Calixarene based receptors for molecules and ions of environmental or bio-medical importance

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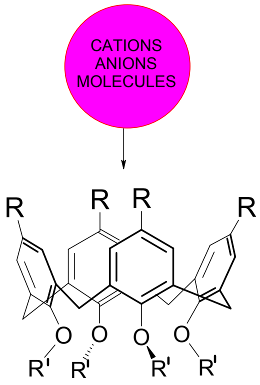
Calixarenes are cup-shaped macrocyclic compounds easily synthesized by the template cyclocondensation of *tert*-butyl-phenol with formaldehyde [1, 2]. Due to their cup-shaped architecture calixarenes can recognize bind and separate similar in properties guests such as anions, cations and neutral organic molecules, up to enantiodiscrimination of optical antipodes. This property opens wide perspectives of their practical application in different branches of chemistry, physics, biology, material science etc[3, 4, 5].

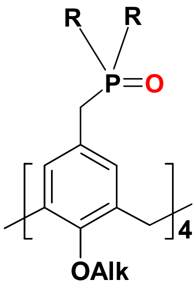


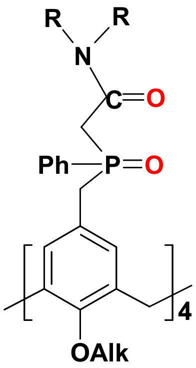
Our activity is mainly focused on synthesis and investigation of organophosphorus derivatives of calixarenes [6, 7, 8, 9, 10, 11, 12, 14, 15, 22, 17, 18]. First of all phosphorus opens wide perspectives in chemical modification of calixarene molecule. From another side organophosphorus external groups can serve as additional complexing centers in recognition and binding of the gust species.

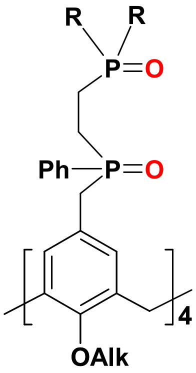
In the report we present some results achieved by of our team in the next topics: design of radionuclide extractants [13, 18, 19, 20, 21]; design of receptor sites for chemosensors [14], drug design [15,16].

Organophosphorus extractants (tributylphosphate, bis-2-ethylhexylphosphoric acid, trialkylphosphine oxides, carbamoylphosphine oxides etc.) are widely used in industrial decontamination of spent nuclear fuel from toxic radioisotopes actinides, lanthanides, uranium and plutonium (TRUEX and PUREX processes).

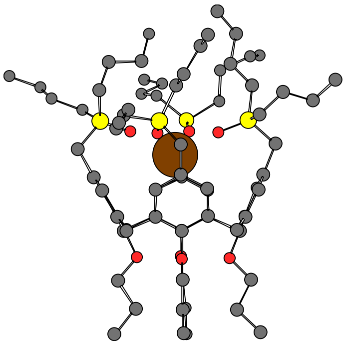
Our approach in the design of highly efficient and selective extractants is based on the functionalization of the cone shaped calix[4]arene platform by four binding groups: phosphine oxide, carbamoylphosphine oxide, diphosphine dioxide.

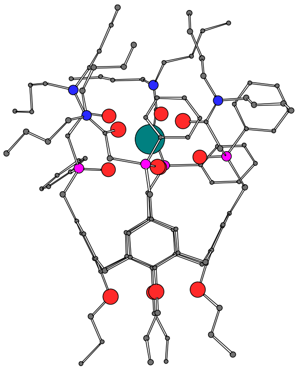


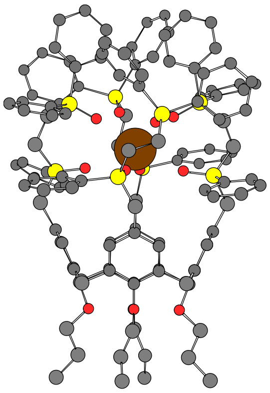




In accordance with the molecular modeling we observe the cooperative effect of phosphoryl groups in the complexation of metal cation. In the case of calix-phosphine oxide four phosphoryl oxygen atoms simultaneously bind metal cation. Calix-CMPO binds the cation by four phosphoryl and additionally by four carbonyl oxygen atoms. In calix-diphosphine dioxide eight PO groups participate in cooperative binding of the cation. The data predict high extraction efficiency of the phosphorylated calixarenes [18].







It is well known that the extraction in liquid-liquid system by organophosphorus compounds is strongly depended on the substituents nature at the phosphorus atom. So we synthesized a big diversity of new calix[4]arenes with different substituents at the phosphorus groups. The extraction properties of the compounds synthesized in respect to main components of the spent nuclear fuel were investigated [18, 19].

