Synergistic effect of ligating and ionic functions, prearranged on a calix[4]arene†

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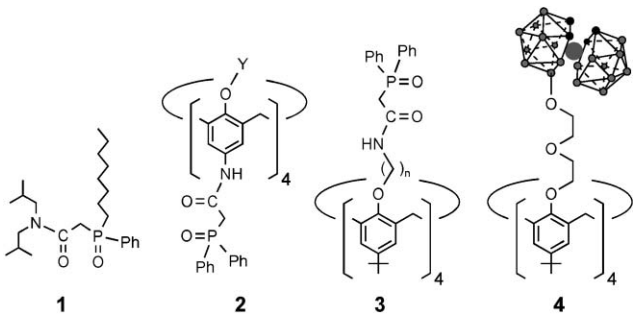
The covalent attachment of two CMPO-functions and two anionic Cosan groups to the narrow rim of *tert*-butylcalix[4]-arene leads to a dramatic increase of the extraction efficiency for the *cone* isomer; Am^{3+} is removed from 5×10^{-8} M solution to more than 99% by a single extraction step with a 3×10^{-6} M solution of the calixarene.

The attachment of several ligating functions (binding groups) in well defined positions and orientations on a common platform may create host molecules with increased complexation constants for a guest due to their cooperative action. Calixarenes, which are easily available and readily undergo chemical modifications[1] are especially appropriate as platforms on which to assemble various functional groups. Numerous examples for cation and anion receptors based on calixarenes are known[2] and more ambitious/demanding compounds include multifunctional catalysts[3] or "enzyme mimics".[4]

Carbamoylmethylphosphine oxides (CMPOs) have been designed as ligands for actindes (and lanthanides), and especially (*N*,*N*-diisobutylcarbamoylmethyl)phenyloctylphosphine oxide (**1**) is used as extractant on a technical scale (TRUEX-process).[5] In early studies we have shown, that the attachment of four CMPO-functions to the wide rim of calix[4]arene tetraethers gives extractants (**2**)[6] which are about 100 to 1000 times more effective‡ than the single CMPO **1**.[7] In addition there is a remarkable selectivity of Am over Eu and of the light over the heavy lanthanides.[8] The attachment of four CMPO-functions to the narrow rim *via* oligomethylene spacers of various length also leads to ligands (**3**) which are more effective than **1**, but less selective than **2**.[9]

For the extraction of actinides, cobalt(III) bis(dicarbollide)(−1), $[(1,2\text{-}C_2B_9H_{11})_2\text{-}3,3'\text{-}Co(III)]^-$ (= "Cosan"), a soft, low coordinating, hydrophobic anion, was proposed as coextractant§ (especially in form of the chloro- or bromo-derivative) in synergistic mixtures with other ligands, *e.g.* CMPO (UNEX-process), TODGA or BTP *etc.*[10] The improved results thus obtained are due to the easier extraction of Cosan than of hard anions such as nitrate. A first covalent connection of Cosan with CMPO, resulted in a significant increase of the extraction ability compared to **1**.[11] This result prompted us to study the effect of preorganization of several Cosan- and CMPO-groups on a common platform.



We recently described the synthesis of the first calix[4]arene derivative **4**, in which up to four Cosan units are bound to the narrow rim *via* diethylene glycol spacers.[12] The alkylating agent **5**, a zwitterionic dioxonium–Cosan derivative was now used, to prepare the first derivatives, in which two Cosan and two CMPO functions are combined at the narrow rim (Scheme 1).

Starting with the dinitrile **6** (easily prepared by alkylation of *tert*-butylcalix[4]arene with bromobutyronitrile[13]) the alkylation with **5** led to a mixture of conformational isomers, from which the pure **7(cone)** was isolated in about 30% yield. The *1,3-alternate* isomer **7(alt)** was formed as the only product and isolated in 48% yield, when Cs_2CO_3 was used as base. Both compounds were converted in two steps (reduction of the nitrile functions with BH_3SMe_2, acylation of the amino groups by *p*-nitrophenyl(diphenylphosphoryl)acetate **9**) into the isomeric derivatives **8(cone)**, where two CMPO- and two Cosan groups reside at the same side of the calix[4]arene skeleton, and **8(alt)** where these groups point into opposite directions. Due to the (pairwise) different ether groups the *cone* and *1,3-alternate* conformations of **7** and **8** are both C_{2v}-symmetrical. An unambiguous distinction is nevertheless possible by the pair of doublets for the methylene protons which is separated by ~1,3 ppm in the *cone* and by only 0.1–0.2 ppm in the *1,3-alternate* isomers.

