

# Calixarene receptors of environmentally hazardous and biorelevant molecules and ions\*

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**Abstract:** In the paper, a report on the rational design of the calixarene receptors bearing ligating, H-donor, H-acceptor fragments at the wide and/or narrow rim of the macrocycle is presented. The calixarenes form supramolecular complexes with various cations, anions, organic molecules, and biomolecules in solution, in the crystalline state and even in the gas phase. The calixarenes or their complexes can be used as materials for radionuclide extraction, construction of chemosensors, and drug design.

**Keywords:** calixarenes; sensors; analytical chemistry; nuclear waste; drug design.

## INTRODUCTION

Calixarenes are macrocyclic vases which are easily available through the cyclocondensation of para-substituted phenols with formaldehyde [1,2]. Calixarenes are widely used as molecular platforms for the construction of specific receptors capable of highly selective recognition between fairly similar substrates. Apparently, the outstanding receptor properties of functional calixarenes make them highly promising materials for sensor technology [3], radioactive waste management [4], pharmaceutical science [5], and analytical application [6–8].

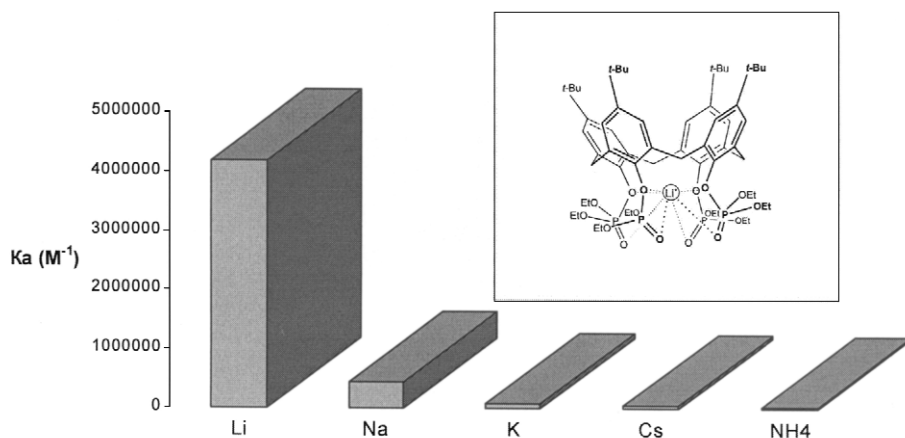
The present paper summarizes the results of the project devoted to the molecular design of calixarene receptors and their complexation with various substrates. The objective of the research was the design and synthesis of highly selective receptors for ecologically hazardous and biologically problematic cations, anions, and neutral molecules and their practical application. The objects of the studies were calix[*n*]arenes (*n* = 4, 5, 6, 8), calixresorcinarenes, and thiacalixarenes. The strategy of the molecular design consisted of the preorganization of various N-, O-, S-, and P-containing binding fragments at the calixarene platforms, which could result in a high efficiency and selectivity of the complexation. The list of publications on the synthesis of the calixarene receptors and the library of the compounds obtained within the project can be found at <[www.ioch.kiev.ua/calix](http://www.ioch.kiev.ua/calix)>.

## CATION RECEPTORS

In order to obtain efficient and selective cation receptors, the parent calixarenes were functionalized with phosphoryl-containing ligating functional groups. For example, the calix[4]arene bearing four phosphoryl groups at the narrow rim of the macrocycle selectively binds Li<sup>+</sup> in the presence of Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>, and NH<sub>4</sub><sup>+</sup> (Fig. 1) [9]. The calculated  $K_{aLi^+}/K_{aNa^+}$  selectivity 9.5 is among the highest values for the calixarene-based Li selective receptors reported to date.

