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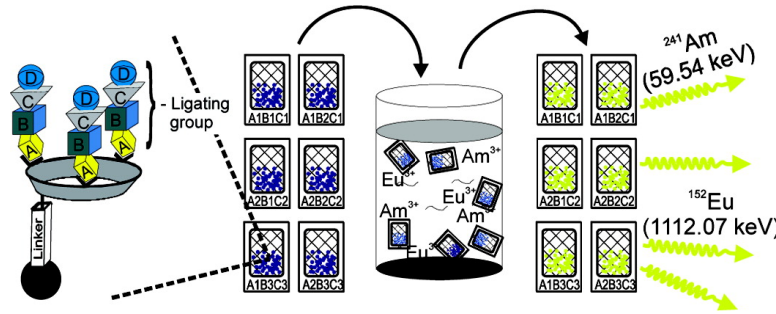

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In the Pursuit for Better Actinide Ligands: An Efficient Strategy for their Discovery

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Abstract: A novel method for the efficient discovery of new types of minor actinide (MA) ligands is based on the unique combination of "tea bag" split pool combinatorial chemistry and screening based on the inherent radioactivity of the complexed cations. Four multicoordinating Am^{3+} chelating groups, such as CMPO (diphenylcarbamoylmethyl)phosphine oxide), PICO (picolinamide), DGA (*N,N*′-dimethyldiglycolamide), and MPMA (*N*-methyl-*N*-phenylmalonamide), on a trityl platform immobilized on TentaGelS served as a model library for the development of the screening method. This model library was screened under various conditions (i.e., 0.001 M $\leq$ [HNO_3] $\leq$ 3 M, $NaNO_3 \leq$ 4 M, and [Eu] $\leq$ 10 $\times$ [ligand]) showing competitive extraction of the four ligands. Other libraries of 9 and 72 members were synthesized by functionalization of the trityl platform with ligating groups that are composed of four building blocks (including at least one amide and one (phosphoric) hydrazone moiety). The screening of these two libraries resulted in the discovery of two multicoordinate ligands that contain ligating groups previously not known to complex Am^{3+}. Both are *N*-isopropyl amides terminated with a *p*-methoxyphenyl hydrazide (A2B1C1D10 K_D(Am) = 2197) or a *p*-nitrophenyl hydrazide (A2B1C1D11 K_D(Am) =1989) moiety, respectively. They are more efficient than the immobilized tritylCMPO ligand (K_D(Am) = 1280) at 3 M HNO_3. This method has the advantages of a high analytical sensitivity and the direct comparison of the extraction results. The method also allows the competitive screening of multiple nuclides which can be quantified by their radioactive emission spectrum.

Introduction

A crucial problem associated with nuclear energy is the resulting nuclear waste. Although the amount of nuclear waste produced is relatively small, the high and long lasting radioactivity renders the costs for processing high.

Most waste processing strategies include the separation of the smaller fraction (<10%) of harmful elements, the minor actinides (MA) Np, Am, and Cm with half-lives ($T_{1/2}$) in the order of 10^3-10^6 years, from the bulk. Nuclide transmutation by neutron bombardment[1] can transform these highly radioactive elements into less harmful nuclides. A promising method for the separation of the MA is extraction using organic ligands. These ligands should have both a high selectivity and affinity for the MA since the fraction of the nuclear waste that is processed (i.e., high level liquid waste, HLLW) contains a large excess of lanthanides[2] (Ln). Some of the Ln (i.e., Sm, Gd, and Eu) have high neutron capture cross sections,[3] which means that their presence would interfere with the transmutation of the MA. Hence, there is a need for a selective separation process, but the An(III) and Ln(III) ions of the same group are very similar (i.e., identical oxidation states, small differences in ionic radii),[4–6] and there are no satisfactory ligands available. Moreover, such ligands must function in a highly acidic[7] and radiolytic environment. Therefore, the rational design of suitable, novel types of An(III) ligands is very difficult. A combinatorial approach could be a useful and effective alternative. The research in this area is mainly focused on derivatives of known

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(1) The partitioning and transmutation (P&T) concept is a strategy that aims at the reduction of the radiotoxic lifetime of nuclear waste prior to vitrification. See for example: *The Economics of the Nuclear Fuel Cycle*; Nuclear Energy Agency (NEA), Paris: OECD, 1994; Salvatores, M. *Nucl. Eng. Des.* **2005**, *235*, 805.

(2) The rear elements (RE) are 10−20 times more present in quantity depending on the "exposure" (the integrated energy released by fission of the heavy nuclides initially present in the fuel) of the reactor. At 45 GWd/tHM (gigawatt days per ton of heavy metal) the ratio is 16 (13.9 kg RE, 0.870 kg Am-Cm per tHM spent fuel). Sometimes also given as the burn-up (number of fissions per 100 heavy nuclides (U and Pu) initially present in the fuel) of the reactor. (International Atomic Energy Agency, Implications of Partitioning and Transmutation in Radioactive Waste Management, Vienna, Technical Reports Series, 2004, 435).

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(7) HLLW contains on average 3 M nitric acid.

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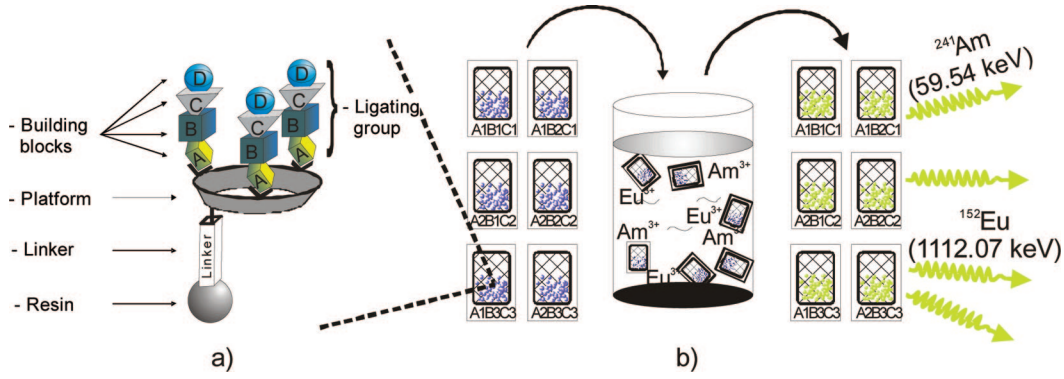