Extraction of trivalent cations (Eu, Am) from aqueous (nitric acid) solution was checked, using HMK–TPH (2-octanone–hydrogenated tetrapropylene 1 : 1) or dichloroethane (DCE) and due to the low solubility of **8(alt)** also nitrobenzene (NB) as organic solvents. Table 1 contains selected data, including also calixarenes **3** and **4** which contain either four CMPO ***or*** four

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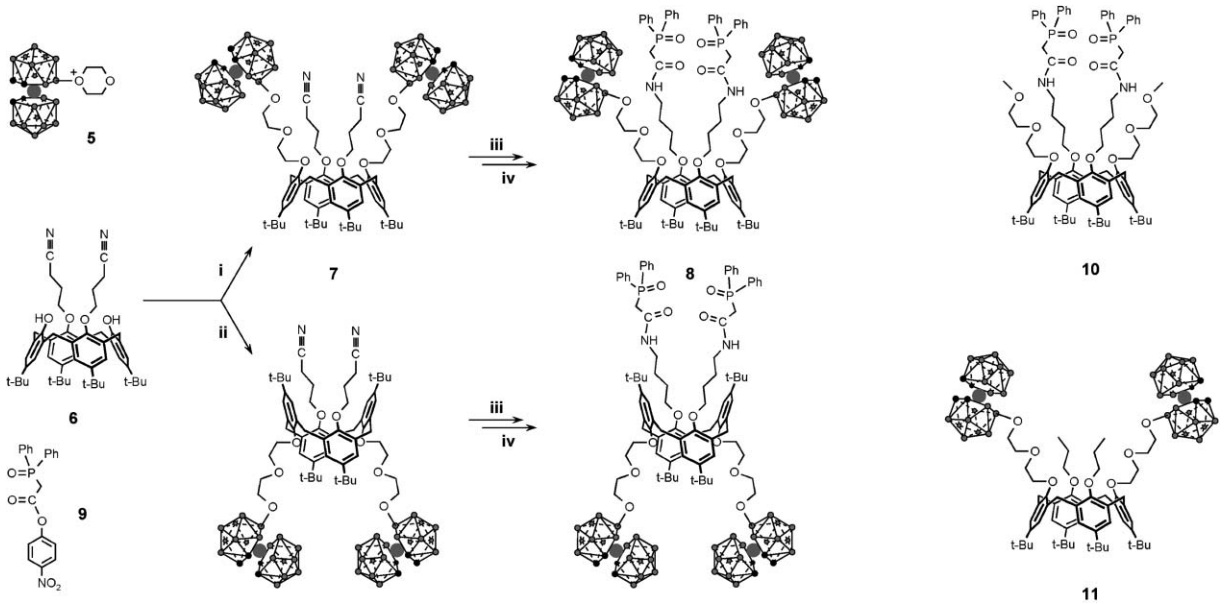

Scheme 1 Synthesis of calix[4]arene derivatives bearing two CMPO and two Cosan groups at the narrow rim including reagents (**5**, **9**) and model compounds (**10**, **11**). *Reagents and conditions*: (i) **5**, NaH, DME–toluene; (ii) **5**, Cs_2CO_3, DME–toluene; (iii) BH_3SMe_2, THF; (iv) NaH, **9**, THF.

Cosan groups¶. To obtain meaningful distribution coefficients $D < 100$ the tetra-CMPO compounds **2** and **3** were usually checked in concentrations of 1 mM. For **8(cone)** such a concentration is much too high and also for **8(alt)** some of the distribution coefficients D are higher than 100. However, this concentration is appropriate to reveal a strong synergistic effect for the combination of di-CMPO **10** and di-Cosan **11**.[12] For c_{HNO_3} = 0.1 M their distribution coefficients D are both <0.01, while their 1 : 1 mixture with the same concentration of 1 mM each gives $D > 100$, an increase of at least 10^4.