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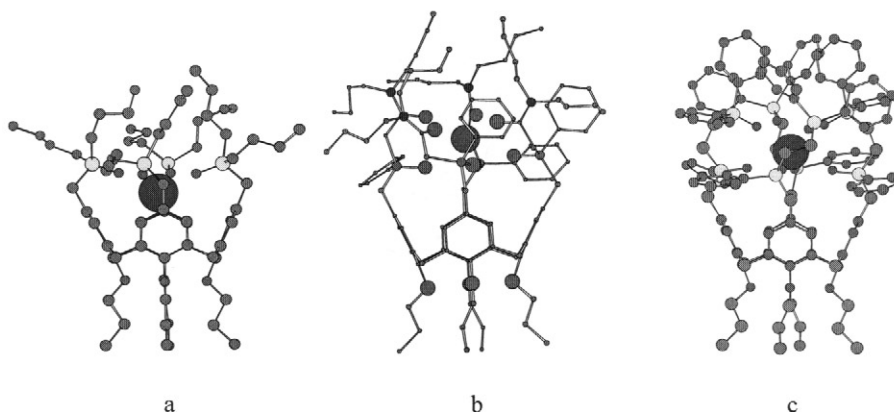
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**Fig. 1** Association constants for the complexes of the calix[4]arene tetraphosphate with metal cations (<sup>1</sup>H NMR in CDCl<sub>3</sub> solution).

Molecular mechanics calculations show that the size of the cavity formed by the cationoacceptor oxygen atoms of the phosphoryl and phenolic groups is the most suitable for binding Li<sup>+</sup>, whereas the larger cations cannot be efficiently hosted.

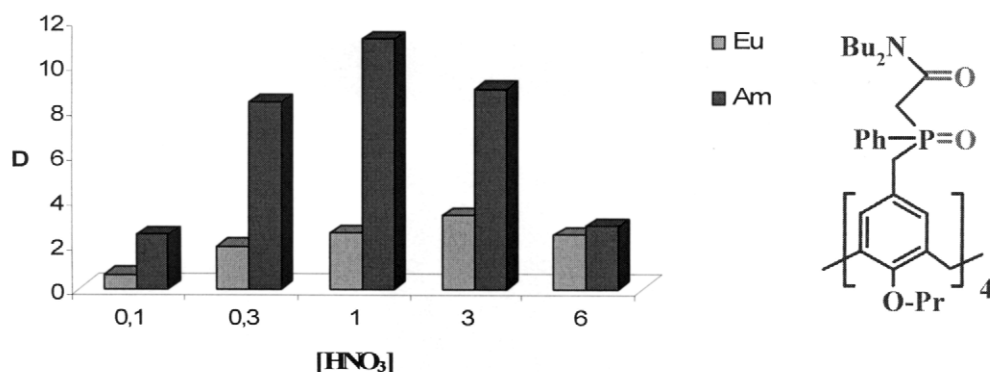
In order to obtain receptors for multicharged cations, we have obtained calixarenes bearing cationoacceptor groups such as phosphine oxide, carbamoylphosphine oxide, and diphosphine dioxide at the wide rim of the macrocycle [10–12]. Molecular modeling has suggested that all the oxygen atoms of the pendant ligating groups could cooperatively bind the metal cation (Fig. 2).



**Fig. 2** Cooperative binding of a multicharged metal cation by the calixarene tetraphosphine oxide (a), the calixarene tetracarbamoylphosphine oxide (b), and the calixarene tetradiphosphine dioxide (c) (MacroModel, Monte Carlo).

The results of theoretical studies correlate well with the experimental results. For instance, the calixarene tetraphosphine oxides are much more efficient extractants for Eu<sup>3+</sup> and Am<sup>3+</sup> than such industrial reagents as carbamoylphosphine oxide and trialkylphosphine oxide.

