NJC

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *New J. Chem.*, 2013, **37**, 391

Pyrazine-functionalized calix[4]arenes: synthesis by palladium-catalyzed cross-coupling with phosphorus pronucleophiles and metal ion extraction properties†

Nicolai I. Nikishkin,[a] Jurriaan Huskens,[a] Seraj A. Ansari,[b] Prasanta K. Mohapatra[b] and Willem Verboom*[a]

Received (in Gainesville, FL, USA) 4th September 2012,
Accepted 22nd October 2012

DOI: 10.1039/c2nj40791d

www.rsc.org/njc

A series of pyrazine-based calix[4]arene extractants was prepared by a stepwise functionalization, comprising palladium-catalyzed exhaustive cross-coupling of di- and tetrasubstituted calix[4]arenes bearing chloropyrazine moieties. The extraction behavior of the synthesized ligands was studied on Am–Eu mixtures under acidic feed conditions similar to those prevailing in nuclear wastes. Phosphorylpyrazine-bearing extractants exhibited a very high acid resistivity and a high affinity for americium giving *D* values as high as 794 at pH 1. The synergistic effect of the chlorinated cobalt bis(dicarbollide) anion $[(B_9C_2H_8Cl_3)_2Co]^-$ (CCD-anion), as well as the effect of the calix[4]arene platform compared to monovalent ligands, was investigated. The presence of 1 mM CCD resulted in a 10^5 times increase in the *D* value.

Introduction

Since their discovery, calixarenes have become widely employed as platforms for molecular and ionic recognition, enzyme mimicking, and in many other domains of supramolecular chemistry.[1] The high level of preorganization and the well understood conformational behavior of calix[4]arenes have boosted the development of highly efficient and selective calixarene-based extracting agents.[2] The attachment of monovalent ligating units to a rigid scaffold (such as calix[4]arene) is known to give a certain degree of preorganization to a resulting multivalent ligand favoring metal complexation. On the other hand, ligand multivalency[3] results in a stronger binding than that is expected from the same number of monovalent units. The use of the multivalency effect to improve the extractant's properties has become quite popular in the field of actinide (An(III))–lanthanide (Ln(III)) separation for nuclear waste remediation.[4] A large enhancement of the metal ion extractability was observed for CMPO-,[5] DGA-,[6–8] phosphoryl-,[9–11] and diamide[12]-functionalized calix[4]arenes compared to the respective monovalent ligands.

Recently, a solvent extraction process based on heterocyclic polynitrogen ligands,[13] called Selective ActiNide EXtraction (SANEX), has been proposed and successfully tested for An(III)–Ln(III) separation from 1 M nitric acid solutions.[14] Moreover, it was found that supramolecular calixarene-based ligands incorporating heterocyclic N-donor units are generally the most efficient in the extraction of both actinides and lanthanides.[11,12] However, pyridine-based ligands, such as picolinamide-bearing calixarenes, being good extractants, display moderate to low selectivities towards actinides over lanthanides.[15,16] Due to the decreased basicity of nitrogen in pyrazine compared to pyridine one should expect more pronounced discrimination of lanthanides over actinides in the extraction process, since the latter are known to be the softer cations.[17,18] Recently,[19] we have found that appropriately functionalized monovalent water-soluble pyrazine-based ligands exhibit a very good selectivity and affinity towards americium over europium in the back-extraction process. At the same time, pyrazine-based ligands with lipophilic diphenylphosphoryl and dioctylcarbamoyl groups failed to extract trivalent f-block metal cations into a non-polar organic phase, presumably due to the lack of lipophilicity.[19] The idea of the present work to employ the *p-tert*-butylcalix[4]arene platform comprises two presumable improvements: to enhance the ligand binding *via* multivalency and to increase the extractant lipophilicity.

The traditional approach to obtain functionalized calix[4]arenes bearing ionophores focuses on a convergent synthesis strategy that involves the independent synthesis of an ionophore fragment followed by coupling it to the calixarene

[a] *Laboratory of Molecular Nanofabrication, MESA+ Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands. E-mail: w.verboom@utwente.nl*
[b] *Radiochemistry Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400085, India*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2nj40791d

platform in the final step. However, the convergent strategy is simply not applicable to the synthesis of most of the presented extractants due to incompatibility of the functional groups of the reactants. Bearing various functionalities, both reactive towards amines and phenols, makes it impossible to achieve the desired selectivity. On the other hand, a divergent synthesis is typically associated with problems such as incomplete reaction and the use of a vast excess of reagents to accomplish full functionalization that complicate the purification of the final product.

In the present paper we report the synthesis of novel calix[4]arene-based extractants employing a divergent strategy based on a stepwise build-up of the ionophore groups on the platform. The drawbacks of the divergent synthesis, described above, were mostly overcome by employing (or *in situ* generating) highly reactive alkylating and acylating agents. Special attention is paid to the palladium-catalyzed exhaustive cross-coupling of di- and tetrafunctionalized calix[4]arenes, bearing a chloropyrazine moiety, with diphenylphosphine as a remarkable example of autocatalysis. The extraction behavior and acid resistivity of the new multivalent ligands compared to the corresponding monovalent ones are studied to probe their potential applicability in nuclear waste treatment.

Results and discussion

Synthesis

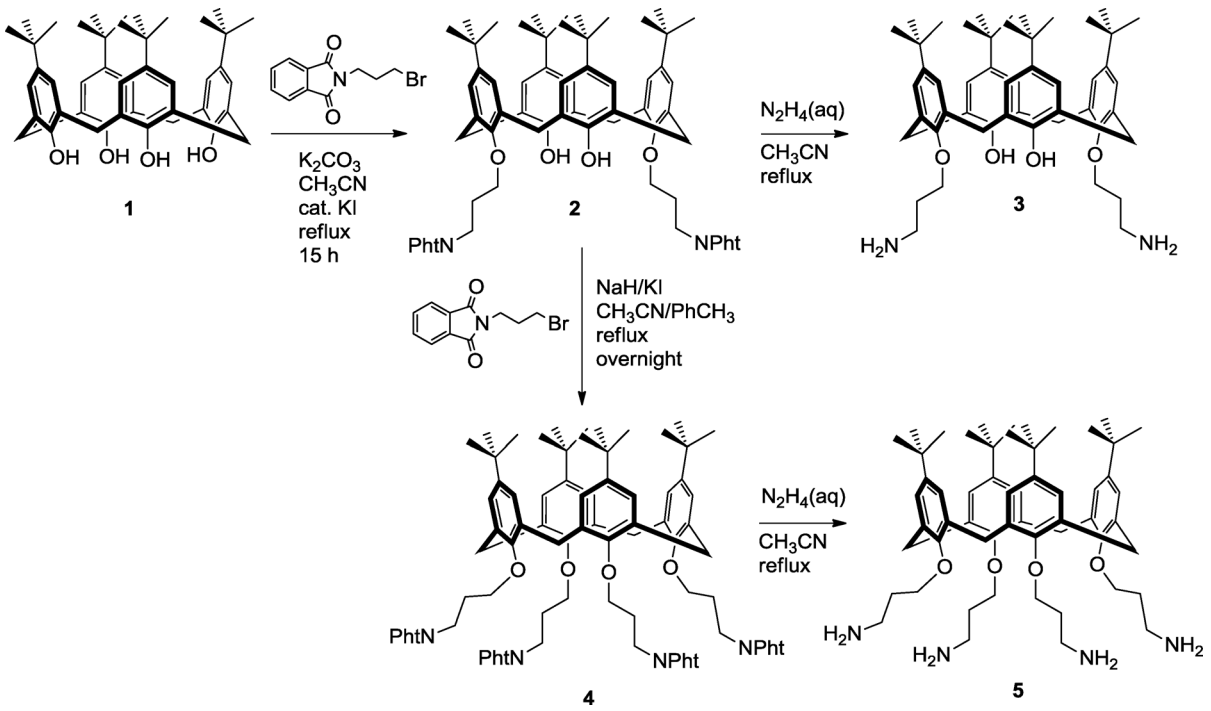
Narrow rim-difunctionalized calix[4]arenes are readily accessible *via* the standard procedure for selective 1,3-dialkylation of calix[4]arenes, developed by our group previously.[20] Dialkylated calixarene **2** was prepared by reaction of calix[4]arene **1** with bromopropylphthalimide in the presence of K_2CO_3. Interesting to note is that simple addition of a catalytic amount of KI decreased the reported[20] reaction time from 2 days to 15 h and at the same time increased the yield from 54% to almost quantitative. In order to obtain tetraalkylated *p-tert*-butylcalix[4]arene **4** in the cone conformation the second dialkylation of calix[4]arene **2** with bromopropylphthalimide was performed in the presence of NaH. Using also in this case Finkelstein conditions by the addition of KI, the reaction time decreased drastically, from 4 days to 20 h, and the yield of the tetraalkylated product **4** increased from 34 to 83%, compared to the procedure reported by Vatsouro *et al.*[21] Phthalimide deprotection with hydrazine gave 1,3-bis(aminopropyl)-*p-tert*-butylcalix[4]arene (**3**) and tetrakis(aminopropyl)-*p-tert*-butylcalix[4]-arene (**5**) in 95 and 87% yield, respectively (Scheme 1).[22]

The resulting aminopropylcalixarenes **3** and **5** were successfully acylated with 6-(dioctylcarbamoyl)pyrazine-2-carbonyl chloride (**6**) affording bis-diamide **8** and tetrakis-diamide **10** in 65% and 72% yield, respectively (Scheme 2). The corresponding acylation of **3** and **5** with 6-chloropyrazine-2-carbonyl chloride (**7**) gave calix[4]arenes **9** and **11**, bearing two and four 6-chloropyrazine-2-carboxamide moieties, in 87% and 92% yield, respectively. The somewhat lower yield of acylated products in the case of the difunctionalized calixarenes may be attributed to the presence of unprotected phenol groups.