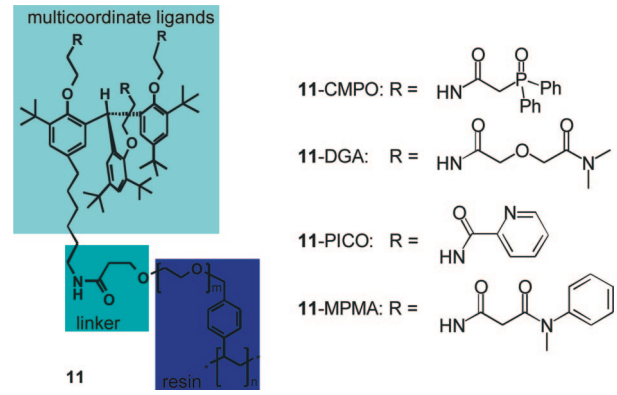
Figure 1. (a) Representation of an immobilized multicoordinate ligand. (b) Schematic representation of the screening procedure.

ligands such as carbamoylmethylphosphine oxides (CMPOs),[8,9] malonamides,[10] diglycol amides (DGAs),[11,12] picoline amides (PICOs),[13] N-containing aromatics,[14–16] and sulfoxides.[17]

In this paper, we introduce a novel method for the fast discovery of better, new types of MA ligands. It is based on the unique combination of combinatorial chemistry[18,19] and a fast screening method using the inherent radioactivity of the complexed cations (Figure 1). The synthesis is performed on a solid phase immobilized platform (Figure 1a). In each step of the split pool synthesis,[18a,19] the building blocks are connected to the platform. The combined building blocks yield ligating groups which are synthesized in a preorganized sequence, resulting in multicoordinate ligands.[20]

In a split pool synthesis, the resulting library consists of a mixture of compounds. This would give difficulties in the subsequent analysis of the libraries,[21,22] and therefore, we have adapted the ''tea bag'' split pool method,[23] in which the chemistry takes place on a resin confined in a porous bag.[24] These physically isolated objects are provided with a unique code. The library of compounds formed consists of bags containing one unique compound. This strategy allows a strongly simplified screening procedure. The entire tea bag library is submersed into a radiotracer solution of the respective nuclide(s) (Figure 1b). After extraction and removal of solvent, the amount of complexed nuclides is quantified by measuring its specific γ-radiation. The label provides the structure of the lead compound(s). The additional advantage of this method is the direct comparison of the selectivities and affinities of multiple hits in a competitive environment. Furthermore, the addition of a known MA ligand prior to the screening protocol provides an internal standard.

Chart 1



Results and Discussion

Synthesis of the Model Library. The trityl platform **11** has three sites available for the preorganization of ligating groups,[12,25] is sufficiently inert in concentrated HNO_3, and offers the possibility of orthogonal functionalization with a linker. A small model library,[26] which comprises known Am(III) ligating groups (i.e., CMPO,[8,9] DGA,[11,12] PICO,[13] and MPMA[10]) (Chart 1), was prepared to test the screening method.

The trityl derivative **6** was functionalized with a linker such that the influence of immobilization on the preorganization of

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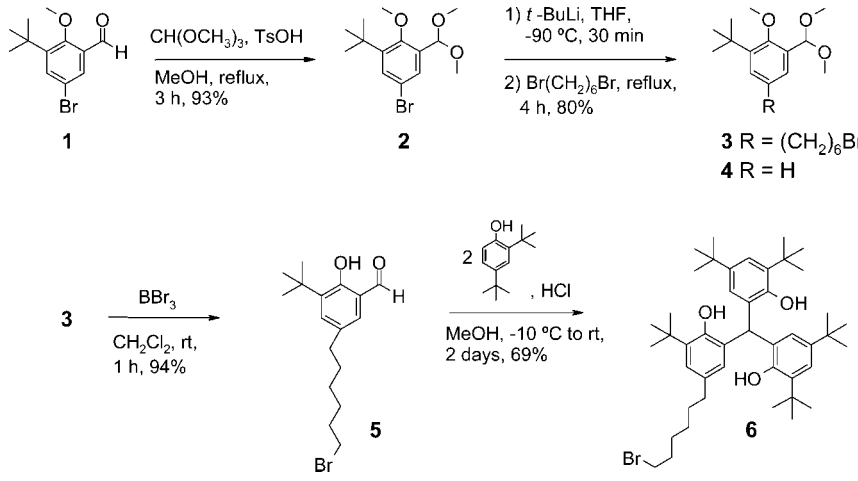
(24) The bags are inert to most organic reagents and almost all solvents, which makes a broad organic synthetic methodology accessible for the synthesis of new libraries (see also Experimental Section).
(25) Peters, M. W.; Werner, E. J.; Scott, M. J. *Inorg. Chem.* **2002**, *41*, 1707.
(26) The *model* library cannot be considered as being synthesized according to the combinatorial build up principle shown in Figure 1a. It only serves to demonstrate the principle.

Scheme 1



attached ligands is minimal. The synthesis started from the known benzaldehyde **1**,[27] in which the aldehyde moiety was protected by reaction with trimethoxymethane to give acetal **2**. Subsequent bromolithium exchange in THF followed by reaction with 1,6-dibromohexane gave compound **6**, which was deprotected using 2 equiv of BBr_3, yielding aldehyde **5**. Condensation of **5** with 2 equiv of 2,4-*tert*-butylphenol under acidic conditions gave the trityl scaffold **6**, as reflected by the methyne proton peak at δ 5.58 in the ^{1}H NMR spectrum.[25] Following this procedure, **6** was synthesized starting from **1** in four steps, in gram quantities with an overall yield of 48% (Scheme 1).

Since the hydroxyl groups of **6** are sterically hindered due to the bulky *tert*-butyl groups and consequently are less reactive, they were reacted with the reactive chloroacetonitrile to give **7** in 99% yield. Subsequent reduction of the cyano groups gave the corresponding amino moieties which are much more reactive for further functionalization than the original hydroxyl groups (vide infra).

In our studies, a linker is needed which is sufficiently stable in concentrated HNO_3 (considering the screening conditions) and which does not cleave during the combinatorial synthesis. Therefore, the bromo substituent in **7** was converted by reaction with potassium phthalimide followed by a subsequent treatment with hydrazine giving the amino-functionalized trityl derivative **9** in 73% yield over two steps.

The platform was immobilized on TentaGelS[28] resin since it swells in most known organic solvents and in water. Reaction of **9** with TentaGelS−COOH resin under peptide coupling conditions gave trityl resin **10**. The disappearance of the COOH group was verified using the malachite green test,[29] and the amount of nitrogen was determined by elemental analysis. Reduction of the cyano groups (positive Kaiser test[30]) in **10** with borane in refluxing THF afforded trityl resin **11** (Scheme 2).