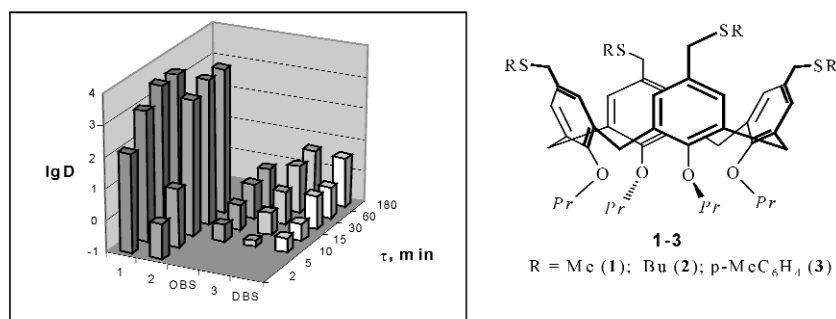
The calixarenes containing four bidentate carbamoylphosphine oxide and diphosphine dioxide groups are even more efficient extractants than the calixarenes-tetraphosphine oxides. It is noteworthy that carbamoylphosphine oxides are capable of selectively extracting Am<sup>3+</sup> in the presence of Eu<sup>3+</sup> (Fig. 3).



**Fig. 3** Separation of  $\text{Am}^{3+}$  and  $\text{Eu}^{3+}$  by the calixarene tetracarbamoylphosphine oxide ( $D$  – distribution coefficient between  $m\text{-CF}_3\text{C}_6\text{H}_4\text{NO}_2$  and 0.1–6 M aqueous  $\text{HNO}_3$ ).

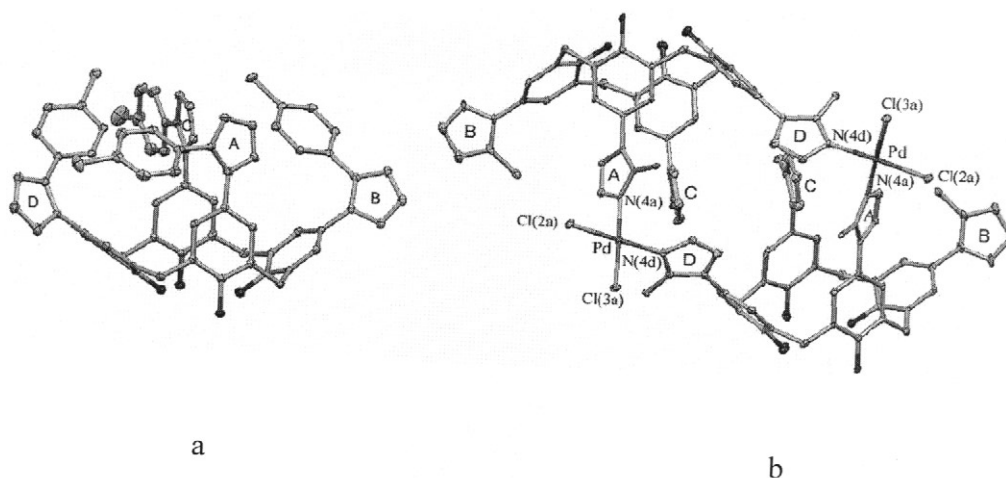
Monomeric and polymeric 1:2 complexes of the calix[4]arene-tetraphosphine oxide with  $\text{Co}^{2+}$  or  $\text{Ni}^{2+}$  nitrates were synthesized and analyzed by the X-ray method [13]. In the monomeric complexes, each metal cation is coordinated by two bidentate  $\text{NO}_3^-$ -ligands as well as by two proximal  $\text{P}=\text{O}$  groups at the calixarene skeleton. In the nickel metallopolymer one sort of the cations is bound by the two proximal  $\text{P}=\text{O}$ -groups but other cations link neighboring calixarene molecules through  $\text{P}=\text{O}\cdots\text{Ni}\cdots\text{O}=\text{P}$  chains. The complexes possess molecular cavities or channels filled by solvent molecules.

Transition metals, the metals of platinum group, Au, and Ag are efficiently bound by the calixarenes functionalized with soft N- and S-containing ligating functions [14–16]. For instance, the calixareneethioethers are 100–1000 times more efficient extractants of Pd than the monodentate dialkylsulfides (Fig. 4).



**Fig. 4** Extraction of Pd by calix[4]areneethioethers (**1–3**), octylbenzylsulfide (OBS), and dibenzylsulfide (DBS) from 1 M aqueous HCl into toluene.