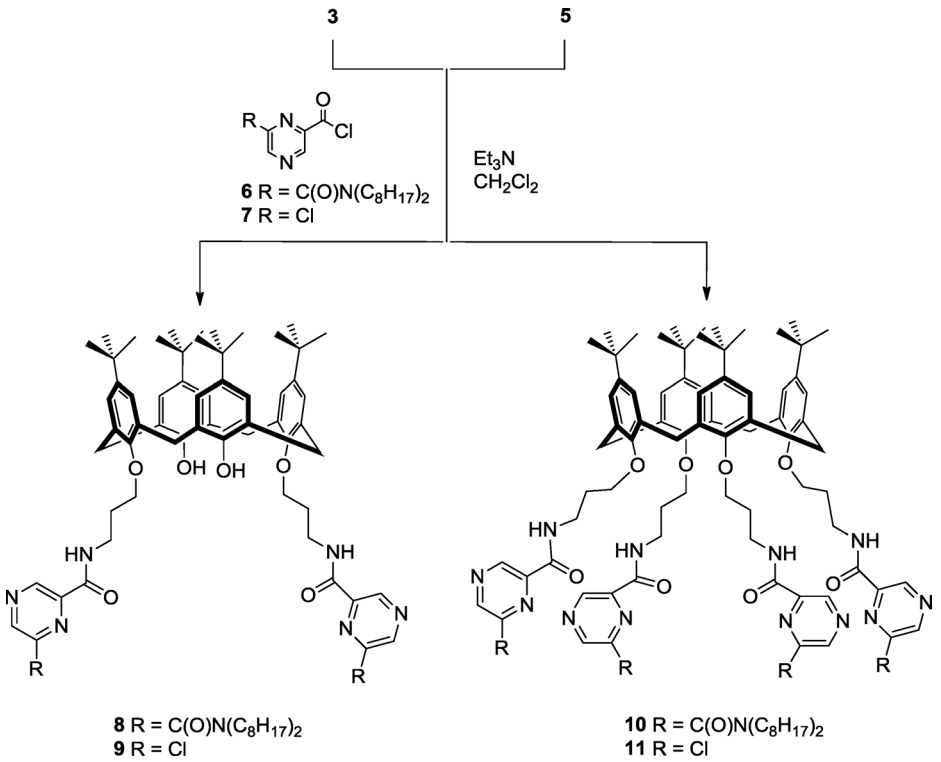
The pyrazine-containing calix[4]arenes **9** and **11** were subjected to further functionalization involving palladium-catalyzed coupling with various phosphorus pronucleophiles.

Palladium-catalyzed cross-coupling reactions with chloropyrazine bearing calix[4]arenes

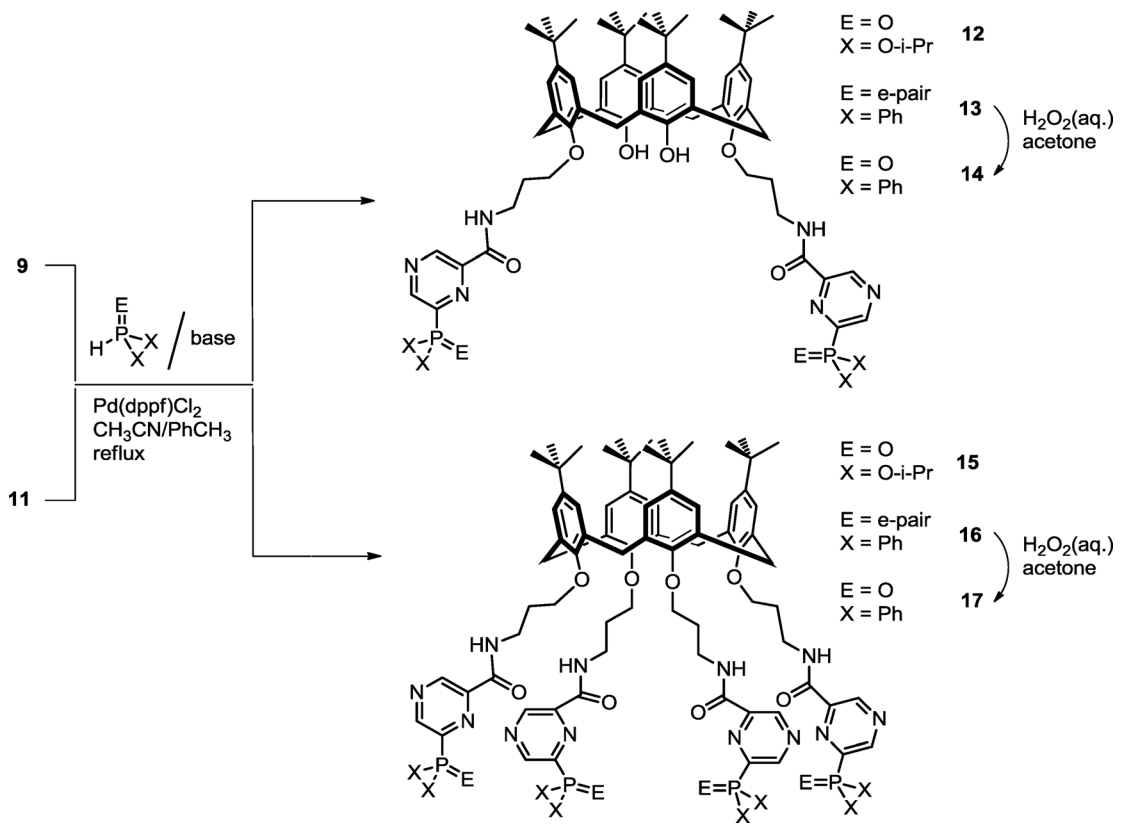
The palladium-catalyzed P–C cross-coupling reaction, developed earlier by our group,[19] was successfully performed on the bis- (**9**) and tetrakis(chloropyrazine)-functionalized calix[4]arenes **11**. To



Scheme 1 Synthesis of aminoalkylated calix[4]arenes.



Scheme 2 Acylation of aminopropylcalix[4]arenes **3** and **5**.



Scheme 3 Palladium-catalyzed P–C cross-coupling performed on calixarenes bearing chloropyrazine moieties.

the best of our knowledge it involves the first example of a cross-coupling reaction implemented on calix[4]arenes and presenting a versatile method for the terminal functionalization of platform molecules with multiple reacting sites. Reaction of **9** and **11** with a phosphorus coupling partner in the presence of a suitable base and a catalyst (1 mol% per chloropyrazine moiety) in a refluxing 1 : 1 mixture of acetonitrile and toluene afforded calix[4]arenes **12**, **13**, **15**, and **16** (Scheme 3).

$Pd(dppf)Cl_2$ was selected as the catalyst, since it was previously found to be the best catalyst for the coupling of simple chloropyrazines with dialkylphosphites that provides high yields of coupled products in cases where most of the other palladium phosphine complexes were not successful.[19] Reaction of **9** with 2.2 equivalents of diisopropyl phosphite in the presence of 2.2 equivalents of Huenig base and 2 mol% of $Pd(dppf)Cl_2$ for 72 h afforded calix[4]arene **12** in 79% yield. Performing the reaction of **11** under exactly the same conditions with 4.2 equivalents of diisopropyl phosphite in the presence of 4.2 equivalents of Huenig base and 4 mol% of $Pd(dppf)Cl_2$ for 8 days afforded calix[4]arene **15** in 61% yield.[23]

Using DBU as a stronger base for the less acidic diphenyl phosphine (1.05 equivalents of both per chloropyrazine moiety), and $Pd(OAc)_2$ as a catalyst (1 mol% per chloropyrazine moiety) the coupling reaction of **9** and **11** was accomplished in 30 h giving diphosphine **13** and tetraphosphine **16**. Subsequent oxidation of the phosphines **13** and **16** with hydrogen peroxide (1.5 equivalents per diphenylphosphino group) in acetone afforded the corresponding phosphine oxides **14** and **17** in 79 and 71% yield, respectively, calculated on **9** and **11**.

In contrast to simple chloropyrazines,[19] chloropyrazine-bearing calix[4]arenes exhibited a much higher reactivity towards diphenylphosphine than towards diisopropyl phosphite, displaying reaction times of 30 h and 8 days, respectively. Moreover, the yields of the corresponding bis- and tetrakis(diphenylphosphinopyrazine)-bearing calixarenes **13** and **16** were much higher than that is expected, *viz.* 52% yield at maximum as calculated from the 85% yield of the coupling reaction of non-tethered chloropyrazine carboxamide. In addition, it was found that cross-coupling reactions with diphenylphosphine proceed with the same high rate in the presence of bare $Pd(OAc)_2$ as the catalyst without an extra phosphine ligand. This increased reactivity may be attributed to an autocatalytic effect of the partially phosphine-functionalized calix[4]arene, which most probably complexes palladium, bringing the active catalyst into close proximity of the reacting functionality. In such a scenario, the interaction between the substrate and the catalytic center is better described as an intramolecular reaction, which is generally much faster than an intermolecular one because of the higher effective molarity, and which becomes possible after the first site has been functionalized.