On Figure **1** you see extraction of europium from nitric acid into nitrobenzotrifluoride solution by a series of calix-phosphine oxides possessing different alkyl substituents at the phosphorus atom or at the calixarene lower rim. Due to the above mentioned calixarene cooperative effect the compounds more that two order of magnitude superior the classical extractants carbamoylphosphine oxide or trialkylphosphine oxide.

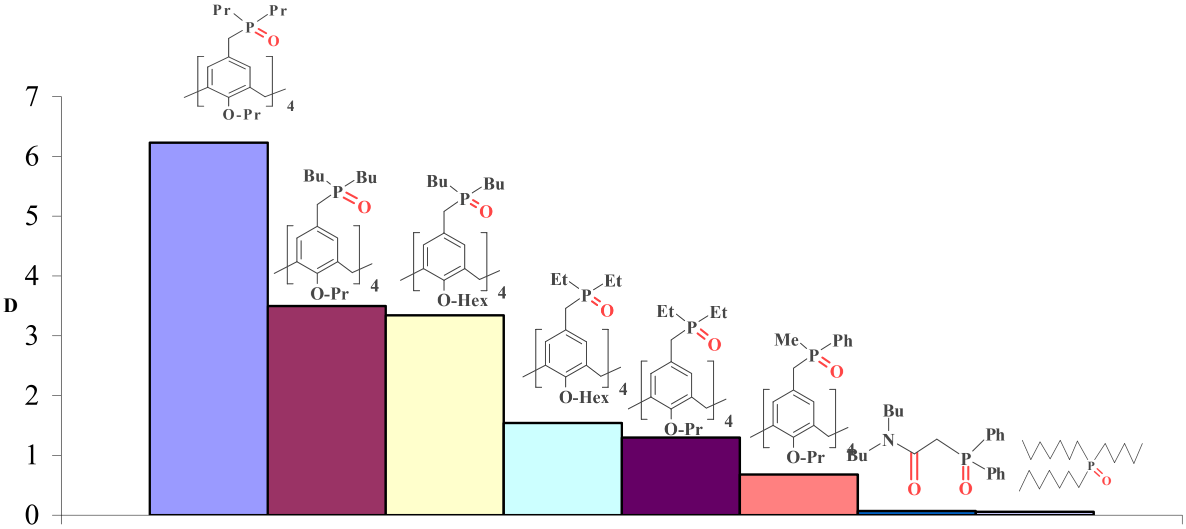


Figure 1. Extraction of Eu^{3+} from HNO_3 (0.3M) into NBTF

The similar cooperative effect is observed for extraction of amerithium by the calix-phosphine oxides. However the distribution coefficients of amerithium is slightly decreased compared to europium.

As it was shown a remarkable amerithium selectivity is observed in the case of the calixarene bearing carbamoylphosphine oxide groups at the macrocyclic upper rim. The best efficacy and distribution coefficient is observed for concentration of nitric acid one mole per liter.

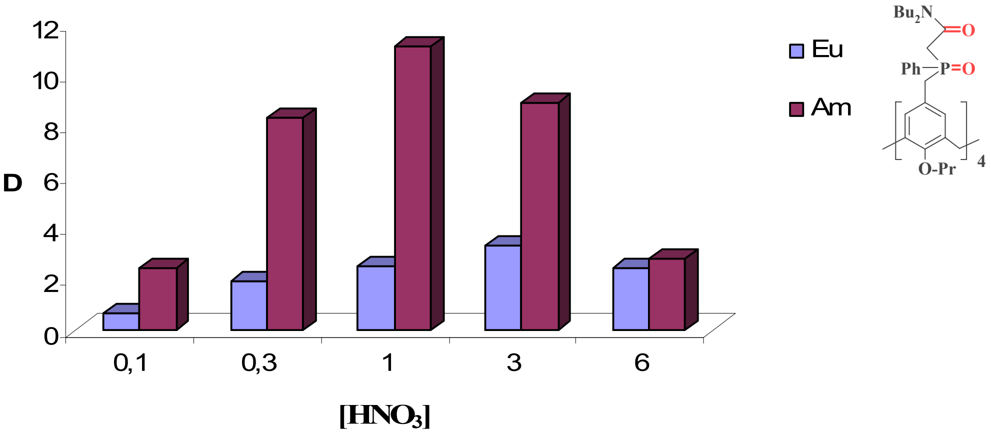


Figure 2. Extraction of Eu^{3+} and Am^{3+} from HNO$_3$ into NBTF

The phosphorylated calixarenes are also effectively extract the such important component of the spent nuclear fuel as technetium, ruthenium and platinum [17,18, 19, 20, 21]. So, calix[4]arenes bearing P=O groups at the wide rim afford the combined recovery of actinides, lanthanides, technetium and platinides from acidic media. The increase in Eu^{3+} and Am^{3+} distribution coefficients by a factor of up to 200 for the calixarenes comparing to the industrial extractants TAPO, CMPO and DIEHPA was achieved.