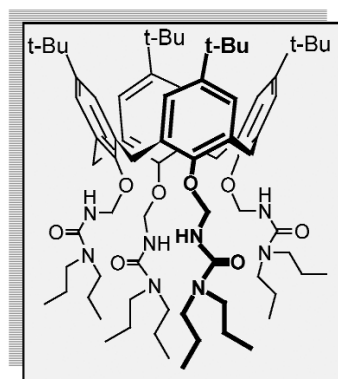
The calixarene bearing four tetrazole fragments at the wide rim of the macrocycle forms the solid complex with  $\text{PdCl}_2$  (Fig. 5) [17]. The X-ray diffraction study revealed that in this complex two Pd atoms link two molecules of the tetrazolecalixarene through the coordination with the nitrogen atoms of the tetrazole rings.



**Fig. 5** Single-crystal X-ray structure of the calixarenetetrazole (a) and its complex with PdCl<sub>2</sub> (b).

### ANION RECEPTORS

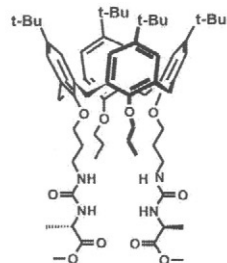
Molecular recognition of anions is an important topic in supramolecular chemistry and sensor technology since anions play a crucial role in many biochemical processes and in chemical technology [18–21]. Four carbamide functions were attached to the narrow rim of the macrocycle in order to achieve strong and selective binding of halide anions through multiple and cooperative hydrogen bonding (Fig. 6) [22].

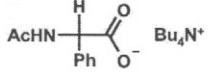
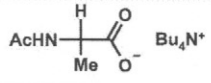


Guest	Bu <sub>4</sub> N <sup>+</sup> I <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup> Br <sup>-</sup>	Me <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> N <sup>+</sup> Cl <sup>-</sup>
<b>K<sub>a</sub>, M<sup>-1</sup></b>	<b>23</b>	<b>220</b>	<b>230</b>

**Fig. 6** Association constants of the complexes of the calixarenes tetracarbamide with tetraalkyl-ammonium halides (<sup>1</sup>H NMR in CDCl<sub>3</sub> solution).

The chiral calixarene carbamides, bearing two fragments of L-Ala are capable of stereoselective binding the anion forms of amino acids (Fig. 7) [23]. For example, D-phenylalanine anion is bound four times stronger than its L-enantiomer.

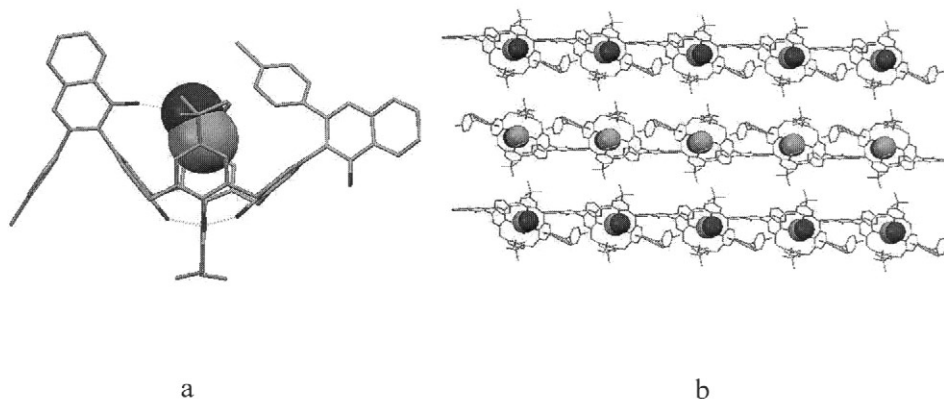


Guest		$K_{\text{ass}}, \text{M}^{-1}$	D/L selectivity
	L	302	4.14
	D	1250	
	L	2460	0.96
	D	2400	
Cl <sup>-</sup> Bu <sub>4</sub> N <sup>+</sup>		2730	

**Fig. 7** Stereoselective binding of the amino acid anions by the chiral calixarene carbamate ( $^1\text{H}$  NMR in  $\text{CDCl}_3$  solution).