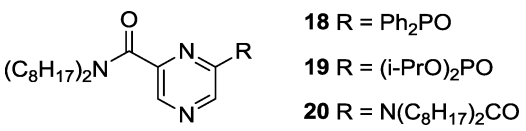
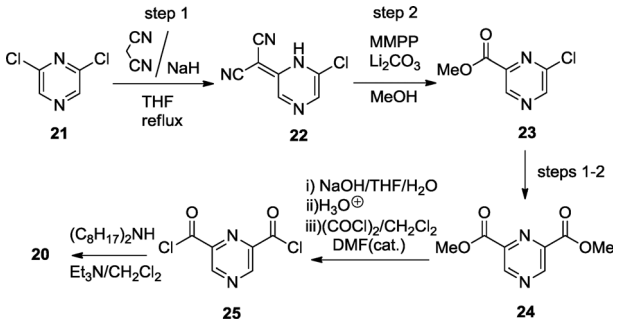


Chart 1 Monovalent pyrazines.



Scheme 4 Synthesis of diamidopyrazine **20**.

A series of monovalent pyrazines **18**, **19**, and **20**, mimicking the ligating units of the described calix[4]arenes, was prepared to compare the extraction behavior (Chart 1).

The synthesis of pyrazines **18** and **19** has already been described previously.[19] However, it was found that the reaction conditions can be simplified. The palladium-catalyzed P–C cross-coupling of simple chloropyrazines with diphenylphosphine can also be catalyzed by $Pd(OAc)_2$ without an additional ligand with the same yield as in the presence of the DPPF ligand. This indicates that diphenylphosphine acts as a ligand itself forming the active palladium catalyst *in situ*.

Diamidopyrazine **20** was prepared starting from 2,6-dichloropyrazine (**21**) (Scheme 4). Dimethyl pyrazine-2,6-dicarboxylate (**24**) can be prepared in one step by palladium-catalyzed carbonylative coupling in methanol at 40 atm of CO and 150 °C.[24] However, to avoid these conditions, we developed a simple stepwise procedure consisting of an aromatic nucleophilic substitution reaction and subsequent mild oxidation[25] of the resulting arylated malononitrile **22**. Treatment of **21** with 2 equivalents of malononitrile in the presence of NaH in THF, using Colbon's procedure for malonate compounds,[26] gave 2-(6-chloropyrazin-2(1*H*)-ylidene)malononitrile (**22**) in 95% yield. Oxidation of **22** with magnesium monoperoxophthalate (MMPP) as a mild oxidant in the presence of Li_2CO_3 occurred selectively at the malononitrile carbon instead of the pyrazine nitrogen with formation of the corresponding carbonyl cyanide, which was methanolized affording methyl 6-chloropyrazine-2-carboxylate (**23**) in 76% yield. Subsequent repetition of the above steps on

Table 1 Distribution ratios of Am(III) and Eu(III) for extractions by pyrazine-bearing calix[4]arene ligands **8**, **10**, **12**, **14**, **15**, and **17** and monovalent pyrazine ligands **18**, **19**, and **20** (5.0 mM in nitrobenzene) from aqueous HNO_3

	D_{Am}			D_{Eu}		
Ligand	0.01 M HNO_3	1 M HNO_3	3 M HNO_3	0.01 M HNO_3	1 M HNO_3	3 M HNO_3
8	0.001	0.001	0.001	0.001	0.001	0.001
10	0.001	0.001	0.001	0.001	0.001	0.001
12	0.09	0.01	0.01	0.06	0.01	0.01
14	0.48	0.03	0.19	0.46	0.03	0.17
15	0.001	0.001	0.05	0.001	0.001	0.03
17	0.06	0.44	13.5	0.06	0.45	14.0
18	0.06	0.01	0.002	0.03	0.002	0.003
19	0.001	0.001	0.001	0.01	0.02	0.006
20	0.01	0.001	0.001	0.12	0.002	0.003

Table 2 Distribution constants of Am(III), D_{Am}, for extractions using calix-pyrazine-based ligands **10**, **15**, and **17** and monovalent pyrazine ligands **18**, **19**, and **20**, containing 5.0 mM of the extractant in nitrobenzene in the absence or presence (1.0 mM) of CCD

	D_{Am} at 3 M HNO_3		D_{Am} at 0.1 M HNO_3		D_{Am} at 0.01 M HNO_3	
Ligand	Without CCD	With CCD	Without CCD	With CCD	Without CCD	With CCD
10	0.001	0.002	—	0.5	0.001	360
15	0.05	0.01	—	173	0.001	350
17	13.5	39.8	—	794	0.06	450
18	0.002	0.001			0.06	370
19	0.001	0.001			0.001	335
20	0.001	0.002			0.01	280

23 afforded dimethyl pyrazine-2,6-dicarboxylate (**24**) in 56% yield. The diester **24** was successfully converted into N^2,N^2,N^6,N^6-tetraoctylpyrazine-2,6-dicarboxamide (**20**) *via* pyrazine-2,6-dicarbonyl dichloride (**25**) in 92% yield.

Solvent extraction

Though *n*-dodecane is widely used for actinide separation studies, the pyrazine-based extractants were evaluated in polar diluents for solubility reasons (see for the solubility in different solvents the ESI†). The extraction data of the different ligands presented in Table 1 indicate for ligand **17** a reasonably high extraction with nitrobenzene as the diluent. However, moderate extraction was seen with PTMS (commercially known as FS-13) and almost no extraction with diluents such as chloroform and NPOE. Surprisingly, both Am(III) as well as Eu(III) extraction decreased substantially to almost zero when the substituent was changed from phosphoryl to either dioctylcarbamoyl (**8**) or diisopropyl phosphonate (**15**) (Table 1). It is also interesting to note that even with the pyrazine-bearing calix[4]arenes with two side arms containing phosphoryl groups (**14**), the extraction was significantly higher as compared to the other ligands (Table 1).

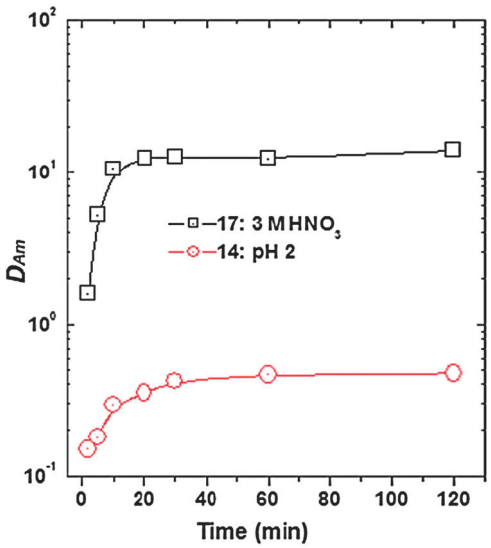


Fig. 1 Distribution constants for Am(III), D_{Am}, *vs.* time for the Am(III) extraction using 5.0 mM ligand in nitrobenzene at the given acidity.

Ligands **18**, **19**, and **20** hardly showed any extraction of the metal ions (Table 1). The use of chlorinated cobalt dicarbollide (CCD) as the auxiliary extractant to enable a synergistic effect on metal ion extraction was successful at 0.01 M HNO_3 (Table 2) (*vide infra*).

Extraction kinetics studies. The effect of the equilibration time on the Am(III) extraction was studied for both **14** and **17**. As will be discussed below, the extraction of Am(III) with **14** was higher at 0.01 M than at 3 M HNO_3 as the feed. Therefore, while 3 M HNO_3 was taken as the aqueous phase for **17**, 0.01 M HNO_3 was used for **14**. As shown in Fig. 1, the extraction kinetics was relatively slow and about 60 and 20 minutes were required for attaining equilibrium D_{Am} values with **14** and **17**, respectively. The kinetics data indicate that the extraction in the case of divalent ligand **14** requires coordination of two ligand molecules, compared to the tetravalent ligand **17** and hence takes more time. However, conformational changes or a difference in extraction mechanism may also play a role.

Effect of aqueous phase acidity. The effect of aqueous phase acidity was also investigated by carrying out extraction studies with all six pyrazine-bearing calix[4]arene ligands (**8**, **10**, **12**, **14**, **15**, and **17**) at three different acidities *viz.*, 0.01 M, 1 M, and 3 M HNO_3 and the results for Am(III) and Eu(III) extraction are listed in Table 1.

As discussed before, the extraction with the phosphoryl-substituted pyrazine-bearing calix[4]arenes resulted in significant extraction at 3 M HNO_3 and the calix[4]arene **14** with two side arms resulted in significantly lower *D* values than calix[4]arene **17** with four side arms. This is understandable, since **17** contains four pendent arms for complexation and consequently has a higher affinity for the metal ion than **14**, which has only two pendent arms. However, it is rather surprising that although the *D* values of **14** decreased upon changing the feed acidity from 3 M to 1 M HNO_3, an increase was seen when the acidity was further decreased to 0.01 M HNO_3 (Table 1). This can only be explained by the ion-pair extraction mechanism, by which metal cations are extracted into an organic phase accompanied by anions, and thus, effective extraction is achieved under highly acidic conditions. On the other hand, the higher metal ion extraction at lower acidity may be attributed to a contribution of the phenolic OH groups.