Phosphorylated calixarenes are effective receptors not only for metal cation but also for different classes of organic molecules uncluding bio-active or toxic substances, for example uracil and adenine derivatives (Figure 3). Stability constants for uracil or adenine complexes in a water medium are summarized on the diagram. They lie in a wide region dependently on substituents nature in the heterocycle Guest, as well as calixarene Host structure. Nitrouracil forms most strong complex with calixarene [22, 23].

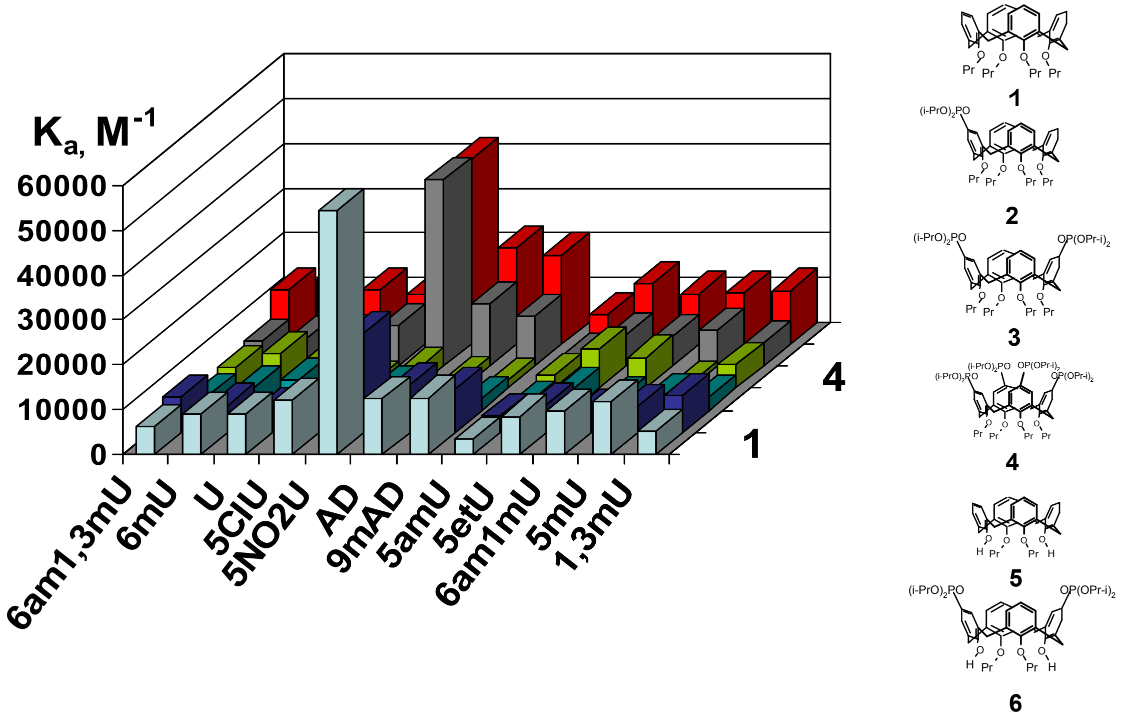
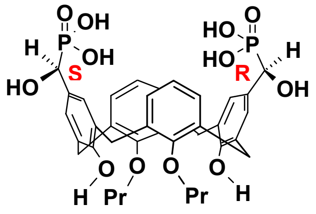


Figure 3. Stability constants of the Host – Guest Complexes

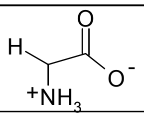
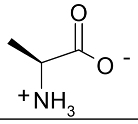
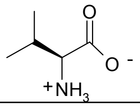
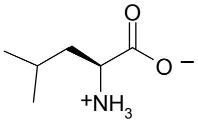
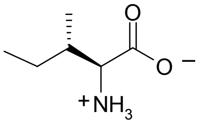
In Table 1 you see binding parameters of the Host-Guest complexation of a series of aminoacids with calixarene bis-hydrohyphosphonic acid in methanol solution. Stability constants of the complexes and binding free energies of the complexation are rather high. Substituent at the amino acid alpha carbon atom (hydrogen, methyl, iso-propyl and iso-butyl) plays important role in stabilization of the complex [24].