Table 1 Extraction of Am^{3+} and Eu^{3+} ($c_{M^{3+}} = 3.0 \times 10^{-7}$ M) from aqueous nitric acid of different concentrations (0.01, 0.1, 1 M) to HMK–TPH (1 : 1), 1,2-dichloroethane (DCE) or nitrobenzene (NB)

				c_{HNO_3}/M		
c_L/M	Extractant	Solvent		0.01	0.1	1
10^{-3}	**8(cone)**	DCE	D_{Am}	>100	>100	>100
			D_{Eu}	>100	>100	>100
	8(alt)	NB	D_{Am}	>100	>100	24
			D_{Eu}	94	>100	11
	3 (n = 4)	DCE	D_{Am}	2.1	1.2	2.6
			D_{Eu}	1.2	0.65	1.4
	4	DCE	D_{Am}	14	0.18	0.02
			D_{Eu}	8.2	0.15	<0.01
	10	DCE	D_{Am}	<0.01	<0.01	0.02
			D_{Eu}	<0.01	<0.01	0.01
	11	DCE	D_{Am}	0.11	<0.01	<0.01
			D_{Eu}	0.09	<0.01	<0.01
	10/11 (1:1)	DCE	D_{Am}	>100	>100	6.1
			D_{Eu}	>100	>100	4.6
10^{-5}	**8(cone)**	HMK–TPH	D_{Am}	>100	>100	7.5
			D_{Eu}	>100	>100	7.0
		DCE	D_{Am}	>100	>100	2.3
			D_{Eu}	>100	>100	2.5
		NB	D_{Am}	>100	>100	0.33
			D_{Eu}	>100	>100	0.32
	10/11 (1:1)	DCE	D_{Am}	0.16	0.01	<0.01
			D_{Eu}	0.11	0.01	<0.01

This "intermolecular" synergistic effect of **10/11** disappears for lower concentrations. However, **8(cone)** shows even at $c_L = 10^{-5}$ M an extremely good extraction ability for $c_{HNO_3} \leqslant 0.1$ M. Thus, we decided to explore the limits further. We diluted the extractant and checked the extraction from 0.1 M nitric acid with $c_{Am^{3+}} = 5 \times 10^{-8}$ M. For comparison Table 2 contains again similar studies with **8(alt)** and with 1 : 1 mixtures of di-CMPO **10** and di-Cosan **11** for which the total concentration of calixarene bound CMPO and Cosan groups is identical. Both calixarenes **8** bearing two CMPO and two Cosan groups on the same calixarene skeleton are much better extractants than the mixture **10/11**. Comparison of the two isomeric calixarenes **8** in nitrobenzene solution, where the distribution coefficients obviously are slighly lower than in HMK–TPH or DCE (Tables 1 and 2), reveals that the cone isomer is better by a factor of about 10 down to concentrations of $c_L = 3 \times 10^{-6}$ M, and even at $c_L = 10^{-6}$ M, which means for a ratio $c_L/c_{Am^{3+}}$ as low as 20, more than 98% of Am^{3+} is extracted in a single step by compound **8(cone)** in HMK–TPH.

There is obviously a noticeable *intermolecular* synergistic effect for mixtures of **10** and **11**. Such an effect may be working also with **8(alt)** but cannot explain the strong increase in D. Since the CMPO and Cosan groups can hardly interact *intramolecularily* the main reason for the high extractibility shown by **8(alt)** must be sought in

Table 2 Distribution coefficient D for the extraction of Am^{3+} ($c = 5.1 \times 10^{-8}$ M) from 0.1 M nitric acid by different extractants and different concentrations

	8(cone)	**10/11** (1 : 1)	**8(cone)**	**8(alt)**
c_L/M	HMK–TPH (1:1)		NB	
1×10^{-4}				>100
3×10^{-5}		1.1	>100	92
1×10^{-5}	>100	0.34	>100	9.6
3×10^{-6}	>100	<0.01	7.5	0.65
1×10^{-6}	53		0.16	0.063
3×10^{-7}	1.8		0.04	0.015
1×10^{-7}	0.11		0.01	<0.01

its generally higher lipophilicity and in an unspecific (partial) compensation of the positive charge of the extracted cation by the anionic Cosan groups.