Nature of the extracted species. The nature of the extracted species was studied by carrying out Am(III) as well as Eu(III) extractions at varying concentrations of the extractants **14** and **17** at 0.01 M HNO_3 and 3 M HNO_3, respectively, as the aqueous phase. As shown in Fig. 2a, linear plots with slope values close to 1 were obtained for both Am(III) as well as Eu(III) extraction, when the concentration of **17** was varied from 5.0×10^{-4} to 5.0×10^{-3} M. These results suggest that 1 : 1 M : L complexes are formed with possibly three co-extracted nitrate ions acting as the counter anions. In view of the high dielectric constant of nitrobenzene ($\varepsilon_{20} = 35.7$), ion-pair complexed species are expected to be extracted and the following extraction equilibrium can be predicted:

$$M^{3+}{}_{aq.} + L_{org.} + 3NO_3^-{}_{aq.} \leftrightarrow (ML)^{3+}\cdot(NO_3^-)_{3org.} \quad (1)$$

where M and L represent the metal (Am or Eu) and the ligand, respectively, and the subscripts 'aq.' and 'org.' refer to the aqueous and the organic phases, respectively.

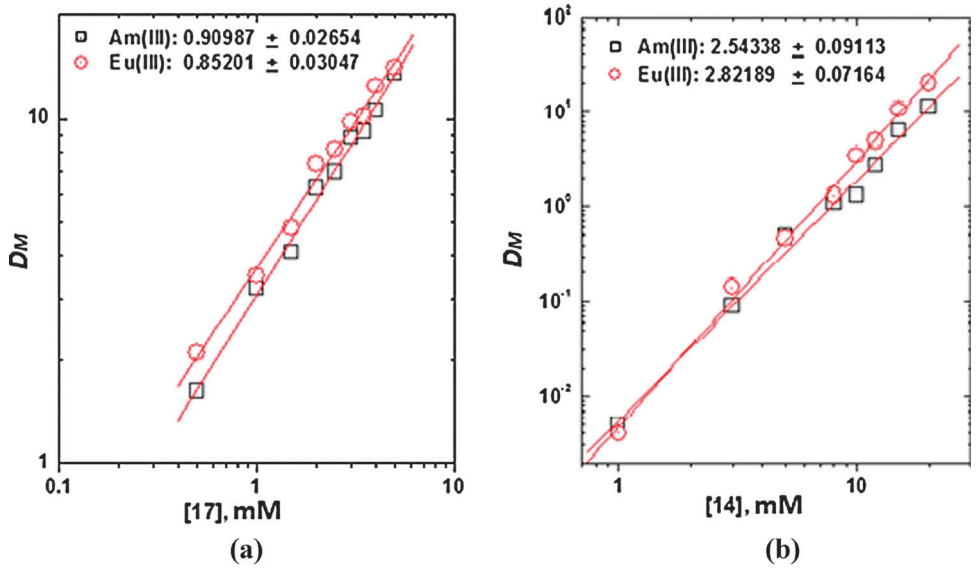


Fig. 2 Distribution ratios for Am(III) and Eu(III) *vs.* ligand concentration at the given acidities: (a) extractant **17** at 3 M HNO_3 and (b) extractant **14** at 0.01 M HNO_3.

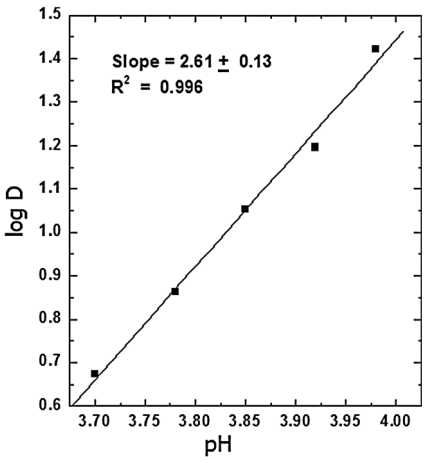


Fig. 3 Distribution ratios for Am(III) and Eu(III) *vs.* aqueous phase pH using 5.0 mM of extractant **14**.

The ligand concentration variation studies carried out with **14** indeed proved the association of three ligand units in the extracted species (Fig. 2b). pH variation experiments showed a sharp rise in the extraction profile for Am(III) at lower acidities (see Fig. S1, ESI†).

pH variation experiments using 5.0 mM **14** gave linear extraction profiles with slope values close to 3 (Fig. 3). This can only be explained by the following extraction equilibrium:

$$M^{3+}{}_{aq.} + 3HL_{org.} \leftrightarrow (ML_3)_{org.} + 3H^{+}{}_{aq.} \qquad (2)$$

The ligand concentration and pH dependencies on the Am extraction with fractional slope values indicate extraction of 1 : 3 metal : ligand species with a partial contribution from the 1 : 2 species.

Studies carried out with CCD as the auxiliary ligand. Studies with calixarene-based picolinamide extractants have shown a promising extraction of Am(III) and Eu(III) in the presence of Br-Cosan in nitrophenyl hexyl ether (NPHE) as the diluent.[27] In another recent study,[16] calix[6]arene picolinamide extractants with Br-Cosan in a mixture of NPHE and acetophenone as the diluent resulted in a much higher metal ion extraction, although the separation factor (SF) values have become lower, compared to those in the previous report. The separation factors depended on the Br-Cosan concentration. Similar extraction studies were carried out in the present work in nitrobenzene as the diluent. Solvent extraction studies were carried out using a mixture of the pyrazine-bearing calix[4]arenes **10**, **15**, **17** and monovalent ligands **18**, **19**, and **20** along with chlorinated cobalt dicarbollide (CCD) as the auxiliary ligand. The D_{Am} values obtained with the synergistic extraction system are listed in Table 2. The D_{Am} values show a significant enhancement (about 3 times) in the presence of CCD at 3 M HNO_3 with **17** as the primary extractant, while there was no change in the D_{Am} values with both **10** and **15**. On the other hand in all cases, a very high, about 10^4 to 10^5 times, enhancement in the extraction of Am(III) was seen when the experiments were carried out at 0.01 M HNO_3 in the presence of 1.0 mM CCD. The role of the CCD concentration in the metal ion extraction was investigated at 0.1 M HNO_3 and the results for both Am(III) and Eu(III) extraction along with the separation factor values are presented in Fig. 4. It shows an increasing trend for the extraction of both metal ions with increasing CCD concentration. The SF values, however, depend on the nature of the primary extractant. The SF values changed marginally with the CCD concentration when **15** was used as the primary extractant (Fig. 4b). On the other hand, while an increasing trend in SF with increasing CCD concentration was seen for **10** (Fig. 4a), there is an opposite trend when **17** (Fig. 4c) was used as the primary extractant. The results are in line with those of the calix-picolinamide ligands mentioned above.

Conclusions

An effective and versatile stepwise synthetic strategy has been developed for the preparation of a novel class of multivalent pyrazine-based calix[4]arene extractants, including palladium-catalyzed exhaustive