### RECEPTORS FOR ORGANIC COMPOUNDS AND BIOLOGICALLY RELEVANT MOLECULES

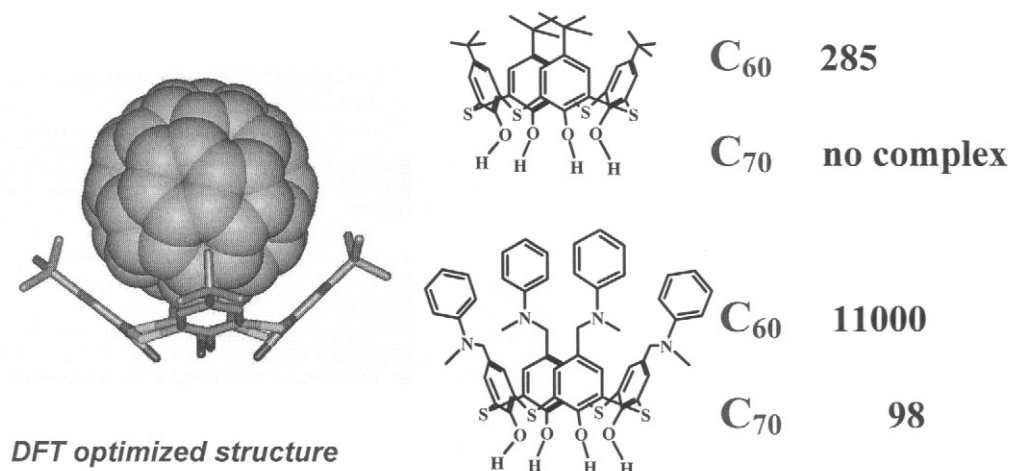
We obtained new calixarene receptors which bind various organic molecules in the crystalline state and in solution. The calixarene functionalized with two quinazolinone fragments includes one molecule of methanol (Fig. 8a) [24] the methyl group of which is residing in the cavity of the calixarenes most probably due to the C–H... $\pi$  bonds with the aromatic rings. On the other hand, the OH group of the methanol molecule forms a hydrogen bond to the carbonyl group of the quinazolinone fragment. The crystal packing of the methanol complex is shown in Fig. 8b.



**Fig. 8** Molecular (a) and crystal structure (b) of the complex of the calixarene-bis-quinazolinone with methanol.

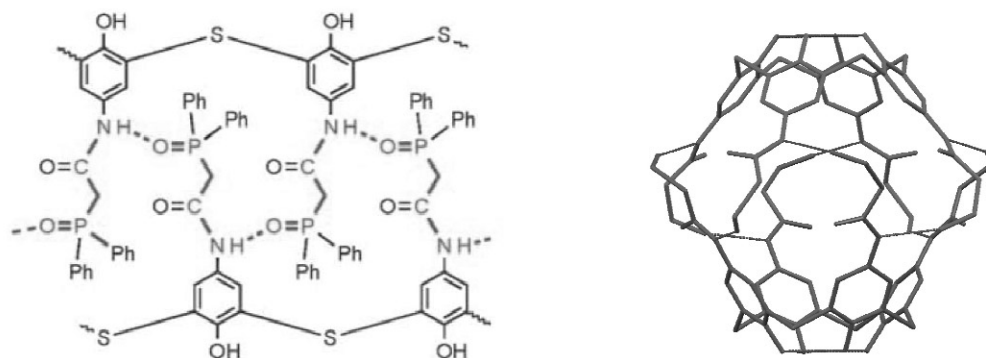
The calix[4]arene derivatives bearing two or four dihydroxyphosphoryl groups form stable host–guest complexes with herbicides (2,4-D and atrazine) in water solution [25]. The stability constants of the complexes were determined by the earlier developed chromatographic (HPLC) method based on the dependence between the guest retention time on the calixarene concentration in the eluent [26]. The binding constants ( $800\text{--}6650 \text{ M}^{-1}$ ) depend on the conformation and stereochemical rigidity of the calixarene skeleton, the number of phosphoryl groups attached to the wide rim of the macrocycle, and the acidity (basicity) of the guest. The complexes may be stabilized by hydrophobic, electrostatic, and  $\pi\text{--}\pi$  interactions.

The thiacalix[4]arenes functionalized at the wide rim of the macrocycle with *tert*-butyl or aniline residues selectively bind fullerenes (Fig. 9). The stronger binding of C<sub>60</sub> compared to C<sub>70</sub> can be explained by a better geometrical fit between the host and the guest [27].



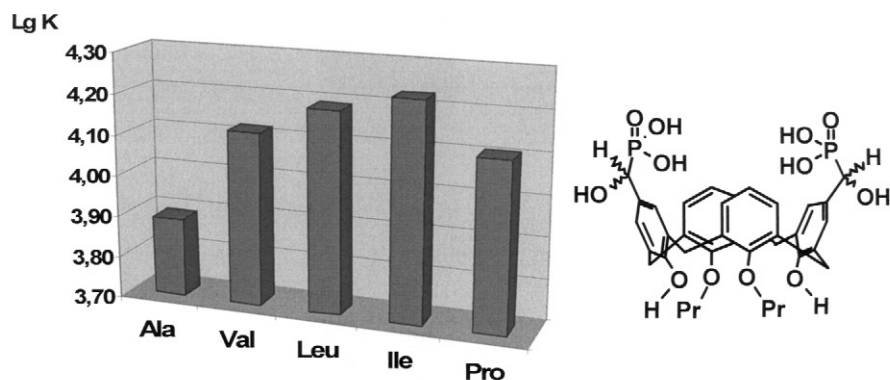
**Fig. 9** Association constants ( $M^{-1}$ ) of the complexes of fullerenes with thiacalixarenes (UV/vis in toluene solution).

Molecular capsules are promising self-assembling receptors which may be used as sensitive materials in chemosensors [28]. Two molecules of the thiacalixarene bearing four carbamoyl-phosphine oxide groups at the wide rim of the macrocycle form dimeric capsules stabilized by a seam of eight  $NH \cdots O=P$  hydrogen bonds. The volume of the cavity was estimated to be  $370 \text{ \AA}^3$ . This can be filled with a solvent molecule (chloroform, benzene, toluene) or such a complementary cation as tetraethylammonium or cobaltocenium (Fig. 10) [29].



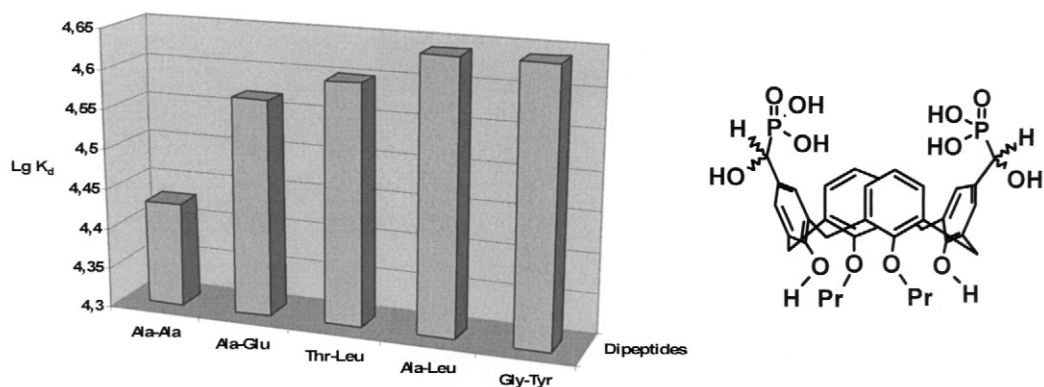
**Fig. 10** The crystal structure of the dimeric capsule including a cobaltocenium cation.

The design of receptors for biorelevant molecules is an important trend in sensor technology since it enables the rational construction of the sensitive materials for diagnostic systems of biomedical application. On the basis of phosphorylated calixarenes, we have obtained novel receptors for amino acids (Fig. 11) [30].



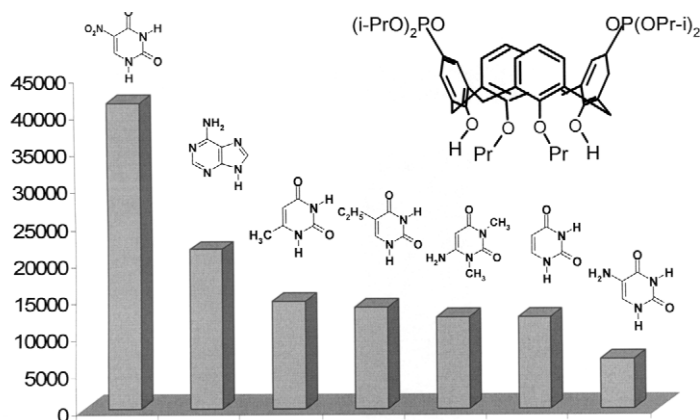
**Fig. 11** Association constants of the complexes of calixarene-bis-hydroxyphosphonic acid with amino acids (microcalorimetry in methanol).

The calixarene-bis-hydroxymethylphosphonic acid forms stable complexes with dipeptides (Fig. 12) [31] which are found in many biologically relevant compounds such as hormones, antibiotics, toxins, and enzyme inhibitors.



**Fig. 12** Association constants of the complexes of calixarene-bis-hydroxyphosphonic acid with dipeptides (microcalorimetry in methanol).

The calixarene platforms were used for the design of receptors binding the biologically and medically relevant uracil and adenine derivatives [32,33]. The stability constants of the complexes with a set of uracil and adenine derivatives determined by HPLC in acetonitrile/water mixtures are shown in Fig. 13.



**Fig. 13** Association constants ( $M^{-1}$ ) of the complexes of diphosphorylcalixarene with uracil and adenine derivatives (HPLC in acetonitrile/water solution).

The calixarenes functionalized at the wide rim of the macrocycle with methylenebisphosphonic acid residues inhibit the alkaline phosphatases [34] with inhibition constants up to  $0.38 \mu M$ .

The efforts were also made to design the chiral calixarenes hosts and inhibitors [35–37]. The chiral calixarene bisaminophosphonic acid shows stereoselective inhibition of alkaline phosphatase. Namely, the *RR* isomer is about 50 times more effective than its *SS* counterpart (Table 1) [37].

**Table 1** Stereoselective inhibition of porcine kidneys alkaline phosphatase by the calixarene aminophosphonic acids (UV/vis, 0.1 M Tris-HCl buffer, pH 9, 296 K).

Inhibitor		Inhibition Constants, $\mu M$	Selectivity
	<i>R</i>	73	2.28
	<i>S</i>	32	
	<i>RR</i>	1.7	50.5
	<i>SS</i>	86	

## CONCLUSIONS

Calixarenes functionalized with metal-coordinating, H-donor, and H-acceptor groups are efficient and selective receptors for various cations, anions, neutral molecules, and biorelevant compounds. The calixarenes obtained were used as sensitive layers in the chemosensor devices [39–41] for volatile or-



ganic molecules. This sensor technology will be used for the determination of toxic and hazardous compounds in the environment as well as for quality control of food and cosmetics.