To obtain the optimum it is not sufficient, however, to combine just two CMPO-functions and two Cosan-groups within the same molecule. This must be done also in the *correct mutual* position, like in **8(cone)**. Although the structure of the extracted species is not exactly known, it is justified to assume that the two anionic Cosan-groups are in close neighborhood to the cation bound by the two bidentate CMPO-functions.[14] In that sense the dramatic increase of the extractability may be due to a kind of "*intramolecular*" synergistic or cooperative effect.

In conclusion we have shown, that a trivalent cation (*e.g.* Am^{3+}) present in trace amounts (5×10^{-8} M) can be quantitatively (>99%) removed by a single extraction step with an extractant applied in concentrations as low as 3×10^{-6} M. We have not observed any pronounced selectivity between Eu^{3+} and Am^{3+} which suggests a certain generality for all the lanthanides.

This result may be of interest not only from a fundamental point of view, but also for applications (*e.g.* for analytical or decontamination purposes). Further modifications of the molecule (*e.g.* number or ratio of Cosan/CMPO groups, variation of the spacers) are presently being undertaken. The replacement of *tert*-butyl groups in **8(cone)** by suitable functional groups should also allow its covalent attachment to solid surfaces, including for instance μm-sized (magnetic) particles,[15] where a high efficiency is especially important.

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Notes and references

‡ The ratio of the concentration of CMPO-functions (four in a molecule **2** or **3**), leading to the same distribution coefficient under otherwise identical conditions is used for this comparison. The exact value depends not only on the cation to be extracted, but also on the conditions, *e.g.* extracting solvent, concentration of nitric acid or sodium nitrate, *etc.*

§ Cosan alone without synergistic agents is able to extract effectively only caesium cations.

¶ Note that even the tetra-Cosan **4** is a reasonable extractant at $c_L = 10^{-3}$ M at low c_{HNO_3}.

Analytical data for the sodium salts of **8(cone)** and **8(alt)**:

Na_2**8(cone)**: orange powder; yield 64%, MS (−80 eV, ESI) *m/z*: 2122 (5%) 2115 (100%) $[M + Na]^-$ (calc. 2122, 2115), R_f = 0.67 (CH_2Cl_2–CH_3CN = 3 : 1); mp 268–272 °C (decomp.). ^{11}B NMR (128 MHz, [D_6]acetone, 25 °C, $BF_3{\cdot}Et_2O$): δ 23.5 (s, 1B; B8), 4.5 (d, ^1J(B,H) = 142 Hz, 1B; B8′), 0.5 (d, ^1J(B,H) = 139 Hz, 1B; B10′), −2.5 (d, ^1J(B,H) = 145 Hz, 1B; B10), −4.4 (d, ^1J(B,H) = 154 Hz, 2B; B4′, 7′), −7.5 (2d, overlap, 6B; B4, 7, 9, 12, 9′, 12′), −17.3 (d, ^1J(B,H) = 146 Hz, 2B; B5′, 11′), −20.4 (d, ^1J(B,H) = 163 Hz, 2B; B5, 11), −21.6 (d, ^1J(B,H) = 173, Hz, 1B; B6′), −28.4 ppm (d, ^1J(B,H) = 139 Hz, 1B; B6); ^{1}H NMR (400 MHz, [D_6]acetone, 25 °C, TMS): δ 7.92 (t, *J*(H,H) = 8 Hz, 8H; ArH), 7.63 (t, *J*(H,H) = 8 Hz, 4H; ArH), 7.54 (m, 4H; ArH), 7.16 (s, 4H; ArH), 6.62 (s, 4H; ArH), 4.44 (d, ^2J(H,H) = 12 Hz, 4H; $ArCH_2Ar$, H_{ax}), 4.23, 4.21 (s, 8H; cage CH), 3.95 (t, ^2J(H,H) = 8 Hz, 4H; CH_2O), 3.87 (br t, 4H; CH_2O), 3.78 (t, *J*(H,H) = 5 Hz, 4H; CH_2O), 3.78 (d, ^2J(P,H) = 6 Hz, 4H; CH_2P), 3.59 (t, *J*(H,H) = 5 Hz, 8H; CH_2O), 3.24 (q, 4H; CH_2NCO), 3.17 (d, ^2J(H,H) = 12 Hz, 4H; $ArCH_2Ar$, H_{eq}), 1.95 (m, 4H; CH_2), 1.64 (m, 4H; CH_2), 1.31 (s, 18H; *t*Bu), 0.91 ppm (s, 18H; *t*Bu); $^{31}P\{^1H\}$ NMR (400 MHz, [D_6]acetone, 25 °C, H_3PO_4): δ 34.7 ppm (s). B–H signals from $^1H\{^{11}B$ selective} NMR (400 MHz, [D_6]acetone, 25 °C, TMS): δ 2.92 (H10′), 2.76 (H(4′, 7′), 2.72 (H10), 2.44 (H8′), 2.94, 2.02, 1.80 (H 4, 7, 9, 12, 9′, 12′), 1.68 (H5′,11′), 1.56 (H5, 11), 1.48 (H6′), 1.26 ppm (H6);