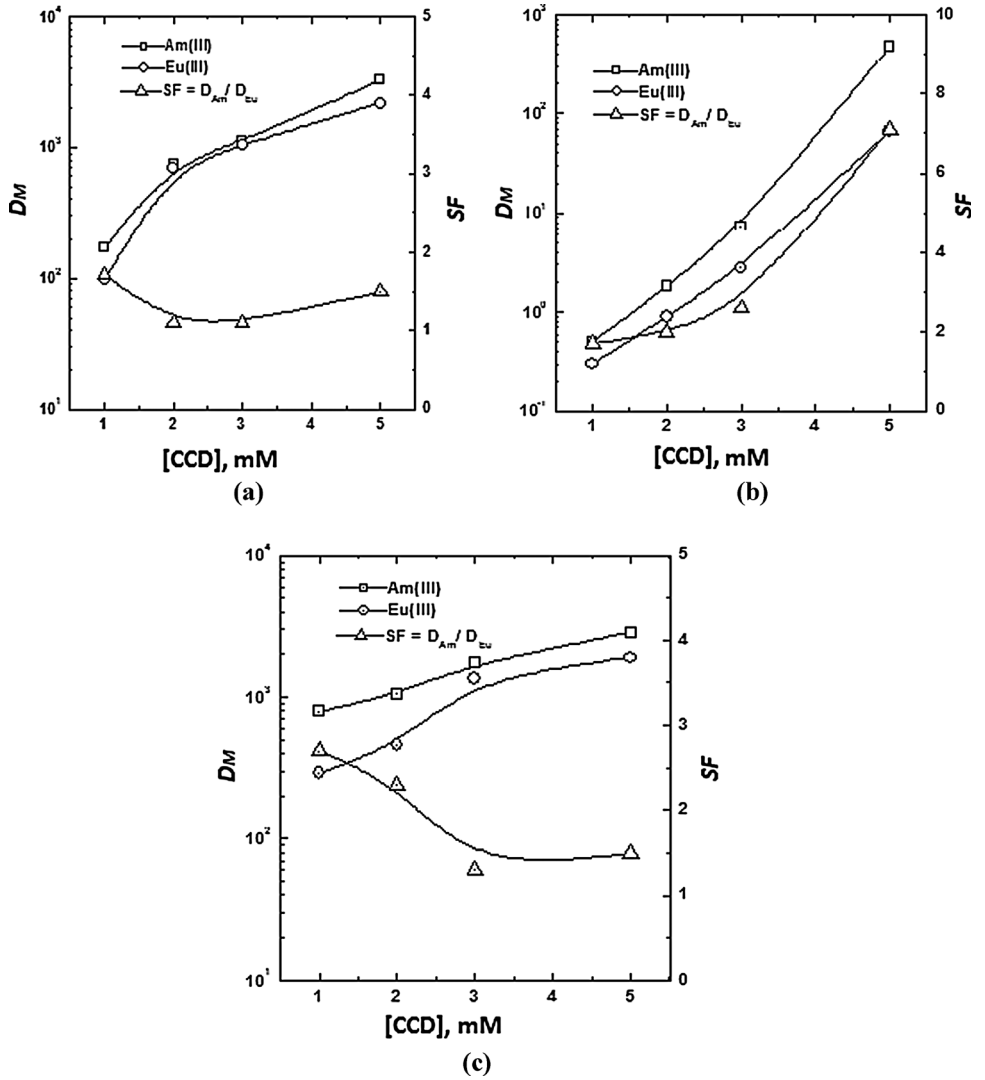


Fig. 4 Distribution ratios of Am(III), D_{Am}, and Eu(III), D_{Eu}, and separation factors, $SF_{Am/Eu}$, for extractions using 5.0 mM ligand in the presence of CCD; diluent: nitrobenzene; aqueous phase: 0.1 M HNO_3; (a) **10**; (b) **15**; (c) **17**.

cross-coupling. The reaction rate in the particular case of coupling with $HPPh_2$, being much higher than that expected from statistical probability, indicates an autocatalytic effect of the substrate molecule that is able to coordinate an active catalyst species. The newly synthesized multivalent ligands revealed a very high affinity towards f-block metal ions and a good selectivity for Am(III) with a maximum SF value close to 7 in the presence of a synergist (CCD), preserving a good extractability even in highly acidic solutions up to 3 M HNO_3 (in the case of **17**). In the case of **17** the effect of grouping together the ligating sites on the calix[4]arene platform was reflected in the exceptionally high enhancement of 10^4 to 10^5 times in metal ion extraction, compared to the corresponding monovalent ligands, demonstrating that multivalency is a powerful way of making more potent extractants.

Experimental

The solvents, catalysts, and all reagents were obtained from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. ^{1}H NMR chemical shift values (300 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ = 7.257). ^{13}C NMR chemical shift values (75 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ = 77.0 ppm). Infrared spectra were taken on a Thermo Scientific spectrometer. Electrospray ionization (positive mode) mass spectra were recorded on a WATERS LCT mass spectrometer. Silica gel-60 (mesh 230–400 ASTM) was used for column chromatography. Calixarenes **8**, **10**, **12**, and **15**, purified by column chromatography, were additionally dried from the residual solvent by azeotropic distillation of CH_2Cl_2 from a solution of a compound.

Bis(3-*N*-phthalimidopropyl)-*p*-*tert*-butylcalix[4]arene (2) (improved procedure)

To a suspension of *p*-*tert*-butylcalix[4]arene (**1**) (13.0 g, 20 mmol), anhydrous K_2CO_3 (5.6 g, 40 mmol), and *N*-(bromopropyl)phthalimide (12.1 g, 45 mmol) in CH_3CN (500 mL)

a small pinch of KI was added and the resulting mixture was refluxed for 15 h. After evaporation of the solvent, the mixture was taken up in $CHCl_3$ (500 mL) and washed with 1 M HCl (2 × 100 mL) and brine (2 × 100 mL). The crude reaction mixture was recrystallized from $CHCl_3$/MeOH to afford pure **2** as a white solid (20.1 g, 98%). The spectral characteristics of the obtained compound were consistent with those reported in the literature.[22]

Tetrakis(3-*N*-phthalimidopropyl)-*p*-*tert*-butylcalix[4]arene (4) (improved procedure)

A suspension of calix[4]arene **2** (10.2 g, 10 mmol) and NaH (60% in oil, 0.9 g, 22 mmol) in dry toluene (200 mL) was stirred for 1 h, and then a solution of *N*-(bromopropyl)phthalimide (5.6 g, 21 mmol) in dry CH_3CN (200 mL) and a small pinch of KI were added to the reaction mixture. The resulting mixture was refluxed for 20 h. After evaporation of the solvent, the mixture was taken up in $CHCl_3$ (200 mL), washed with 1 M HCl (100 mL) and brine (100 mL). The crude reaction mixture was recrystallized from $CHCl_3$/MeOH to afford pure **4** as a white solid (11.6 g, 83%). The spectral characteristics of the obtained compound were consistent with those reported in the literature.[22]

Bis(3-(6-dioctylcarbamoylpyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (8)

A solution of bis(aminopropyl)calix[4]arene (**3**) (2.3 g, 3 mmol) and Et_3N (1.8 mL, 12 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a solution of 6-dioctylcarbamoylpyrazine-2-carbonyl chloride (**6**; 6 mmol), freshly prepared from 6-dioctylcarbamoylpyrazine-2-carboxylic acid (2.1 g, 6.0 mmol) and oxalyl chloride, in CH_2Cl_2 (60 mL) under vigorous stirring. The resulting mixture was stirred for 15 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and hexanes (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (EtOAc/$CHCl_3$, 40 : 60) affording pure **8** as an amber oil (3.0 g, 65%). Mp 59–62 °C. ^{1}H NMR: δ = 9.38 (s, 2H, PyzH), 8.90 (s, 2H, PyzH), 8.13 (t, 2H, J = 6.0 Hz, NH), 7.71 (s, 2H, ArOH), 7.04 (s, 4H, ArH), 6.86 (s, 4H, ArH), 4.25 (d, 4H, J = 12.9 Hz, $ArCH_2Ar$), 4.07 (t, 4H, J = 6.2 Hz, $ArOCH_2CH_2$), 3.96 (q, 4H, J = 6.2 Hz, CH_2CH_2NH), 3.40 (t, 4H, J = 7.7 Hz, $NCH_2C_7H_{16}$), 3.32 (d, 4H, J = 12.9 Hz, $ArCH_2Ar$), 3.14 (t, 4H, J = 7.7 Hz, $NCH_2C_7H_{15}$), 2.36 (quintet, 4H, J = 6.2 Hz, $OCH_2CH_2CH_2N$), 1.66 (m, 4H, octyl), 1.50–0.80 (m, 56H, octyl), 1.28 and 1.01 (s, 18H, *t*-Bu). ^{13}C NMR: δ = 165.9, 163.2, 156.6, 149.7, 148.6, 147.5, 142.6, 142.0, 132.9, 127.9, 126.1, 125.9, 125.6, 125.4, 73.4, 46.5, 46.3, 34.3, 34.1, 32.1, 31.9, 31.3, 29.6, 29.5, 29.4, 29.3, 26.8, 22.9, 22.8, 14.4. IR (ν_{max}/cm^{-1}): 2953, 2925, 2855, 1676, 1635, 1522, 1499, 1461, 1362, 1298, 1193, 1167, 1123, 1019, 909, 871, 732, 669. HRMS-TOF (m/z): $[M + H]^+$ calcd 1511.0906, found 1511.4041.

Bis(3-(6-chloropyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (9)

A solution of bis(aminopropyl)calix[4]arene (**3**) (2.3 g, 3 mmol) and Et_3N (1.8 mL, 12 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a solution of 6-chloropyrazine-2-carbonyl chloride (**7**; 6 mmol), freshly prepared from 6-chloropyrazine-2-carboxylic acid (0.8 g, 6.0 mmol) and oxalyl chloride, in CH_2Cl_2 (60 mL) under vigorous stirring. The resulting mixture was stirred for 2 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4, the solution was passed through a short plug of silica and then all the volatiles were removed *in vacuo*. The crude product was crystallized from CH_2Cl_2–hexane affording pure **9** (2.8 g, 87%). Mp 115–120 °C. ^{1}H NMR: δ = 9.21 (s, 2H, PyzH), 8.61 (s, 2H, PyzH), 8.36 (t, 2H, J = 6.0 Hz, NH), 7.70 (s, 2H, ArOH), 7.01 and 6.80 (s, 4H, ArH), 4.21 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 4.05 (t, 4H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.93 (q, 4H, J = 6.0 Hz, CH_2CH_2NH), 3.30 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 2.39 (quintet, 4H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.25 and 0.97 (s, 18H, *t*-Bu). ^{13}C NMR: δ = 162.5, 150.6, 148.6, 147.8, 147.5, 147.4, 144.4, 142.0, 132.9, 129.0, 127.8, 125.9, 125.8, 125.5, 125.3, 34.3, 34.1, 31.9, 31.8, 31.3, 31.2, 31.1. IR (ν_{max}/cm^{-1}): 2954, 2868, 1670, 1521, 1484, 1362, 1298, 1193, 1168, 1124, 1011, 909, 872, 731, 669. HRMS-TOF (m/z): $[M + H]^+$ calcd 1044.5002, found 1044.9526.