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## REFERENCES

1. C. D. Gutsche. *Calixarenes*. Monographs in Supramolecular Chemistry, Royal Society of Chemistry (1989).
2. Z. Asfari, V. Boehmer, J. Harowfield, J. Vicens (Eds.). *Calixarenes 2001*, Kluwer Academic, Dordrecht (2001).
3. D. Diamond, K. Nolan. *Anal. Chem.* **73**, 23 (2001).
4. F. Arnaud-Neu, M.-J. Swing-Weill, J.-F. Dozol. In *Calixarenes 2001*, Z. Asfari, V. Boehmer, J. Harowfield, J. Vicens (Eds.), pp. 642–662, Kluwer Academic, Dordrecht (2001).
5. E. Da Silva, A. N. Lazar, A. W. Coleman. *J. Drug Del. Sci. Technol.* **14**, 3 (2004).
6. R. Ludwig. *Microchim. Acta* **152**, 1 (2005).
7. K. Menon, M. Sewani. *Rev. Anal. Chem.* **25**, 49 (2006).
8. L. Mutihac, H. J. Buschmann. *J. Incl. Phenom. Macrocycl. Chem.* **51**, 1 (2005).
9. O. V. Lukin, M. O. Vysotsky, V. I. Kalchenko. *J. Phys. Org. Chem.* **14**, 468 (2001).
10. L. Atamas, O. Klimchuk, V. Rudzevich, V. Pirozhenko, V. Kalchenko, I. Smirnov, V. Babain, T. Efremova, A. Varnek, G. Wipff, F. Arnaud-Neu, M. Roch, M. Saadioui, V. Bohmer. *J. Supramol. Chem.* **2**, 421 (2002).
11. O. Klimchuk, L. Atamas, S. Miroshnichenko, V. Kalchenko, I. Smirnov, V. Babain, A. Varnek, G. Wipff. *J. Incl. Phenom.* **49**, 47 (2004).
12. I. Smirnov, M. Karavan, V. Babain, I. Kvasnitsky, E. Stoyanov, S. Miroshnichenko. *Radiochim. Acta* **95**, 97 (2007).
13. G. A. Kostin, A. O. Borodin, V. G. Torgov, N. Y. Kurat'yeva, D. Yu. Naumov, S. I. Miroshnichenko, V. I. Kalchenko. *J. Incl. Phenom. Macrocycl. Chem.* **59**, 45 (2007).
14. V. Torgov, G. Kostin, T. Korda, E. Stoyanov, V. Kalchenko, A. Drapailo, O. Kasyan, G. Wipff, A. Varnek. *Solvent Extr. Ion Exch.* **23**, 781 (2005).
15. V. Torgov, G. Kostin, V. Mashukov, T. Korda, A. Drapailo, V. Kalchenko. *Solvent Extr. Ion Exch.* **23**, 171 (2005).
16. V. Torgov, G. Kostin, V. Mashukov, T. Korda, V. Kalchenko, A. Drapailo, O. Kasyan. *IV International Symposium "Design and Synthesis of Supramolecular Architectures"*, p. 28, Kazan, Russia (2006).
17. V. Boyko, R. Rodik, O. Danylyuk, L. Tsymbal, Ya. Lampeka, K. Suwinska, J. Lipkowski, V. Kalchenko. *Tetrahedron* **61**, 12282 (2005).
18. A. Bianchi, K. Bowman-James, E. García-España (Eds.). *The Supramolecular Chemistry of Anions*, Wiley-VCH, Weinheim (1997).
19. F. Schmidtchen, M. Berger. *Chem. Rev.* **97**, 1609 (1997).
20. P. D. Beer, P. A. Gale. *Angew. Chem., Int. Ed.* **40**, 486 (2001).
21. V. Amendola, L. Fabbrizzi. *Acc. Chem. Res.* **39**, 343 (2006).
22. V. I. Boyko, A. V. Yakovenko, I. F. Tsymbal, V. I. Kalchenko. *Mendeleev Commun.* 24 (2006).
23. A. V. Yakovenko, V. I. Boyko, V. I. Kalchenko, L. Baldini, A. Casnati, F. Sansone, R. Ungaro. *J. Org. Chem.* **72**, 3223 (2007).

24. R. Rodik, A. Rozhenko, V. Boyko, V. Pirozhenko, O. Danylyuk, K. Suwinska, J. Lipkowski, V. