from TREN to TRPN (ligand **NN**), virtually all extraction ability was lost.[119] When the size of the scaffold was decreased, and the hydrophobicity of the CMPO groups was increased to give ligand **OO**, the extraction ability shifted to the larger An ions Th^{4+} and UO_2^{2+} with percent extraction values of 47% and 44%.[122] The authors explained this last result by suggesting that the size of the ligand was too small to allow all three CMPO groups to bind to the metal, so the ligand bound the metal with only two groups making, in essence, a larger binding pocket that better accommodated the larger An ions.

It is noteworthy that uranyl extraction was also seen to vary significantly for this series of tripodal ligands as a function of capping scaffold, with moderate extraction for the phosphine oxide capped **OO** agent comparable to other similar, tripodal CMPO systems[117] and low extraction for the TREN-capped ligand **MM**. The relatively low extraction efficiency seen for **MM** is consistent with another tripodal, TREN capped diglycolamide(DGA)-functionalized ligand reported by Mohapatra and coworkers.[123] As noted by the authors, the TREN-DGA ligand exhibited poor $UO2^{2+}$ extraction under similar liquid-liquid conditions due to steric issues and the inability of this ligand motif to effectively complex the uniquely linear uranyl ion. The same may be said for the case of TREN based **MM**, while **OO** likely exhibits the more open binding mode noted above favoring extraction of such An ions.

Table 8. Selected extraction values for tripodal CMPO ligands **LL**-**OO**. Organic phase: 1 mM ligand in CH_2Cl_2; aqueous phase: 0.1 mM metal in 1 M HNO_3. %E = extraction efficiency ($[\text{metal}]_{\text{extracted}}/[\text{metal}]_{\text{total}}$); *D* = distribution ratio [M_{org}/M_{aq}]; SF = separation factor (D_{M1}/D_{M2}). [a] numbers in parentheses are from experiments where the organic phase was 10 mM ligand in 1,2-dichloroethane, and the aqueous phase was 0.01 mM metal in 1 M HNO_3. Also, please note that the numbers from this set of experiments were generated by reading the *D* values from graphical

representations in the original publication. The %E and SF numbers were then calculated from the *D* values shown. Some error is inherent in each number in this table; [b] = [ligand] = $1x10^{-4}$ M.

Ligand	Structure	%E[a]	*D*[a]	SF
LL[118, 119]		La: 6 (80) Nd: 8 (67) Eu: 4 (62) Tb: 11 (50) Ho: 7 (23) Lu: 10 (17)	La: 0.06 (4) Nd: 0.08 (2) Eu: 0.4 (1.6) Tb: 0.1 (1) Ho: 0.08 (0.3) Lu: 0.1 (0.2)	Tb/La: 1.7 (0.3) Tb/Nd: 1.3 (0.5) Tb/Ho: 1.3 (3) Tb/Lu: 1 (5)
MM[119, 120]		La: 5 Nd: 4 Tb: 18 Ho: 9 Lu: 2 Th: 6 UO_2: 8	La: 0.05 Nd: 0.04 Tb: 0.2 Ho: 0.1 Lu: 0.02 Th: 0.06 UO_2: 0.09	Tb/La: 4 Tb/Nd: 5 Tb/Ho: 2 Tb/Lu: 10 Tb/Th: 3 Tb/UO_2: 2
NN[119]		La: 5 Nd: 4 Tb: 4 Ho: 5 Lu: 4	La: 0.05 Nd: 0.04 Tb: 0.04 Ho: 0.05 Lu: 0.04	Tb/La: 0.8 Tb/Nd: 1 Tb/Ho: 0.8 Tb/Lu: 1
OO[122]		La: 5 Nd: 5 Eu: 6 Tb: 4 Ho: 7 Lu: 8 Th: 47 UO_2: 44	La: 0.05 Nd: 0.05 Eu: 0.06 Tb: 0.04 Ho: 0.08 Lu: 0.08 Th: 0.9 UO_2: 0.8	Th/La: 18 Th/Eu: 8 Th/Tb: 22 Th/Lu: 11 Th/UO_2: 1
A[42]		Th^{4+}: 63[b] Eu^{3+}: 68	Th^{4+}: 1.7 Eu^{3+}: 2.1	Th/Eu: 0.8
J[74]		Eu: (90) Am: (99)	Eu: (9) Am: (90)	Eu/Am: (10)

3. Comparison of extraction results to previously discussed ligands. This section represents a unique opportunity to compare extraction results of different ligand types, since some of these extraction experiments were carried out under identical conditions. For instance, both Böhmer's tetrapodal calixarene ligand **A** (Table 2) and the tripodal phosphine oxide capped ligand **OO** from the Biros and Werner groups present CMPO groups bearing a -Ph substituent and were characterized with $1x10^{-3}$ M ligand in CH_2Cl_2 and $1x10^{-4}$ M $Ln(NO_3)_3$ in 1 M HNO_3. For ease of comparison the relevant Böhmer data has been added to Table 8 above. The tetrapodal calixarene ligand **A** extracted Eu^{3+} with 68 %E, while the tripodal ligand **OO** extracted this metal at a %E of 6%. Interestingly, however, the tetrapodal calixarene ligand **A** extracted 63% of Th^{4+} out of aqueous solution with 1×10^{-4} M ligand, while the tripodal ligand **OO** required a ligand concentration of 1×10^{-3} M to extract 47% of Th^{4+}. Both CMPO-substituted ligands are better extractants for Th^{4+}, which is not surprising since CMPO groups are known for their higher affinity for actinide metals. However, in both cases the tetrapodal ligand **A**, which presents more chelating groups to the metal, is the better extractant. We also note that ligand **A** is of a higher molecular weight and much more hydrophobic than **OO**. At this point, it is difficult to know what feature of the ligand is more responsible for the greater extraction efficiency without carrying out systematic studies that vary the either the hydrophobicity or denticity of the ligand while keeping the extraction conditions consistent.

Another set of ligands that were studied under similar extraction conditions were those of the Paine (Table 3) and Odinets groups. Here, the dipodal pyridine-*N*-oxide scaffold **J** presents two phenyl-substituted CMPO groups and boasts a %E for Eu^{3+} of 90% (extraction conditions: 1×10^{-2} M ligand in 1,2-dichloroethane, 1×10^{-4} M $Ln(NO_3)_3$ in 1 M HNO_3). Under the same extraction conditions, the tripodal ligand **LL** extracts Eu^{3+} with only a 62 %E. In this case, Paine's *N*-oxide scaffold presents an additional hard oxygen donor, which may be partly responsible for its higher extraction efficiency. Conversely, Odinet's tertiary amine TREN scaffold is relatively hydrophilic, and is likely protonated under the extraction conditions.

G. Use of the 1,3,5-triethylbenzene scaffold by Rebek and co-workers. Rebek and co-workers designed a series of supramolecular structures to address the problem of UO_2^{2+} sequestration from the Earth's oceans.[124] Rebek and co-workers have also appended CMPO groups to resorcin[4]arene cavitands, although the application of *f*-element separations was not the focus of this work.[125, 126]

1. Synthesis of tricarboxylic acid ligands based on a 1,3,5-triethylbenzene scaffold. Rebek and co-workers prepared two supramolecular ligands that present three carboxylate groups based on the

1,3,5-triethylbenzene scaffold. The synthesis of the first ligand begins with 1,3,5-tribromomethyl-2,4,6-triethylbenzene **47** made popular by Anslyn and co-workers (Figure 18).[127] Substitution of the benzylic bromides with sodium cyanide followed by hydrolysis under acidic conditions gives the tricarboxylic acid **48**.[128] The carboxylic acids were then esterified with methanol in acid, and reacted with hydrazine hydrate to give the tri-acylhydrazide **49**. Exposure of this compound to three equivalents of Kemp's anhydride acid chloride **50** resulted in the tripodal ligand **QQ**,[129] where the three carboxylic acid groups are forced to occupy the same side of the benzene scaffold by the alternating ethyl groups. Interestingly, the amide hydrogen atoms of the ligand are positioned well to interact with the oxygen atoms of a prospective uranyl ion.

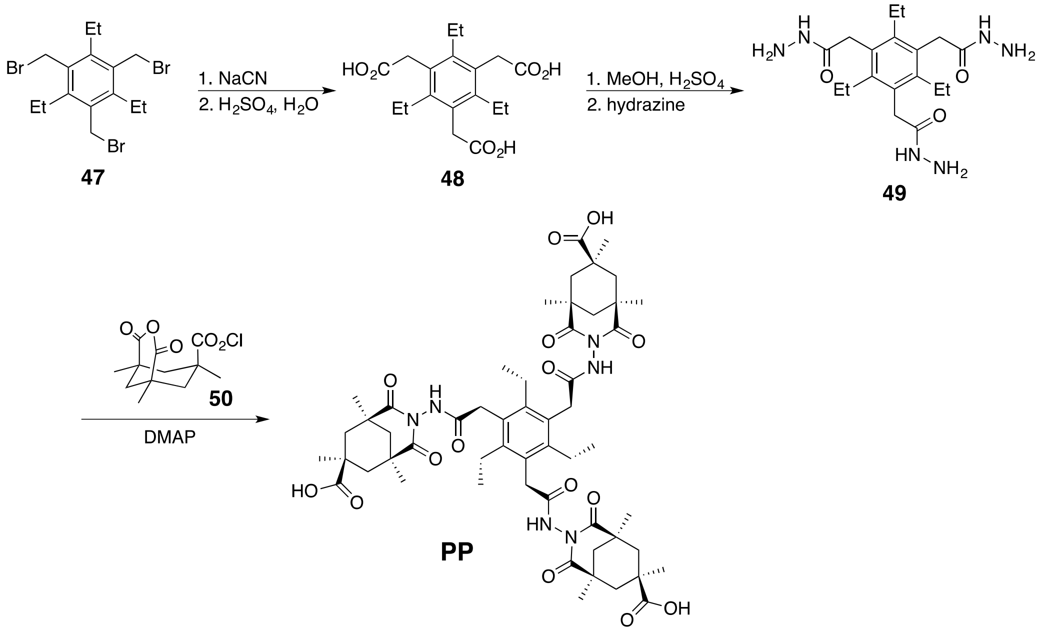


Figure 18. Synthesis of supramolecular triscarboxylic acid ligand **PP**.

Preparation of the second set of tripodal ligands follow a similar synthetic pathway to that described above, and begins with the bromine-substituted terphenyl compound **51** (Figure 19).[130] Exposure of this aryl bromide to butyl lithium results in a smooth lithium-halogen exchange, which when condensed with trialdehyde **52** results in the tripodal compound **53**. Oxidation of the alcohol groups with PCC followed by ester hydrolysis with acetic and hydrobromic acids gave the tripdodal receptor **QQ**. Rebek and co-workers also prepared a related derivative, **RR**, which has methylene groups, rather than a carbonyl group, linking the terphenyl rings to the 1,3,5-benzene scaffold.

Reduction of the intermediate hydroxyl groups was accomplished using triethyl silane and boron trifluoride, again followed by hydrolysis of the ester groups under acidic conditions.

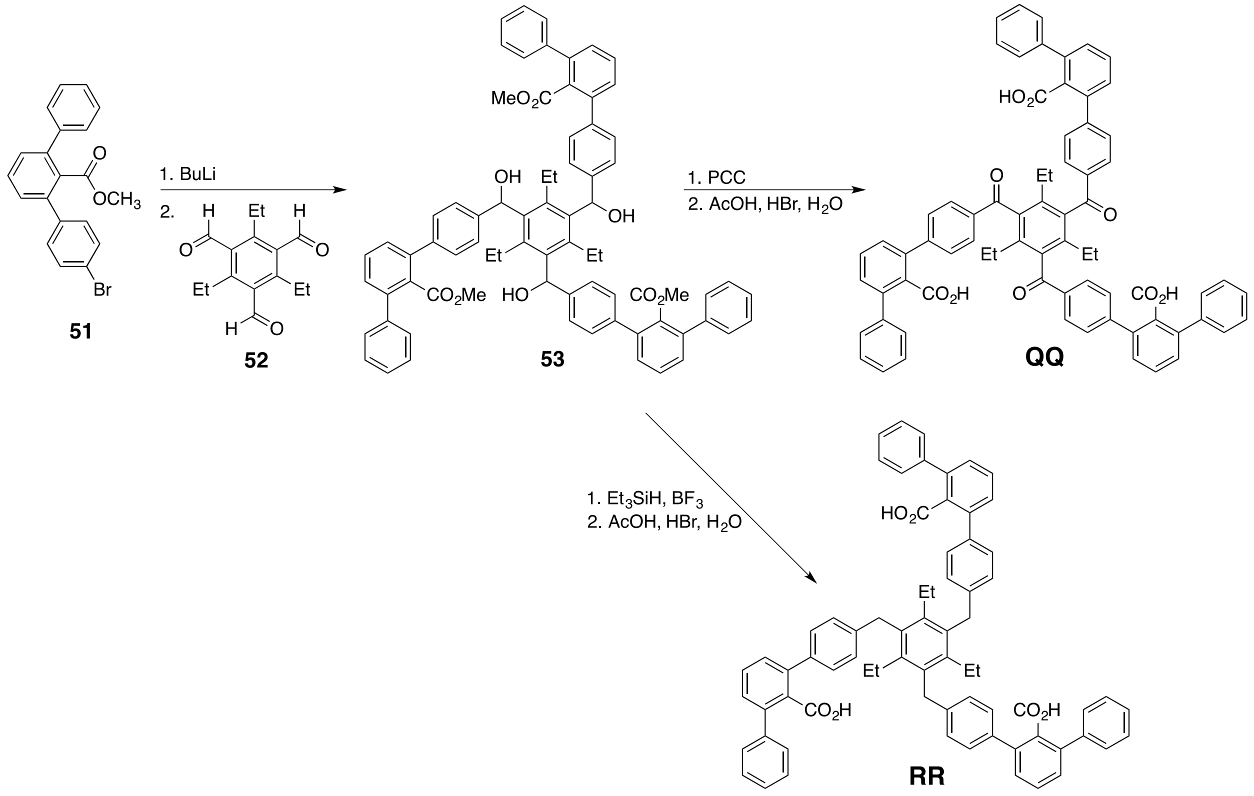


Figure 19. Synthesis of two tripodal receptors **QQ** and **RR**.

2. Uranyl extraction results with tripodal ligands PP-RR. Rebek and co-workers tested the ability of receptors **PP**-**RR** to extract the uranyl ion from aqueous solutions, most notably seawater. A variety of extraction conditions were tested for each ligand, but we summarize only a selection here. For an aqueous solution, buffered to pH 5 with acetate, that contained 400 ppm $UO_2(NO_3)_3$, receptor **PP** was able to extract 59% ($D = 1.4$) of the uranyl ion into the organic phase (0.6 equivalents ligand in $CHCl_3$).[130] Notably, *this extraction efficiency held* in the presence of ions commonly found in seawater (Cl^-, Na^+, Mg^+, Ca^{2+}, K^+, SO_4^{2-}). The authors then attached this ligand to a solid resin, and this system recovered 85% of UO_2^{2+} from a aqueous solutions.[131] To put these extraction numbers in context, the authors also carried out similar experiments with the Chelex 100 resin, which is used in commercial applications. Chelex 100 extracted 88% of UO_2^{2+} out of an aqueous solution containing 400 ppm uranyl (buffered to pH 5 with acetate). However, when this aqueous solution was seawater (at pH 8.4, 400 ppb uranyl) while the Rebek resin's extraction efficiency held at 83%, Chelex 100 was only able to extract 10% of the uranyl ion into the organic layer. As for ligands **QQ** and **RR**, these compounds extracted UO_2^{2+} from aqueous solutions, again buffered to pH 5 with acetate, with extraction percentages of 22 and 23 ($D = 0.3$), respectively.

III. Scope and outlook. The guidelines for this review ask the authors to "aim to identify areas in the field where further developments are needed". The results presented here have shown that a supramolecular approach to the development of better Ln and An extractants is advantageous and has resulted in extraction efficiencies and selectivities that outweigh their monomeric precursors. To quote Eric Schelter: "*A molecular-based approach to RE separations is desirable to probe how subtle changes in RE interactions with organic molecules affect separation efficiencies.*"[99] One of the most powerful ways to create systems that allow for these types of subtle changes is through supramolecular structures.

As a group of synthetic chemists, perhaps we can begin to build supramolecular systems that recognize the cation as well as the anion through two separate binding sites. Such systems should pay some of the enthalpic cost of extracting the anion into organic solution by coordination to the ligand. Pellet and co-workers have built such systems[88, 89] which have demonstrated intriguing results.

Another strategy that is at the forefront of this field is the incorporation of Ln or An ions into the supramolecular structure itself, in essence a type of templating effect.[132] Bu and co-workers have shown that the structure of metal organic frameworks are influenced by the identity of the Ln ion that is in the reaction mixture.[133] Hooley and co-workers have shown that self-assembling metal-ligand cages select one Ln ion over another during the formation process.[134] This concept was also demonstrated by Sun and Bünzli, and it was then exploited to develop an extraction system that demonstrated an exceptional La/Lu separation factor of 87.7(!).[135]

Finally, we encourage researchers in this area to consider designing supramolecular systems that completely surround the target Ln or An ion. Rebek has demonstrated throughout his career that the encapsulation of guests can have astounding effects on the reactivity[136] and conformation[137] of the sequestered species, and that small changes to the structure of the encapsulator can have marked, and often unexpected, effects on guest binding.[138] His self-assembled system where three 2,6-terphenyl carboxylic acids surrounded the uranyl ion and created an encapsulation complex was able to extract 74% of uranium from an aqueous solution in the presence of excess NaCl.[139] Two additional examples we present that are specific to the binding of Ln ions come from: (1) Matt Allen's group with respect to the unique luminescence properties of a crown-ether bound Eu^{2+} ion,[140] and (2) the encapsulation of Ln ions in the cavity of curcurbit[*n*]urils.[141] All of the research described in this review has shown that, although Ln and An ions are similar in size, subtle changes in the structure of the ligand can have a marked effect on extraction selectivity. These effects should be multiplied as the ligands become more complex and completely surround the target metal.

IV. Conflicts of interest

There are no conflicts of interest to declare.

V. Acknowledgements

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