Tetrakis(3-(6-dioctylcarbamoylpyrazine-2-carboxamido)propyl)-*p*-*tert*-butyl calix[4]arene (10)

A solution of tetrakis(aminopropyl)calix[4]arene (**3**) (2.6 g, 3 mmol) and Et_3N (3.6 mL, 24 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a solution of 6-dioctylcarbamoylpyrazine-2-carbonyl chloride (**6**; 12 mmol), freshly prepared from 6-dioctylcarbamoylpyrazine-2-carboxylic acid (4.2 g, 12.0 mmol) and oxalyl chloride, in CH_2Cl_2 (120 mL) under vigorous stirring. The resulting mixture was stirred for 15 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and hexanes (50 mL). The organic phase was dried over Na_2SO_4, the solution was passed through a short plug of silica and then all the volatiles were removed *in vacuo*. The crude product was purified by column chromatography (EtOAc/$CHCl_3$, 40 : 60) affording pure **10** as an amber oil (5.1 g, 72%). ^{1}H NMR: δ = 9.37 (s, 4H, PyzH), 8.87 (s, 4H, PyzH), 8.11 (t, 4H, J = 5.8 Hz, NH), 6.76 (s, 8H, ArH), 4.36 (d, 4H, J = 12.4 Hz, $ArCH_2Ar$), 3.98 (t, 8H, J = 6.9 Hz, $ArOCH_2CH_2$), 3.67 (q, 8H, J = 6.9 Hz, CH_2CH_2NH), 3.43 and 3.22 (t, 8H, J = 7.2 Hz, $NCH_2C_7H_{15}$), 3.13 (d, 4H, J = 12.4 Hz, $ArCH_2Ar$), 2.35 (quintet, 4H, J = 6.9 Hz, $OCH_2CH_2CH_2N$), 1.68–0.80 (m, 120H, octyl), 1.07 (s, 36H, *t*-Bu). ^{13}C NMR: δ = 166.0, 162.9, 153.4, 148.5, 144.9, 143.0, 133.7, 125.9, 125.4, 125.2, 73.1, 34.0, 32.1, 31.9, 31.6, 29.6, 29.5, 29.4, 29.3, 26.9, 22.9, 22.8, 14.4. IR (ν_{max}/cm^{-1}): 2923, 2854, 1670, 1636, 1522, 1487, 1376, 1362, 1299, 1196, 1167, 1122, 1019, 912, 870, 721, 669. HRMS-TOF (m/z): $[M + H]^+$ calcd 2372.7555, found 2372.7666.

Tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (11)

A solution of tetrakis(aminopropyl)calix[4]arene (**3**) (2.6 g, 3 mmol) and Et_3N (3.6 mL, 24 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a solution of 6-chloropyrazine-2-carbonyl chloride (**7**; 12 mmol), freshly prepared from 6-chloropyrazine-2-carboxylic acid (1.6 g, 12.0 mmol) and oxalyl chloride (2.4 mL)

in CH_2Cl_2 (15 mL), in CH_2Cl_2 (120 mL) under vigorous stirring. The resulting mixture was stirred for 15 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL) three times. The organic phase was dried over Na_2SO_4, the resulting solution was passed through a short plug of silica and the solvent was removed *in vacuo*. The crude product was crystallized from CH_2Cl_2–hexane affording pure **11** (4.0 g, 92%). ^{1}H NMR ($CDCl_3$): δ = 9.33 (s, 4H, PyzH), 8.65 (s, 4H, PyzH), 8.41 (t, 4H, J = 6.0 Hz, NH), 6.73 (s, 8H, ArH), 4.31 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 3.92 (t, 8H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.68 (q, 8H, J = 6.0 Hz, CH_2CH_2NH), 3.14 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 2.39 (quintet, 8H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.07 (s, 36H, *t*-Bu). ^{13}C NMR: δ = 162.4, 162.3, 153.4, 147.8, 147.7, 144.5, 142.5, 142.4, 133.8, 133.7, 133.6, 133.5, 125.4, 125.3, 125.2, 123.0, 73.1, 72.8, 34.1, 31.6. IR (ν_{max}/cm^{-1}): 2954, 2868, 1668, 1533, 1481, 1390, 1362, 1298, 1193, 1168, 1131, 1011, 912, 871, 733, 669. HRMS-TOF (m/z): $[M + H]^+$ calcd 1440.5684, found 1440.5892.

General procedure for the palladium-catalyzed P–C coupling of bis- and tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)-*p-tert*-butylcalix[4]arenes with $HPO(O\text{-}i\text{-}Pr)_2$. Formation of 12 and 15

To a solution of bis- or tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)calix[4]arene (1 mmol) and $Pd(dppf)Cl_2$ (1 mol% per chloropyrazine moiety) in a CH_3CN–toluene (1 : 1) mixture (50 mL) $HPO(O\text{-}i\text{-}Pr)_2$ (1.1 equiv. per chloropyrazine moiety) and $i\text{-}Pr_2NEt$ (1.1 equiv. per chloropyrazine moiety) were subsequently added. The resulting mixture was refluxed for 3 (**12**) and 8 days (**15**), respectively, and then the solvent was removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and all the volatiles were removed *in vacuo* to give the crude **12** and **15**. The crude products were purified by column chromatography (neat EtOAc) affording pure compounds as brown oils which solidified upon standing.

Bis(3-(6-(diisopropylphosphono)pyrazine-2-carboxamido)-propyl)-*p-tert*-butylcalix[4]arene (12)

Yield 1.0 g, 79%. ^{1}H NMR: δ = 9.47 (d, 2H, $^3J_{HP}$ = 3.6 Hz, PyzH), 9.16 (s, 2H, PyzH), 8.24 (t, 2H, J = 5.9 Hz, NH), 7.52 (s, 2H, ArOH), 7.04 (s, 4H, ArH), 6.84 (s, 4H, ArH), 4.92–4.79 (m, 4H, $CH(CH_3)_2$), 4.26 (d, 4H, J = 12.9 Hz, $ArCH_2Ar$), 4.09 (t, 4H, J = 6.6 Hz, $ArOCH_2CH_2$), 3.94 (q, 4H, J = 6.6 Hz, CH_2CH_2NH), 3.34 (d, 4H, J = 12.9 Hz, $ArCH_2Ar$), 2.40 (quintet, 4H, J = 6.6 Hz, $OCH_2CH_2CH_2N$), 1.38 and 1.28 (d, 12H, J = 6.2 Hz, $CH(CH_3)_2$), 1.27 and 0.98 (s, 18H, *t*-Bu). ^{13}C NMR: δ = 162.9, 153.3, 147.3, 146.2, 133.4, 132.9, 127.9, 123.0, 122.0, 73.5–72.0 (multiplet), 34.2, 32.0, 31.9, 31.3, 31.2, 24.5–23.8 (multiplet). IR (ν_{max}/cm^{-1}): 2962, 1671, 1541, 1485, 1387, 1376, 1362, 1298, 1249, 1197, 1124, 1102, 990, 910, 872, 731, 669. HRMS-TOF (m/z): $[M + Na]^+$ calcd 1326.6806, found 1326.6843.

Tetrakis(3-(6-(diisopropylphosphono)pyrazine-2-carboxamido)-propyl)-*p-tert*-butylcalix[4]arene (15)

Yield 1.2 g, 61%. ^{1}H NMR: δ = 9.47 (d, 4H, $^3J_{HP}$ = 3.5 Hz, PyzH), 9.14 (s, 4H, PyzH), 8.26 (t, 4H, J = 6.0 Hz, NH), 6.75 (s, 8H, ArH), 4.92–4.80 (m, 8H, $CH(CH_3)_2$), 4.36 (d, 4H, J = 12.4 Hz, $ArCH_2Ar$), 3.98 (t, 8H, J = 7.2 Hz, $ArOCH_2CH_2$), 3.71 (q, 8H, J = 7.2 Hz, CH_2CH_2NH), 3.13 (d, 4H, J = 12.4 Hz, $ArCH_2Ar$), 2.36 (quintet, 8H, J = 7.2 Hz, $OCH_2CH_2CH_2N$), 1.37 and 1.28 (d, 24H, J = 6.1 Hz, $CH(CH_3)_2$), 1.06 (s, 36H, *t*-Bu). ^{13}C NMR: δ = 162.6, 153.5, 153.4, 148.3, 144.9, 144.7, 144.5, 133.7, 133.6, 125.4, 125.2, 123.0, 73.0–72.3 (multiplet), 37.4, 34.0, 31.8, 31.4, 31.2, 30.7, 30.6, 24.6–23.5 (multiplet). IR (ν_{max}/cm^{-1}): 2963, 1670, 1541, 1485, 1387, 1362, 1299, 1250, 1198, 1136, 1123, 1103, 989, 730, 669. HRMS-TOF (m/z): $[M + 2H]^{2+}$ calcd 979.4864, found 979.5500.

General procedure for the palladium catalyzed P–C coupling of bis- and tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)calix-[4]arenes with $HPPh_2$. Formation of 13 and 16

To a solution of bis- or tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)calix[4]arene (1 mmol) and $Pd(OAc)_2$ (1 mol% per chloropyrazine moiety) in a CH_3CN–toluene (1 : 1) mixture (50 mL) $HPPh_2$ (1 equiv. per chloropyrazine moiety) and DBU (1 equiv. per chloropyrazine moiety) were subsequently added. The resulting mixture was refluxed for 30 h and then the solvent was removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and all the volatiles were removed *in vacuo*. The resulting crude phosphines **13** and **16** were fully characterized as their phosphine oxides **14** and **17**, respectively.