Na_2**8(alt)**: orange powder; yield 56%. R_f = 0.84 (CH_2Cl_2–CH_3CN = 3 : 1); mp 271–274 °C (decomp.), MS (−80 eV, ESI) *m/z*: 2122 (100%) $[M + Na]^-$ (calc. 2122). ^{11}B NMR (128 MHz, [D_6]acetone, 25 °C, $BF_3.Et_2O$): δ 22.6 (s, 1B; B8), 3.5 (d, ^1J(B,H) = 144 Hz, 1B; B8′), 0.6 (d, ^1J(B,H) = 141 Hz, 1B; B10′), −2.4 (d, ^1J(B,H) = 140 Hz, 1B; B10), −4.0 (d, ^1J(B,H) = 154 Hz, 2B; B4′, 7′), −7.6 (2d, overlap, 6B; B4, 7, 9, 12, 9′, 12′), −17.3 (d, ^1J(B,H) = 147 Hz, 2B; B5′, 11′), −20.3 (d, ^1J(B,H) = 152 Hz, 2B; B5, 11), −21.6 (d, overlap 1B; B6′), −28.5 ppm (d, ^1J(B,H) = 141 Hz, 1B; B6); ^{1}H NMR (400 MHz, [D_6]acetone, 25 °C, TMS): δ 7.88 (m, 8H; ArH), 7.64 (t, *J*(H,H) = 7 Hz, 4H; ArH), 7.53 (m, 8H; ArH), 7.15 (s, 4H; ArH), 6.98 (s, 4H; ArH), 4.32, 4.29 (2s, 8H; cage CH), 3.93 (d, ^2J(H,H) = 16 Hz, 4H; $ArCH_2Ar$), 3.73 (d, ^2J(H,H) = 16 Hz, 4H; $ArCH_2Ar$), 3.63 (t, ^3J(H,H) = 6 Hz, 4H; CH_2O), 3.58 (d, ^2J(H,P) = 13 Hz, 4H; CH_2P), 3.57 (t, 4H; CH_2O), 3.45 (t, *J*(H,H) = 5 Hz, 4H; CH_2O), 3.33 (t, ^3J(H,H) = 6 Hz, 4H; CH_2O), 3.16 (t, ^3J(H,H) = 6 Hz, 4H; CH_2O), 3.06 (q, 4H; CH_2NCO, H_{eq}), 1.79 (m, 4H; CH_2), 1.59 (m, 4H; CH_2), 1.36 (s, 18H; *t*Bu), 1.23 ppm (s, 18H; *t*Bu); $^{31}P\{^1H\}$ NMR (400 MHz, [D_6]acetone, 25 °C, H_3PO_4): δ 30.27 (s).

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