Table 1. Calixarene - Aminoacid Host-Guest Complexation

Microcalorimetry in methanol at 298.15 K



Host

Guest	**log K , M^{-1}**	**ΔH°, kJmol^{-1}**	**T ΔS°, kJmol^{-1}**	**ΔG°, kJmol^{-1}**
Gly 	**3.84** **±0.15**	**-9.13** **±0.32**	**12.79**	**-21.91**
Ala 	**3.89** **±0.11**	**-8.19** **±0.21**	**14.00**	**-22.19**
Val 	**4.12** **±0.04**	**-7.11** **±0.24**	**16.42**	**-23.53**
Leu 	**4.19** **±0.04**	**-9.06** **±0.18**	**14.82**	**-23.89**
Ile 	**4.23** **±0.01**	**-7.05** **±0.14**	**17.10**	**-24.15**

The calixarenes binding properties were used for development of Artificial Electronic Nose. For this aim different calixarenes were transferred onto surface of quartz microbalances. On this picture you see the response of each calixarene coated microbalance on vapour of organic molecules in air: toluene, benzene, xylene etc. These balances were organised into sensing array connected to computer equipped by the NeuroDiscovery software. This array similar to human nose can recognize and keep in electronic memory a digital image of different individual organic molecule or their complicated mixtures (Figure 4) [14].

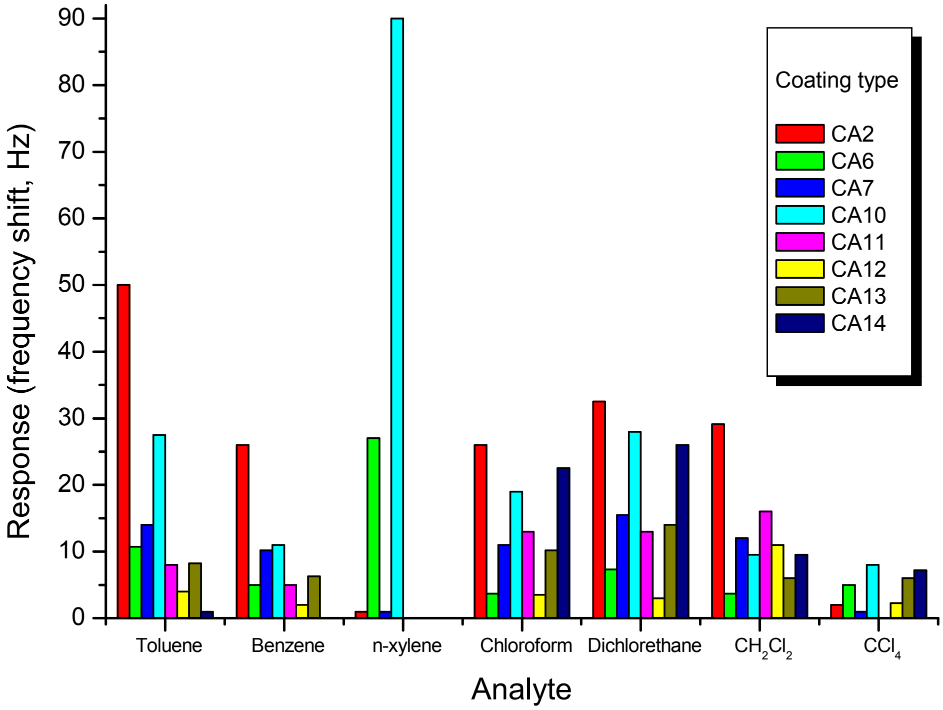


Figure 4. Response of the 8-chanels QCM sensor to various analytes

This is a view of the calixarene based Electronic Nose device constructed in the Institute of Semiconductor Physics National Academy of Sciences of Ukraine(Figure 5).

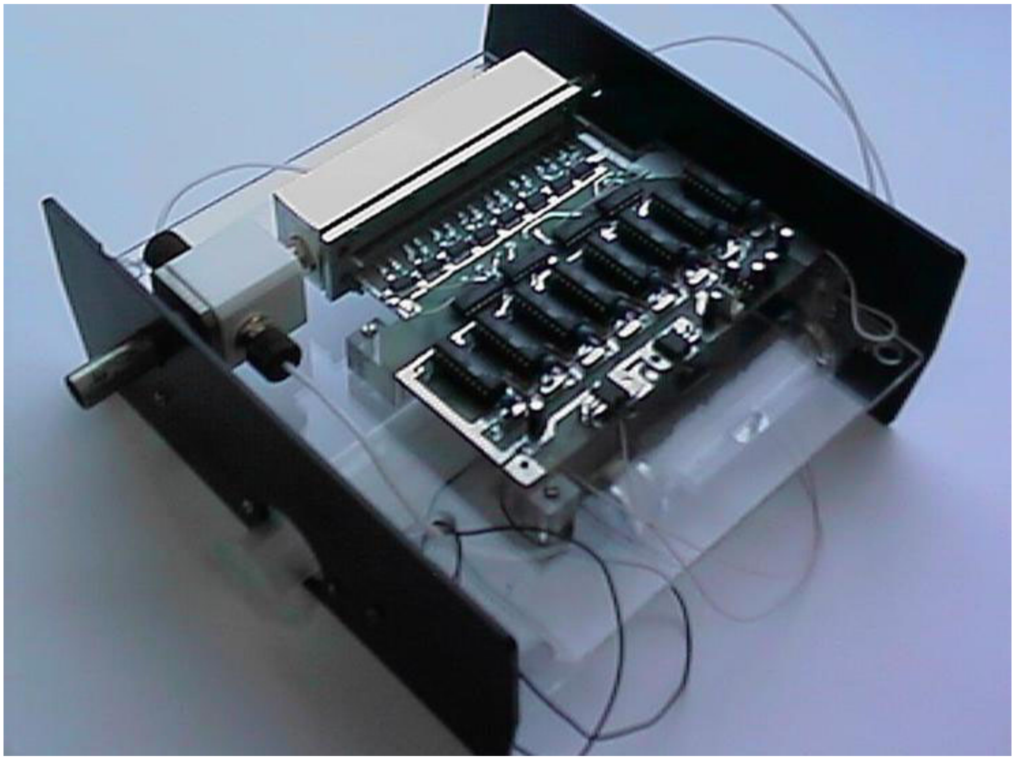


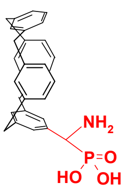
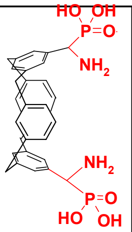
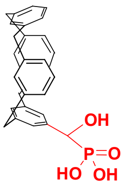
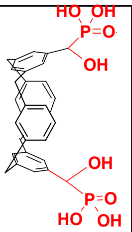
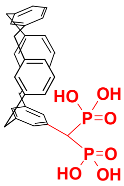
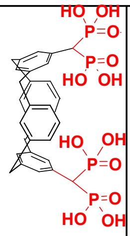
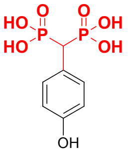
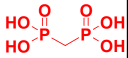
Figure 5. Chemosensor GAZ-1

Calixarenes due to their specific binding of biomolecules are considering as a promising compounds for application in nanomedicine, for example drug delivery systems, diagnostics, artificial enzymes or co-enzymes etc. Calixarenes possessing fragments of alpha-amino-phosphonic , alpha-hydroxy-phosphonic and methylene-bis-phosphonic acids are effective inhibitors of alkaline phosphatase.

Table 2 summarizes the dissociation constants of the enzyme – inhibitor complex as well as the enzyme – nitrophenyl phosphate - inhibitor complex. The constants are strongly depended on the quantity and nature of the phosphonic groups at the calixarene wide rim. Calixarene bearing two methylene–bis-phosphonic group is the most effective inhibitor among the compounds investigated and are one of the best inhibitors described in literature up to now [15].

Table 2. Calf Intestine Alkaline Phosphatase Binding

Tris-HCl buffer (pH 9), Ki, K’I µM

	Binder							
								
K_i	25.1	5.4	12.5	3.4	2.5	0.38	22	67
K_i’	475	90	245	89	46	2.8	290	750

Ki *dissociation constants of the Enzyme-Binder complex*

Ki′ *dissociation constants of the Enzyme-Nitrophenyl Phosphate-Binder complex*

In conclusion, our investigations and literature data demonstrate a promising perspectives for practical application and commercialization of calixarenes. We can propose for a custom synthesis (see ***http://www.ioch.kiev.ua/calix/***) a wide diversity of the next compounds:

- Calixarene Building Blocks
- Chiral Calixarenes

- Amphiphilic or Water-soluble Calixarenes
- Bio-relevant Calixarenes
- Calixarene Extractants
- Calixarene Ligands
- Calixarenes for Chemosensors
- Organophosphorus Compounds

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