Bis(3-(6-(diphenylphosphino)pyrazine-2-carboxamido)propyl)-*p-tert*-butylcalix[4]arene (13)

^{1}H NMR: δ = 9.17 (s, 2H, PyzH), 8.39 (s, 2H, PyzH), 8.08 (t, 2H, J = 6.0 Hz, NH), 7.80 (s, 2H, ArOH), 7.39–7.22 (m, 20H, Ph), 7.01 and 6.88 (s, 4H, ArH), 4.15 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 3.92 (t, 4H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.80 (q, 4H, J = 6.0 Hz, CH_2CH_2NH), 3.21 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 2.22 (quintet, 4H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.23 and 1.04 (s, 18H, *t*-Bu).

Tetrakis(3-(6-(diphenylphosphino)pyrazine-2-carboxamido)propyl)-*p-tert*-butylcalix[4]arene (16)

^{1}H NMR: δ = 9.13 (s, 4H, PyzH), 8.32 (s, 4H, PyzH), 8.05 (t, 4H, J = 6.0 Hz, NH), 7.40–7.15 (m, 40H, Ph), 6.73 (s, 8H, ArH), 4.21 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 3.79 (t, 8H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.48 (q, 8H, J = 6.0 Hz, CH_2CH_2NH), 3.05 (d, 4H, J = 12.0 Hz, $ArCH_2Ar$), 1.99 (quintet, 8H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.07 (s, 36H, *t*-Bu).

Oxidation of phosphines 13 and 16. Formation of 14 and 17

A solution of the crude phosphine and H_2O_2 (30% aqueous, 1.5 equiv., per PPh_2 group) in acetone (25 mL) was stirred for 12 h and then 1 M HCl (10 mL) was added. After stirring the reaction mixture for 30 min all the volatiles were removed *in vacuo* and the residue was partitioned between H_2O (30 mL) and $CHCl_3$ (30 mL). The organic phase was dried over Na_2SO_4, giving the corresponding phosphine oxides after evaporation of the solvent as yellow oils. The crude products were purified by numerous crystallizations from CH_2Cl_2–hexane affording the desired compounds as pale yellow powders.

Bis(3-(6-(diphenylphosphoryl)pyrazine-2-carboxamido)propyl)-*p-tert*-butylcalix[4]arene (14)

Total yield (based on **9**) 1.1 g, 79%. Mp 63–66 °C. ^{1}H NMR: δ = 9.40 (d, 2H, $^3J_{HP}$ = 3.3 Hz, PyzH), 9.38 (d, 2H, $^5J_{HP}$ = 1.2 Hz, PyzH), 7.83 (t, 2H, J = 6.1 Hz, NH), 7.80–7.70 (m, 8H, Ph), 7.52–7.30 (m, 14H, Ph + ArOH), 6.98 (s, 4H, ArH), 6.80 (s, 4H, ArH), 4.15 (d, 4H, J = 12.8 Hz, $ArCH_2Ar$), 3.97 (t, 4H, J = 6.1 Hz, $ArOCH_2CH_2$), 3.86 (q, 4H, J = 6.1 Hz, CH_2CH_2NH), 3.18 (d, 4H, J = 12.8 Hz, $ArCH_2Ar$), 2.27 (quintet, 4H, J = 6.1 Hz, $OCH_2CH_2CH_2N$), 1.25 and 0.99 (s, 18H, *t*-Bu). ^{13}C NMR: δ = 162.6, 150.6, 149.6, 149.1, 147.5, 146.0, 144.5, 144.3, 142.0, 133.0, 132.9, 132.8, 132.3, 131.4, 129.9, 129.1, 128.9, 128.8, 128.7, 127.7, 126.0, 125.8, 125.5, 125.4, 34.3, 34.1, 31.9, 31.3. IR (ν_{max}/cm^{-1}): 2955, 1677, 1522, 1485, 1437, 1393, 1362, 1298, 1178, 1120, 1099, 1016, 908, 873, 731, 696, 669. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 1375.6530, found 1375.6530.

Tetrakis(3-(6-(diphenylphosphoryl)pyrazine-2-carboxamido)-propyl)-*p-tert*-butylcalix[4]arene (17)

Total yield (based on **11**) 1.5 g, 71%. Mp 70 °C (dec). ^{1}H NMR: δ = 9.29 (d, 4H, $^3J_{HP}$ = 3.0 Hz, PyzH), 9.24 (s, 4H, PyzH), 7.95 (t, 4H, J = 6.1 Hz, NH), 7.82–7.66 (m, 16H, Ph), 7.53–7.30 (m, 24H, Ph), 6.76 (s, 8H, ArH), 4.25 (d, 4H, J = 8.3 Hz, $ArCH_2Ar$), 3.83 (t, 8H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.52 (q, 8H, J = 6.0 Hz, CH_2CH_2NH), 3.05 (d, 4H, J = 8.3 Hz, $ArCH_2Ar$), 2.19 (quintet, 8H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.07 (s, 36H, *t*-Bu). ^{13}C NMR: δ = 162.5, 153.3, 149.1, 145.1, 144.8, 144.6, 133.7, 133.1, 133.0, 132.9, 132.8, 132.7, 132.6, 132.5, 132.3, 131.2, 129.8, 129.2, 129.1, 129.0, 128.7, 125.4, 125.3, 34.1, 31.6. IR (ν_{max}/cm^{-1}): 2960, 1669, 1527, 1481, 1437, 1392, 1362, 1299, 1247, 1178, 1120, 1100, 1016, 909, 871, 730, 693, 669. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 2101.8803, found 2101.0251.

Synthesis of pyrazine-based ligands 18 and 19

The synthesis of ligands **18** and **19** is described elsewhere. However, a slight modification was applied for compound **18**, for which the coupling with $HPPh_2$ was performed under $Pd(OAc)_2$ catalysis without the introduction of an extra ligand to the reaction mixture.[19]

2-(6-Chloropyrazin-2(1*H*)-ylidene)malononitrile (22)[28]

To a solution of malononitrile (5.3 g, 80 mmol) in dry THF (500 mL) NaH (50% oil suspension, 1.6 g) was added in small portions. After stirring the mixture for 30 min a solution of **21** (6.0 g, 40 mmol) in dry THF (100 mL) was added dropwise. The resulting mixture was refluxed for 20 h and then acidified with HCl (1 M, 90 mL). The organic phase was separated and all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (150 mL) and Et_2O (150 mL) to wash away all the inorganic salts and excess of malononitrile, yielding 6.8 g (95%) of **22** as dark red crystalline material. Mp 180 °C (dec). ^{1}H NMR (CD_3SOCD_3): δ = 7.80 (s, 1H), 7.57 (s, 1H). ^{13}C NMR: δ = 163.2, 155.3, 132.4, 110.6, 100.8, 58.6, 56.4. IR (ν_{max}/cm^{-1}): 1697, 1647, 1445, 1369, 1235.

Methyl 6-chloropyrazine-2-carboxylate (23)

To a solution of **22** (6.8 g, 38 mmol) in MeOH (400 mL) Li_2CO_3 (4.2 g, 57 mmol) was added. After stirring the mixture for 30 min magnesium monoperoxyphthalate hexahydrate (80% tech., 17.6 g, 28.5 mmol) was added at 0 °C in small portions. The resulting mixture was stirred for 3 h and then filtered. The filtrate was dried *in vacuo* and the residue was partitioned between H_2O (150 mL) and $CHCl_3$ (150 mL). The organic phase was dried over Na_2SO_4, filtered through a short plug of silica and all the volatiles were removed *in vacuo* to give **23** as a pale yellow oil that crystallized upon standing. Yield 5.0 g, 76%. The spectral characteristics of the obtained compound were consistent with those reported in the literature.[29]

Subsequently, repeating two synthetic procedures, described above, on methyl 6-chloropyrazine-2-carboxylate (**23**), the diester **24** was obtained. The spectral characteristics of the obtained compound were consistent with those reported in the literature.[24]

***N*^{2},*N*^{2},*N*^{6},*N*^{6}-Tetraoctylpyrazine-2,6-dicarboxamide (20)**

To a solution of **24** (2.0 g, 10 mmol) in THF (50 mL), an aqueous solution of NaOH (2 M, 10 mL) was added. After stirring for 1 h the resulting mixture was acidified with aqueous HCl (1 M, 21 mL) and all the volatiles were removed *in vacuo.* The residue was dissolved in acetone (100 mL), dried over Na_2SO_4 and all the volatiles were removed *in vacuo* to give pyrazine-2,6-dicarboxylic acid as white crystalline material in quantitative yield. Subsequently, it was converted into pyrazine-2,6-dicarbonyl dichloride (**25**) by stirring it with an excess of oxalyl chloride (3.6 equiv., 36 mmol, 3 mL) in CH_2Cl_2 (100 mL) in the presence of a catalytic amount of DMF. After the complete dissolution of the crystalline material in CH_2Cl_2, the solvent was distilled off from the reaction mixture and the residue was dried under high vacuum to remove the residual oxalyl chloride from the crude product. The crude **25** was dissolved in CH_2Cl_2 (100 mL) and the resulting solution was added dropwise to a mixture of $(C_8H_{17})_2NH$ (6 mL, 20 mmol) and Et_3N (6 mL, 40 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 2 h and then washed with H_2O (2 × 50 mL). The organic phase was dried over Na_2SO_4, filtered through a short plug of silica and all the volatiles were removed *in vacuo* to give **20** as a yellow oil. Yield 5.7 g, 92%. ^{1}H NMR: δ = 8.87 (s, 2H, PyzH), 3.49 and 3.28 (t, 4H, J = 9.0 Hz, $NCH_2C_7H_{15}$), 1.75–0.75 (m, 60H, octyl). ^{13}C NMR: δ = 162.7, 148.6, 145.9, 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 27.3, 26.5, 23.0, 22.6, 21.3, 14.1. IR (ν_{max}/cm^{-1}): 2924, 2855, 1636, 1454, 669. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 615.5577, found 615.5585.