The three amino groups in **11** were functionalized with the four Am^{3+} ligating groups, yielding ligands **11**−CMPO, **11**−DGA, **11**−PICO, and **11**−MPMA (Chart 1) in a similar way as for the free ligands (vide infra, Chart 3). The concentra-

Scheme 2

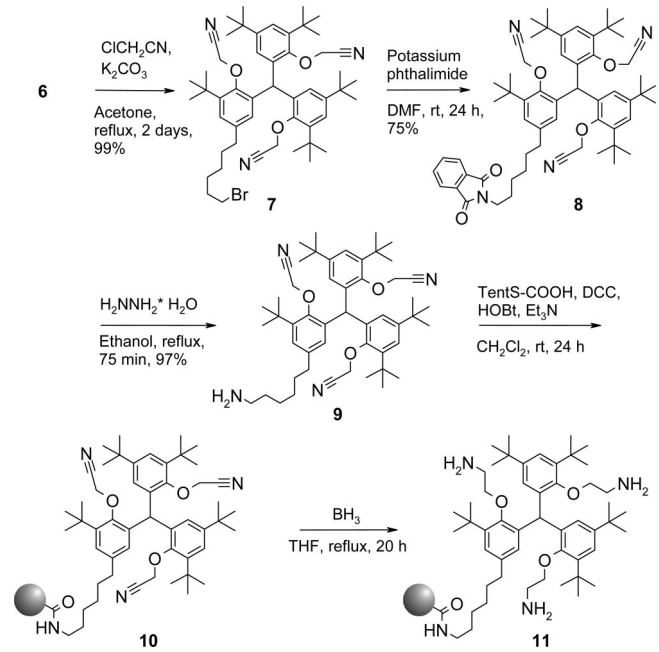


Chart 2

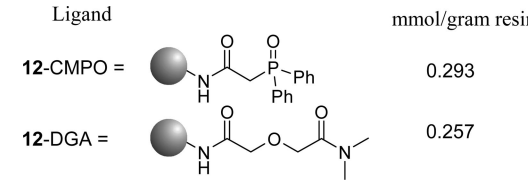
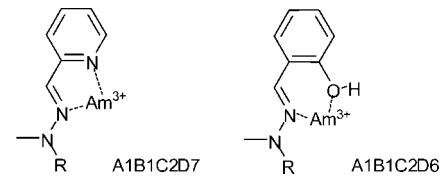


Chart 3



tions of these immobilized ligands **11**−CMPO (0.209), **11**−DGA (0.215), **11**−PICO (0.238), and **11**−MPMA (0.202) (mmol/g resin) were determined via elemental analysis.

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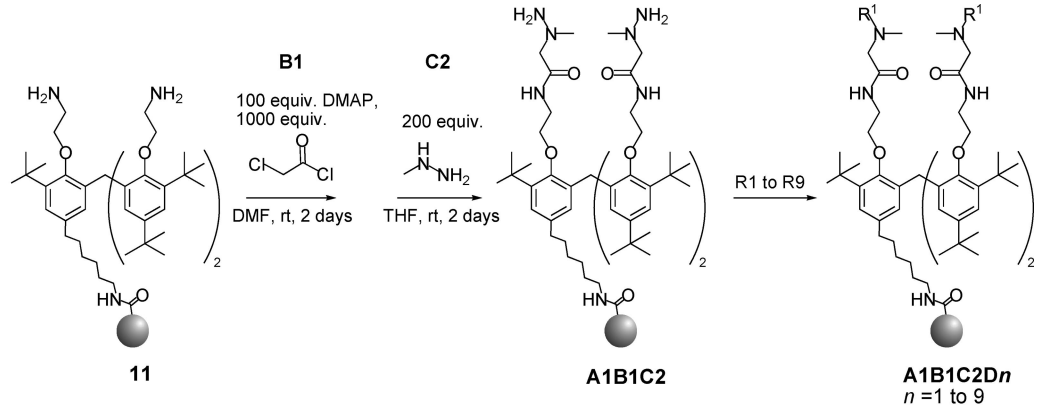
Scheme 3. Synthesis of the 9-Membered Library[a]

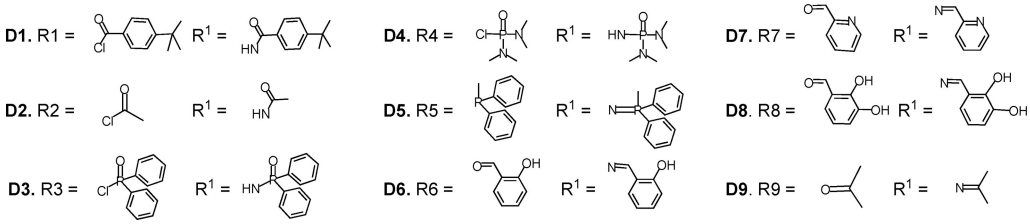


D1, **D2**, **D3**, and **D4** 100 equiv. R1, R2, R3, and R4, 200 equiv. K_2CO_3, THF, rt, 2 days

D5. 100 equiv. R5, 200 equiv. Et_3N, MeCN, rt, 2 days

D6, **D7**, and **D8**. 100 equiv. R6, R7, and R8, MeOH, rt, 2 days

D9. 100 equiv. R9, MeOH, 50 ºC, 2 days



[a] The components of the library are named according their building blocks, A1B1C2D*n* in which the italic *n* stands for all the building blocks of that type (i.e., $n = 1-9$).

In order to address the advantage of such a platform in the extraction of metals,[20] two ligating groups, CMPO and DGA, were also directly coupled to the resin. Starting from TentaGelS$-NH_2$ resin, the corresponding immobilized ligating groups were prepared in the same way as described for the analogous immobilized multicoordinate ligands (Chart 2).

Synthesis of Two Libraries. Two libraries, one of 9 and one of 72 components, were synthesized in four steps using four building blocks A−D (Figure 1). The library members consist of multicoordinate ligands having hard and/or soft donor ligands. Both hard (oxygen[31,57]) and soft (nitrogen,[14,32] sulfur[33]) donor ligands have their advantages and disadvantages with regard to their extraction efficiencies, selectivities, stabilities, and protonation.

Nitrogen atoms were incorporated in the chelating moiety as a (phosphoric) hydrazone or (phosphoric) hydrazine functionality. These types of functionalities were chosen as they were not used before for Am^{3+} extraction.

First a small 9-membered library was synthesized in order to examine 9 different endgroups, that is, (phosphoric) hydrazone and (phosphoric) hydrazine functionalities (Scheme 3). Starting from the immobilized trityl platform **11**, the first step is acylation using a large excess of chloroacetyl chloride. The completion of this step was indicated by using the Kaiser and bromophenol blue tests. The first gives only a blue color in reaction with primary amines,[30] the latter gives a blue color with primary, secondary, and tertiary amines.[34] The second building block, methylhydrazine, was coupled by substituting the α-chloro atom of the amide group; again the beads gave for both tests a blue color. Finally, four different types of endgroups were coupled via amidation, phosphorylation, imine formation, and phosphoryl imine formation[35] giving the 9 different compounds A1B1C2D1–9 shown in Scheme 3.

On the basis of the screening results (vide infra) of this 9-membered library, a library consisting of 72 compounds was designed and synthesized in four successive reaction steps A−D (Scheme 4). After the first step, two different compounds, A1 and A2, are present, though only one synthetic modification was made (viz. a reductive amination of the amine functionality in A2). The completion of this step was confirmed by the Kaiser and bromophenol blue tests. The two building blocks B1 and B2 were introduced by reacting the reaction products of the first step with the corresponding α-chloroacyl chlorides; both the Kaiser and bromophenol blue tests gave no color change. In the third step, three hydrazine derivatives were reacted with the α-chloroamides, resulting in a total of 12 different compounds. Reaction with hydrazine (C1) and methylhydrazine (C2) both resulted in products that gave positive Kaiser and bromophenol blue tests, while reaction with diethylhydrazine (C3) only gave a positive bromophenol blue test. In the fourth and last step, six different building blocks D*n* were introduced by coupling the external hydrazine group either with a carbonic or phosphonic acid chloride functionality. For these compounds,

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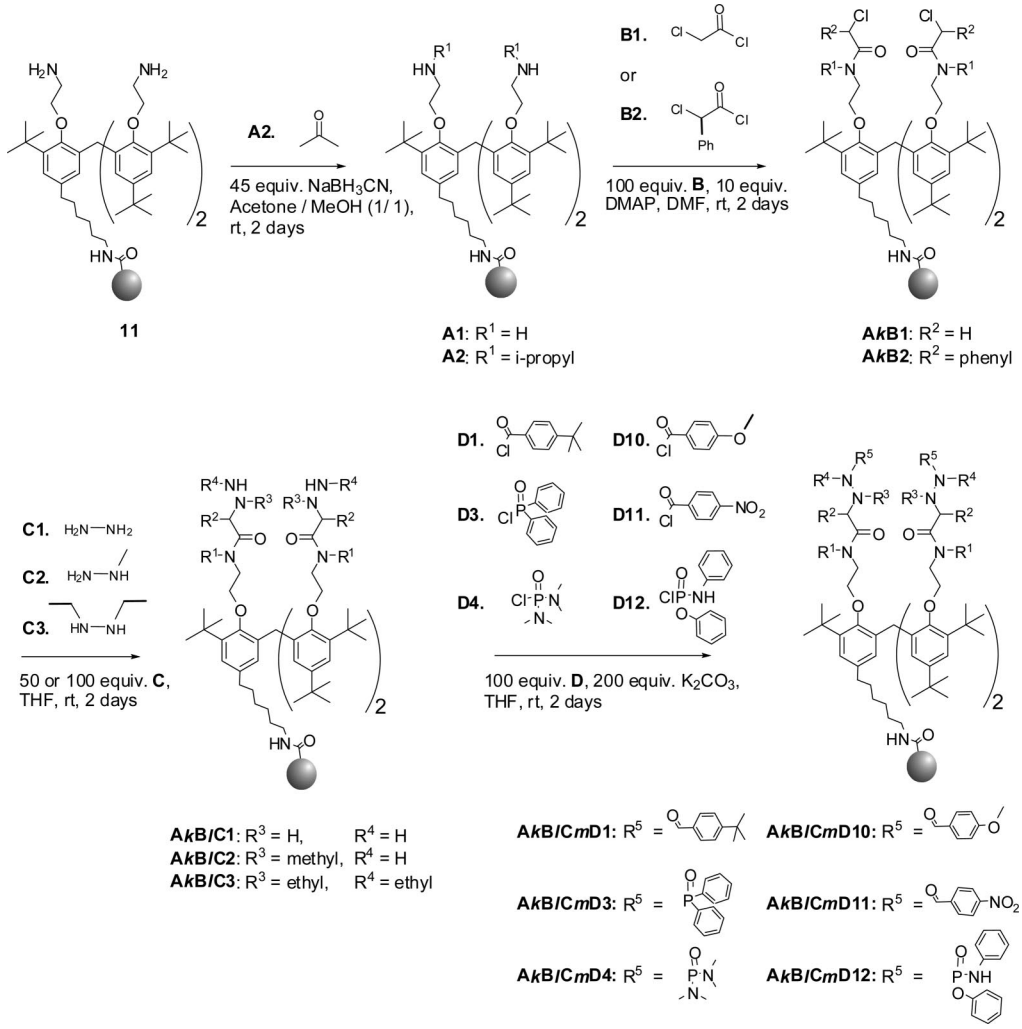
Scheme 4. Synthesis of the 72-Membered Library[a]



[a] The components of the library are named according their building blocks, A*k*B/C*m*D*n* in which each italic letter stands for all the building blocks of that type (i.e., $k = 1, 2$, $l = 1, 2$, $m = 1-3$, and $n = 1-12$.

the Kaiser and bromophenol blue tests were both negative (no color change), indicating that all the amine endgroups had reacted.

Extraction and Screening Results

Liquid–Solid Phase Extractions Using Single Bags. All screening and extraction experiments were performed with the actinide Am^{3+} and with Eu^{3+} as representative of the lanthanides (Ln) since separation of this An/Ln pair is one of the most problematic and is extensively studied in the literature.[20] The amount of complexed nuclide was quantified by measuring the specific γ-radiation from each extracted nuclide in a bag. With this value, the extraction efficiencies of the solid phase[36] immobilized ligands, given by the distribution ratio (K_D), can be calculated.[37]

The Am^{3+} over Eu^{3+} selectivities (separation factor, $S_{Am/Eu}$) of the ligands are given by the quotient of the distribution ratios.[38] TentaGelS terminated with bromine (TentS−Br) was used as a blank. At 0.001 M HNO_3, the blank extracts a small amount of cation ($K_D \leq 2$). This extraction can be attributed to its inner "oxygen donor" environment since TentaGelS consists of a polystyrene core cografted with ethyleneglycol chains.[39] The results given below are not corrected for the extraction by the blank.

In TentaGelS beads of 90 μm, around 99% of the endgroups are homogeneously distributed within the beads.[40,41] Therefore, the kinetics depends on the rate of diffusion of the metal cations into the beads.[40] Therefore, the equilibration time for the complexation with Am^{3+} was investigated. Several **11**−CMPO-containing bags were equilibrated in "single bag extraction" experiments (Figure 1b). The **11**−CMPO ligand reached equilibrium in about 20 min. These extraction experiments also showed that the $S_{Am/Eu}$ values measured at smaller time intervals are not significantly higher than those at equilibrium. Therefore,

(36) In the swollen state of the resin (during extractions), ligands immobilized to TentaGelS resin are not in a solid phase environment but rather in a gel phase environment.

(37) $K_D = ((C_{L,0} - C_L)/C_L) \times (V_L/ms)$, with $C_{L,0}$ the starting activity, C_L the final activity in the aqueous layer, V_L the volume of the aqueous phase, and ms the mass of the solid phase. Böhmer, V.; Dozol, J.-F.; Grüttner, C.; Liger, K.; Matthews, S. E.; Rudershausen, S.; Saadioui, M.; Wang, P. *Org. Biomol. Chem.* **2004**, *2*, 2327.

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Table 1. Distribution Ratios and Separation Factors of the Immobilized Ligands

		3 M HNO_3			0.001 M HNO_3		
ligand[a]	[L] M[b]	K_D(Am)	K_D(Eu)	$S_{Am/Eu}$	K_D(Am)	K_D(Eu)	$S_{Am/Eu}$
Tent−Br		<0.5	<0.5		2	0.7	2.86
11−DGA	6.1×10^{-2}	2278	>3500	<0.7	433	655	0.7
11−CMPO	6.0×10^{-2}	1280	663	1.9	221	202	1.1
11−MPMA	5.8×10^{-2}	6.0	4.3	1.4	23	25	0.9
11−PICO	6.8×10^{-2}	2.3	<0.5		150	132	1.3
12−DGA	7.3×10^{-2}	25	48	0.5	nd	nd	nd
12−CMPO	8.4×10^{-2}	4.5	1.0	4.5	nd	nd	nd

[a] With 20 mg of resin. [b] The concentration of the multicoordinate (ligand) in the microenvironment of a swollen bead with a swelling volume of 3.5 mL/g.

it can be concluded that a kinetic separation is not more efficient than a thermodynamic.

The extraction efficiencies of **11**−CMPO were also measured with 2, 5, 10, 20, 30, and 40 mg of resin. Above 5 mg, the K_D(Am) and K_D(Eu) values were independent of the amount of resin. Below this value, the error is relatively large, resulting in rather large deviations in the K_D values. We have used quantities of ≥20 mg resin in a single bag for the extraction experiments.

Whether originating from preorganization[20] and/or from concentration effects, the multicoordinate ligands **11** gave a higher extraction efficiency (Table 1)[42] than the single ligating groups **12**−CMPO and **12**−DGA (Chart 2), which shows the advantage of using a platform.

Testing of the Screening Method. Results of the extraction experiments with ligands **11** are presented in Figure 2 ($\%E = 100(A_{res}/A_0)$, where A_{res} symbolizes the activity of the resin in a bag and A_0 the initial activity of the aqueous phase.[43] These screening results show that there is a competitive extraction between ligands **11**, with **11**−DGA being the best extractant and **11**−CMPO the most selective for Am^{3+}. From Table 1, it is clear that this trend is the same for their K_D values. At 0.001 M HNO_3, the relative extraction behavior is significantly different.[44] The **11**−PICO and **11**−MPMA ligands, which previously did not show any extraction, now start to compete for the nuclides. However, the efficiency is still significantly lower than that of the CMPO and DGA ligands. A decrease in acidity also effects the selectivity; the Am^{3+} selectivity of **11**−CMPO is reversed, whereas the selectivity of **11**−DGA toward Eu^{3+} disappears.

To examine the possibility of screening future libraries in the presence of $NaNO_3$, a salt present at high concentrations in HLLW, extraction experiments were also performed in the presence of 4 M $NaNO_3$. The Na^+ ion could possibly interfere with the extractions since a major part of the resin consists of ethylene glycol chains which can potentially complex Na^+ ions.[45] Also, the swelling properties of TentaGelS can be different due to the high salt concentration. Figure 2 shows that the addition of 4 M $NaNO_3$ has no significant effect on the extraction results using the trityl model library. In this screening experiment, the total amount of tracer is already extracted when $NaNO_3$ is absent. The addition of the salt only results in a lowering of the total or a change in the relative extraction percentages. These screening results show that it is possible to screen tea bag libraries at different HNO_3 concentrations and in the presence of 4 M $NaNO_3$.

When screening the trityl library using a large excess of Eu^{3+} ([Eu] = 10 × [ligand]) ≈ 4×10^9 [Am]), the library members were still able to extract Am^{3+} up to 8% (Figure 3). Under these conditions, only ligands having both a high selectivity as well as a high affinity for Am^{3+} will show a substantial extraction. This is the ultimate target of screening future libraries.

Screening of the Libraries. The 9-membered library was screened at two different acidities, 0.001 and 3 M HNO_3. At 0.001 M HNO_3, all of the 9 members extracted more than 90% of Am^{3+} and Eu^{3+} out of the aqueous phase. There is a large competitive extraction behavior, a maximum extraction of 54.4% of Am^{3+} and Eu^{3+} for compound A1B1C2D4, and a minimum for A1B1C2D8 with 2.1% of Am^{3+} and 1.9% of Eu^{3+}. The difference in the Am^{3+} versus Eu^{3+} selectivities, based on the ratio Am^{3+}/Eu^{3+} in the extracted percentages, is much less pronounced; it ranges from 0.8 to 1.2 (Table 2).

At 3 M HNO_3, only 15% of Am^{3+} and 11% of Eu^{3+} were extracted from the aqueous phase. Dimethylaminophosphonate A1B1C2D4 remains the most efficient ligand but is now followed by the hydrazide A1B1C2D1 (Table 3).

Imines are more stable toward hydrolysis when complexed by trivalent lanthanides.[46,47] A structure as shown in Chart 3 could very well be possible for the complexes with ligands containing the pyridine (A1B1C2D6), phenol (A1B1C2D7), and catechol (A1B1C2D8) moieties. However, in the present case, these ligands and all other ligands having the (phosphoric) hydrazone functionality (D5−D9) do not extract any nuclides. Very likely, the extraction conditions are too harsh; protonation of the nitrogen donor atoms and/or decomposition of the (phosphoric) hydrazone functionalities due to the strongly oxidizing environment are most likely responsible for the observed results. The extraction efficiency at 3 M HNO_3 of the two most efficient ligands, hydrazide A1B1C2D1 and phosphorhydrazide A1B1C2D4, is sufficiently high to warrant further exploration of this type of ligands.

The screening results of the 72-membered library, consisting of multicoordinate ligands having the hydrazide and phosphonic hydrazide endgroups, are summarized in Table 4. From the screening results, it is clear that on average the library members are somewhat better extractants for Am^{3+} (76%) than for Eu^{3+} (64%). The most efficient extractant of the first library (A1B1C2D4) ends up at the twelfth position and A1B1C2D1 at the fifteenth place in the 72-membered library. The other two members of the previous library do not extract nuclides in the second library because of the strong competition.

The K_D (Am and Eu) values of the three most efficient ligands of the 72-membered library were determined via a single bag extraction procedure (see Experimental Section) (Table 5). The most efficient ligand of this library is hydrazide A2B1C1D10 having a *p*-methoxyphenyl end moiety (Chart 4). This ligand has a slightly lower K_D(Am) value than ligand **11**−DGA. Ligands A2B1C1D10 and hydrazide A2B1C1D11 containing

(42) Though the reactive sites are spatially separated, due to the mobility of the ethylene glycol moieties in TentaGelS resin, site−site interactions within the beads occur to a certain extent. Bassoa, A.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 2699.

(43) In this case, the results are presented in extraction percentages, which give a clear view of the relative competitive extraction behavior of the different members of the library.

(44) To avoid missing library members that are efficient extractants at lower acidities, future libraries should be screened as well at a low acidity.

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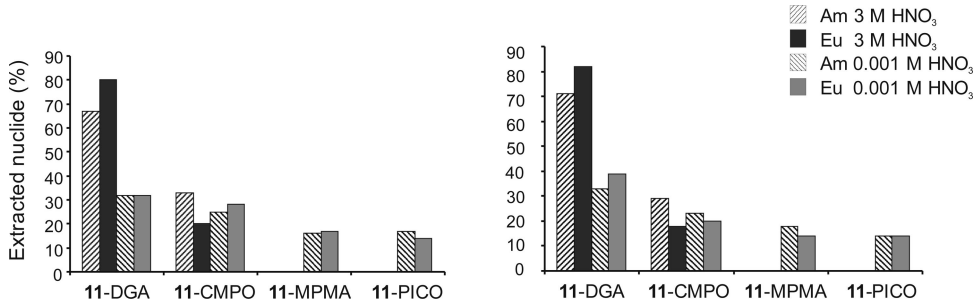

Figure 2. Am^{3+} and Eu^{3+} extraction percentages obtained for competitive screening of the four-membered model library at 3 and 0.001 M HNO_3 (left) and with 4 M $NaNO_3$ (right).

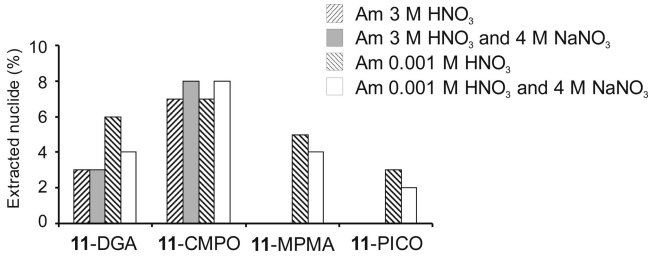

Figure 3. Am^{3+} extraction percentages obtained for competitive screening of the trityl library at 3 and 0.001 M HNO_3 using [Eu] = 10 × [ligand] and 4 M $NaNO_3$. (The amount of extracted Eu^{3+} has not been displayed in this graph since it is out of scale.)

Table 2. Screening Results of the Competitive Extraction of Am^{3+} and Eu^{3+} by the 9-Membered Library at 0.001 M HNO_3

ligand	Am (%)	Eu (%)	Am/Eu	ligand	Am (%)	Eu (%)	Am/Eu
A1B1C2D4	54.4	54.4	1.0	A1B1C2D1	3.0	3.4	0.9
A1B1C2D5	11.2	12.5	0.9	A1B1C2D9	2.8	2.4	1.2
A1B1C2D7	5.8	6.4	0.9	A1B1C2D2	2.2	2.3	0.9
A1B1C2D6	5.1	6.2	0.8	A1B1C2D8	2.1	1.9	1.2
A1B1C2D3	3.6	3.3	1.1	in H_2O phase	9.8	7.3	

Table 3. Screening Results of the Competitive Extraction of Am^{3+} and Eu^{3+} by the 9-Membered Library at 3 M HNO_3 (Ligands That Did Not Extract Any Nuclides Are Not Shown)

compound	Am (%)	Eu (%)	Am/Eu
A1B1C2D4	10.7	8.3	1.3
A1B1C2D1	3.4	2.0	1.7
A1B1C2D2	0.9	0.6	1.6
A1B1C2D3	0.5	0.3	2.0
in H_2O phase	84.5	88.8	

Table 4. Screening Results of the Competitive Extraction of Am^{3+} and Eu^{3+} by the 72-Membered Library at 3 M HNO_3 (Only Ligands That Extracted One or Both of the Nuclides Are Shown)

ligand	Am (%)	Eu (%)	Am/Eu	ligand	Am (%)	Eu (%)	Am/Eu
A2B1C1D10	15.1	11.9	1.3	A2B1C1D3	0.6	0.6	1.0
A2B1C1D11	13.3	10.1	1.3	A1B1C2D4	0.5	0.4	1.2
A2B1C1D1	11.2	9.0	1.2	A1B1C1D4[a]	0.4	0.3	1.2
A1B1C1D10	9.8	8.3	1.2	A1B1C1D3	0.4	0.3	1.4
A1B1C1D1	7.3	6.3	1.2	A1B1C2D1	0.4	0.3	1.2
A2B1C1D4	5.0	5.3	1.0	A1B1C2D10	0.3	0.3	1.0
A2B1C1D12	4.3	3.9	1.1	A2B1C2D12	0.2	0.3	0.7
A1B1C1D11	3.3	2.4	1.4	A1B1C2D12	0.2	0.2	1.0
A2B1C2D4	1.8	2.3	0.8	A1B1C2D11	0.2	0.1	2.0
A1B1C1D12	1.7	1.5	1.1	in H_2O phase	24.1	36.2	

[a] Less than 20 mg of resin was present in the bag due to leaking.

Table 5. Distribution Ratios and Selectivities, Determined via a Single Extraction Procedure, of the Three Most Efficient Ligands of the 72-Membered Library

	3 M HNO_3		
ligand	K_D(Am)	K_D(Eu)	$S_{Am/Eu}$
A2B1C1D10	2197	1243	1.8
A2B1C1D11	1989	1540	1.3
A2B1C1D1	1244	501	2.5

a *p*-nitrophenyl end moiety both have higher extraction efficiencies than ligand **11**−CMPO, though they are less selective for Am^{3+}. Hydrazide A2B1C1D1, having a *p-tert*-butylphenyl end moiety, has a K_D(Am) value comparable to that of **11**−CMPO but is more selective to Am^{3+} than the latter. Striking is the relatively low extraction efficiency of hydrazide A1B1C1D11. It would be expected, with regard to its functional groups, to be somewhere in the fourth position after A1B1C1D1 (Table 4).

From the screening results of this library, some observations can be made. First, all compounds having the A2 (isopropylamine) building block are generally better extractants, except for A1B1C2D10, than their analogues having the A1 (primary amine) building block. A higher extractability of ligands with N-alkylated amides is more often observed, for example, in tripodal DGA[48] and CMPO[49] functionalized multicoordinate ligands. This is sometimes explained as being the result of a higher solubility of the N-alkylated ligands due to an increased lipophilicity. In solid phase extractions, this is, however, less important. Additional effects should therefore be responsible for the observed extraction enhancement, for instance, the increased basicity of the N-alkylated amide carbonyl oxygen,[50] the absence of (intramolecular) hydrogen bonding, or a structural change due to the sterical requirements of the isopropyl group. With respect to the latter, it is interesting to note that the K_D(Am and Eu) values of phosphoramide A1B2C2D3 are somewhat higher than that of the *N*-isopropyl-substituted phoshoramide A2B2C2D3 at both measured acidities. The reverse is observed when the phenyl substituent (B2) is substituted for a hydrogen (B1) (Table 6). This suggests a conformational change, due to the steric crowding between A2 and B2, which negatively influences complex formation.

The increased steric crowding in the B2 ligands may also very well be the reason that none of the 19 extracting compounds

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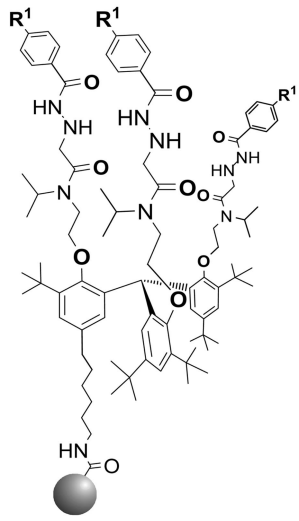
Chart 4



TritylA2B1C1D10, R^1 = OMe
TritylA2B1C1D11, R^1 = NO_2

contains this building block. Second, the extraction efficiency of the ligands decreases from hydrazine (C1) > methylhydrazine (C2) > diethylhydrazine (C3) (Table 4). From extractions performed with A1B1C*m*D1 ($m = 1-3$) at 0.001 M HNO_3 and 3 M HNO_3, the C1 derivative has the highest K_D(Am) (15.3) followed by C2 (K_D(Am) = 5.5) and C3 (K_D(Am) = 2.2) at 0.001 M HNO_3. A similar trend was observed at 3 M HNO_3, C1 (K_D(Am) = 217), C2 (K_D(Am) = 12), and C3 (K_D(Am) = 1.8) (Table 6).

At a higher acidity, the K_D(Am) value for C1 is increasing most,[51] followed by C2; for C3, there is even a slight decrease. The basicity of the central amine nitrogen is increasing in the order C1 > C2 > C3.[50,52] Whether the changes in K_D(Am) values are related to the different basicity remains ambiguous. The difference in basicity is small, and there are multiple factors that may play a role in the observed extraction behavior.

The phosphine oxide containing ligands with the more basic phosphoryl oxygen atom show the highest D_{Am} values at low nitric acid concentrations.[53] At high acidity, this is reversed, and phosphoryl oxygens with a low basicity may even give an increase in their D_{Am} value. From the screening results (Tables 4 and 6), a trend can be observed in the ligands containing the diphenylphosphine oxide D3, bis(dimethylamino)phosphinamide D4, and phenyl-*N*-phenylphosphoramido D12 building blocks that can be related to this. For these ligands, the extraction efficiency follows the order D4 > D12 > D3, a similar trend as seen in the separately measured ligands shown in Table 6 measured at 0.001 and 3 M HNO_3.

Comparison between Solid/Liquid and Liquid/Liquid Extraction. The extraction properties of An^{3+} ligands described in the literature are mainly obtained from liquid/liquid extraction procedures. In order to compare our results with that of ligands described in the literature, the relation between the relative K_D(Am) values of a series of immobilized ligands (Table 1) and the relative D_{Am} values of a series of the corresponding free ligands[54] was examined (Table 7, Chart 5).

Only the relative extraction behavior of a series of immobilized ligands and their corresponding free analogues can be compared since the two extraction systems are inherently different.[55]

When the acidity is increased from 0.001 to 3 M HNO_3, there is a significant increase in the counteranion concentration. In solvent phase extractions, it is usually observed that a higher counteranion or ion concentration results in higher D_M values according to the equation $D_M = K_{ex}[L]^m[NO_3^-]^n$.[56] When the counteranion is added in the form of an acid such as HNO_3, complex formation has to compete with protonation of the ligand. This may result in a decrease of the K_D(M) and D_M values, as observed for ligands containing the PICO and MPMA ligating groups.[13,57] For the DGA and CMPO ligands, the solvent phase extractions show a similar behavior. *The relative extraction behavior of the solvent phase ligands and the immobilized ligands is the same.* This indicates that the results of such screenings can be extrapolated to solvent phase extractions using the free ligands if necessary.

Back Extractions. For back extraction of nuclides, any water-soluble ligand with a sufficiently high complexation constant can in principle be used.[58] Several ligands, EDTA, NTA, DTPA, oxalic acid, citric acid, and HEDPA, were examined for this purpose (Chart 6).[59]

Though EDTA and DTPA are strong ligands, only after three back extraction cycles, using a 0.05 M solution of HEDPA in water, it was possible to completely strip the nuclides from the ligands.

Conclusions

In conclusion, we have shown that our combinatorial screening (by γ-ray analysis) methodology is highly efficient for the discovery of new, potential MA ligands.

Trends in the structure/extraction relationship between ligands can easily be observed. This reveals the influence on the extraction of particular building blocks of the ligating site. These results can be used in the design and synthesis of follow-up libraries. Our methodology has a much wider scope since it is, in principle, possible to use all metal cations that can be identified and quantified by their radioactive emission spectrum, as long as their interaction with TentaGelS is minimal.

Experimental Section

Procedures. Tea Bags. The bags are made of porous (70 μm pores) ethylenetetrafluoroethylene (ETFE) (Figure 4), obtained from Sefar Inc. Filtration Division, Switzerland. The mechanical and chemical properties of ETFE are comparable to that of Teflon, although ETFE does not decompose at high temperatures but instead

(51) A raise of the K_D(Am and Eu) values at higher acidities often results from a coinciding decrease in water activity and an increase in the NO_3^- concentration.
(52) The basicity of the hydrazide ligands is not actually measured. The order of the basicities is based on the basicities found for amides.
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Table 6. Distribution Ratios and Selectivities Obtained from Individual Extraction Experiments of Phosphorhydrazide Ligands Containing *N*-Isopropyl and/or α-Phenyl Substituents, of the A1B1C*m*D1 ($m = 1-3$) Library Members, and of a Series of Ligands Containing the D4, D12, and D3 Building Blocks

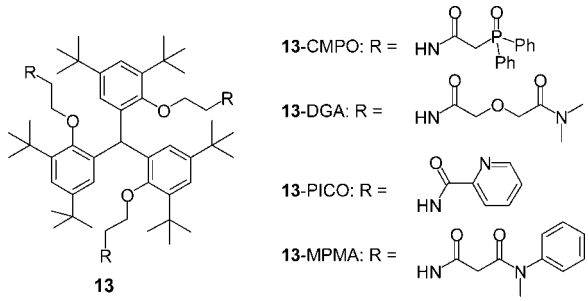
	3 M HNO_3				0.001 M HNO_3		
ligand	K_D(Am)	K_D(Eu)	$S_{Am/Eu}$	ligand	K_D(Am)	K_D(Eu)	$S_{Am/Eu}$
A2B2C2D3	1.3	1.7	0.8	A2B2C2D3	2.4	1.9	1.2
A1B2C2D3	1.7	3.7	0.5	A1B2C2D3	3.4	6.6	0.5
A2B1C2D3	6.4	4.5	1.4				
A1B1C2D3	2.7	2.0	1.4				
A1B1C1D1	217 (84%)	137 (77%)	1.6	A1B1C1D1	15.3 (27%)	14.2 (25%)	1.1
A1B1C2D1	12.0 (22%)	8.0 (16%)	1.5	A1B1C2D1	5.5 (12%)	3.6 (7.8%)	1.5
A1B1C3D1	1.8 (4.2%)	1.4 (3.3%)	1.3	A1B1C3D1	2.2 (4.9%)	2.1 (4.7%)	1.0
A2B2C2D4	0.62	0.65	0.95	A2B2C2D4	214	260	0.82
A2B2C2D12	0.81	1.05	0.77	A2B2C2D12	17.4	12.8	1.36
A2B2C2D3	1.33	1.70	0.78	A2B2C2D3	2.35	1.94	1.21

Table 7. Distribution Ratios and Separation Factors of the Free Ligands[54]

		3 M HNO_3		
ligand[a]	[L] M[b]	D_{Am}	D_{Eu}	$S_{Am/Eu}$
13−DGA	1×10^{-4}	13.2	36.0	0.37
13−CMPO	8×10^{-3}	17.8	12.3	1.4
13−MPMA	1×10^{-1}	1.4[c]	6.0[c]	0.23
13−PICO	1×10^{-1}	<0.01[c]	<0.01[c]	

[a] The organic phase is nitrobenzene. [b] These are the highest [L] that were measured for these ligands. [c] Major precipitation.

Chart 5



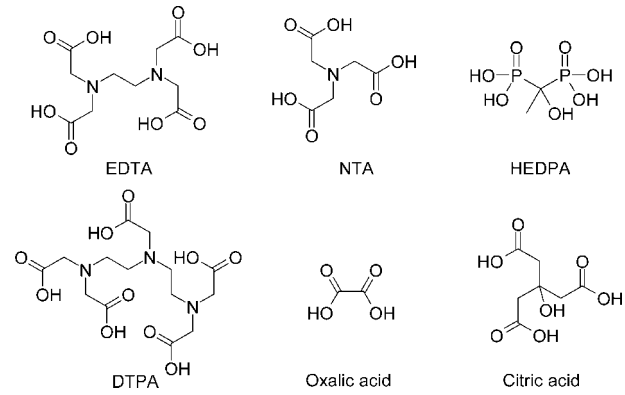
can be melted at 245 °C.[60] This thermoplastic property is used in the preparation of the bags which are made by manually welding sheets of ETFE together with a heat sealer and cutting the bags out.

Single Bag Screenings. The bags were filled with resin (20 mg) and contained in a 3 mL screw cap vial and shaken (1800 rpm) with 1 mL of the appropriate aqueous solution at ambient temperature (22–24 °C) for 30 min for equilibration. After extraction, 0.8 mL of the aqueous layer was pipetted out for analysis, and the rest was discarded. Centrifugation (5 min, 1600 rpm) removed most of the remaining solvent. Finally, the bags were placed into vials and positioned for γ-ray measurement.

Model Library Screening. The bags were filled with resin (20 mg) and contained in a 4 mL screw cap vial and shaken (1800 rpm) with 3 mL of the appropriate aqueous solution at ambient temperature (22–24 °C) for 60 min for equilibration. After extraction, 1.0 mL of the aqueous layer was pipetted out for analysis, and the rest was discarded. Centrifugation (5 min, 1600 rpm) removed most of the remaining solvent. Finally, the bags were placed into vials and positioned for γ-ray measurement.

Library Screening. 9-Membered library: The bags were contained in a 3 mL screw cap vial and shaken (1800 rpm) with 2 mL of the appropriate aqueous solution at ambient temperature (22–24 °C) for 60 min for equilibration. After extraction, 1 mL of the aqueous layer was pipetted out for analysis, and the rest was discarded. Centrifugation (5 min, 1600 rpm) removed most of the remaining solvent. Finally, the bags were placed into vials and positioned for γ-ray measurement. 72-Membered library: The bags were contained in a 100 mL screw cap vial and shaken (1800 rpm) with 50 mL of the appropriate aqueous solution at ambient temperature (22–24 °C) for 60 min for equilibration. After extraction, 6 mL of the aqueous layer was pipetted out for analysis, and the rest was discarded. Centrifugation (5 min, 1600 rpm) removed most of the remaining solvent. Finally, the bags were placed into vials and positioned for γ-ray measurement.

Chart 6. Ligands That Are Commonly Used in the Stripping of Actinides



Isotopes. The ^{241}Am and ^{152}Eu isotopes were used from NRG (Nuclear Research & Consultancy Group) stock.

Tracer Solutions and Measurements. For single bag and model library screenings, 200−400 Bq ^{241}Am and 200 to 400 Bq ^{152}Eu were used. For the 9-membered library, 900 Bq ^{241}Am and 900 Bq ^{152}Eu were used, and for the 72-membered library, 2800 Bq ^{241}Am and 2800 Bq ^{152}Eu were used. Where necessary, the concentration of Eu^{3+} was adjusted by addition of a stable isotope of europium. The γ-activity was determined by measuring for 1 h with a germanium high purity, Ge(HP), detector.

The reported extraction percentages are the averages of at least two experiments. The errors in the duplicates are less than 5%. In

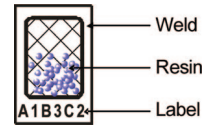


Figure 4. Representation of a tea bag containing resin beads.

(60) Sefar Filtration, Chemical Resistances of selected Polymer Materials data sheet.

the >95% and <5% extraction region, the error in the resulting distribution coefficient may become quite large, resulting in even larger errors in the calculated separation factors.

Acknowledgment. This research was supported by the Technology Foundation STW, applied science division of NWO, and the technology program of the Ministry of Economic Affairs. We gratefully acknowledge the Fuels, Actinides and Isotopes (FAI) Department at the Nuclear Research & Consultancy Group (NRG) in The Netherlands for providing the radionuclear facilities. Especially we would like to thank Tanja Tomasberger and Marco Ooijevaar for their support and work on the measurements.

Supporting Information Available: Detailed experimental procedures and the characterization of the different compounds and functionalized resins. This material is available free of charge via the Internet at http://pubs.acs.org.

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