Reagents and radiotracers

n-Dodecane (Lancaster, UK), nitrobenzene (Fluka, Switzerland), chloroform (Merck, Germany), 1-decanol (Merck, Germany), isodecanol (Merck, Germany), 2-nitrophenyloctyl ether (Fluka, Switzerland) were used as received, while PTMS was prepared as reported earlier.[30] CCD was obtained from Katchem, Czech

Republic and was converted to the H^+-form as reported previously.[30] While suprapur nitric acid (Merck, Germany) was used for making dilute acid solutions for the extraction experiments, all the other reagents were of AR grade. A laboratory stock solution of ^{241}Am tracer was used after freshly purifying, following a reported procedure, and its purity was checked by both gamma as well as alpha spectrometric analyses.[31] ^{152,154}Eu was purchased from the Board of Radiation & Isotope Technology, India and its radiochemical purity was checked by gamma spectrometry using a HPGe detector coupled to a multi-channel analyzer. Radiometric assay of ^{241}Am and ^{152,154}Eu was done by gamma counting using a NaI(Tl) scintillation detector (Para Electronics, India).

Solvent extraction studies

Usually, 5.0 mM solutions of the ligands were prepared in the respective diluents, which were subsequently used for the solvent extraction studies. Pyrex glass tubes containing aqueous phases (usually 1 mL) containing the desired nitric acid concentration and spiked with the required radiotracers (concentration of metal ion in the range of 1.0×10^{-6} to 1.0×10^{-7} M) were equilibrated with equal volumes of the ligand solutions in a rotary thermostated water bath for an hour at 25.0 ± 0.1 °C. The tubes were subsequently centrifuged and assayed radiometrically by taking suitable aliquots from both the phases and measuring the radioactivity by gamma ray counting using a NaI(Tl) scintillation counter interphased with a multi-channel analyzer. The distribution ratio (D) is defined as the ratio of the concentration of a metal ion in the organic phase to that in the aqueous phase. pH measurements of the aqueous phases were carried out using a pH meter (Lab India, Mumbai), which was freshly calibrated using commercial buffer solutions (Merck). The pH measurement of the aqueous phases of the two-phase systems was carried out after equilibration and after carefully removing the organic phases. The extraction experiments were carried out in triplicate and the reproducibility of the mass balance was within ±5%.

References

1 (*a*) C. D. Gutsche, Calixarenes Revisited, in *Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, Royal Society of Chemistry, Cambridge, 1998; (*b*) V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713–745; (*c*) A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713–1734.
2 For a recent review see: B. S. Creaven, D. F. Donlon and J. McGinley, *Coord. Chem. Rev.*, 2009, **253**, 893–962.
3 A. Mulder, J. Huskens and D. N. Reinhoudt, *Org. Biomol. Chem.*, 2004, **2**, 3409–3424.
4 H. H. Dam, D. N. Reinhoudt and W. Verboom, *Chem. Soc. Rev.*, 2007, **36**, 367–377.
5 V. A. Babain, M. Y. Alyapyshev, M. D. Karavan, V. Böhmer, L. Wang, E. A. Shokova, A. E. Motornaya, I. M. Vatsouro and V. V. Kovalev, *Radiochim. Acta*, 2005, **93**, 749–756.
6 P. K. Mohapatra, M. Iqbal, D. R. Raut, W. Verboom, J. Huskens and S. V. Godbole, *Dalton Trans.*, 2012, **41**, 360–363.
7 A. Sengupta, P. K. Mohapatra, M. Iqbal, J. Huskens and W. Verboom, *Dalton Trans.*, 2012, **41**, 6970–6979.
8 M. Iqbal, P. K. Mohapatra, S. A. Ansari, J. Huskens and W. Verboom, *Tetrahedron*, 2012, **68**, 7840–7847.
9 Y. I. Rudzevich, A. B. Drapailo, V. L. Rudzevich, V. I. Miroshnichenko, V. I. Kal'chenko, I. V. Smirnov, V. A. Babain, A. A. Varnek and G. Wipff, *Russ. J. Gen. Chem.*, 2002, **72**, 1736–1742.
10 O. Klimchuk, L. Atamas, S. Miroshnichenko, V. Kalchenko, I. Smirnov, V. Babain, A. Varnek and G. Wipff, *J. Inclusion Phenom. Macrocyclic Chem.*, 2004, **49**, 47–56.
11 M. Karavan, F. Arnaud-Neu, V. Hubscher-Bruder, I. Smirnov and V. Kalchenko, *J. Inclusion Phenom. Macrocyclic Chem.*, 2010, **66**, 113–123.
12 M. Y. Alyapyshev, V. A. Babain, V. I. Boyko, I. I. Eliseev, D. O. Kirsanov, O. V. Klimchuk, A. V. Legin, E. S. Mikhailina, R. V. Rodik and I. V. Smirnov, *J. Inclusion Phenom. Macrocyclic Chem.*, 2010, **67**, 117–126.
13 F. W. Lewis, M. J. Hudson and L. M. Harwood, *Synlett*, 2011, 2609–2632.
14 D. Magnusson, B. Christiansen, M. R. S. Foreman, A. Geist, J.-P. Glatz, R. Malmbeck, G. Modolo, D. Serrano-Purroya and C. Sorel, *Solvent Extr. Ion Exch.*, 2009, **27**, 97–106.
15 M. Galletta, L. Baldini, F. Sansone, F. Ugozzoli, R. Ungaro, A. Casnati and M. Mariani, *Dalton Trans.*, 2010, **39**, 2546–2553.
16 E. Macerata, F. Sansone, L. Baldini, F. Ugozzoli, F. Brisach, J. Haddaoui, V. Hubscher-Bruder, F. Arnaud-Neu, M. Mariani, R. Ungaro and A. Casnati, *Eur. J. Org. Chem.*, 2010, 2675–2686.
17 G. Ionova, S. Ionov, C. Rabbe, C. Hill, C. Madic, R. Guillaumont, G. Modolo and J. C. Krupa, *New J. Chem.*, 2001, **25**, 491–501.
18 M. Heitzmann, C. Gateau, L. Chareyre, M. Miguirditchian, M.-C. Charbonnel and P. Delangle, *New J. Chem.*, 2010, **34**, 108–116.
19 N. I. Nikishkin, J. Huskens, J. Assenmacher, A. Wilden, G. Modolo and W. Verboom, *Org. Biomol. Chem.*, 2012, **10**, 5443–5451.
20 W. Verboom, S. Datta, Z. Asfari, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.*, 1992, **57**, 5394–5398.
21 I. Vatsouro, A. Serebryannikova, L. Wang, V. Hubscher-Bruder, E. Shokova, M. Bolte, F. Arnaud-Neu, V. Böhmer and V. Kovalev, *Tetrahedron*, 2011, **67**, 8092–8101.
22 S. Barboso, A. G. Carrera, S. E. Matthews, F. Arnaud-Neu, V. Böhmer, J.-F. Dozol, H. Rouquette and M.-J. Schwing-Weill, *J. Chem. Soc., Perkin Trans. 2*, 1999, 719–723.
23 The 79% and 61% yields of calixarenes **12** and **15**, respectively, are the result of a side-reaction of the diisopropyl phosphonate group in the products with Huenig base. It is not due to an incomplete main reaction, as it was concluded from the ^{1}H NMR spectra of the reaction mixtures and results obtained for non-tethered pyrazines.

24 R. Takeuchi, K. Suzuki and N. Sato, *Synthesis*, 1990, 923–924.
25 S. Förster, O. Tverskoy and G. Helmchen, *Synlett*, 2008, 2803–2806.
26 P. J. J. Colbon, A. C. Foster and M. E. Giles, *J. Heterocycl. Chem.*, 2008, **45**, 1451–1456.
27 M. Galletta, E. Macerata, M. Mariani, M. Giola, A. Casnati, O. D'Arpa and R. Ungaro, *Czech. J. Phys.*, 2006, **56**, D453–D458.
28 This compound has been used in a spectroscopic study, but the synthesis and the spectral characterization are not given: B. Pilarski, H. Foks, K. Osmialowski and R. Kaliszan, *Monatsh. Chem.*, 1984, **115**, 179–185.
29 M. J. C. Scanio, L. Shi, W. H. Bunnelle, D. J. Anderson, R. J. Helfrich, J. Malysz, K. K. Thorin-Hagene, C. E. Van Handel, K. C. Marsh, C.-H. Lee and M. Gopalakrishnan, *J. Med. Chem.*, 2011, **54**, 7678–7692.
30 P. K. Mohapatra, A. Bhattacharyya and V. K. Manchanda, *J. Hazard. Mater.*, 2010, **181**, 679–685.
31 P. K. Mohapatra, PhD Thesis , University of Bombay, 1993.

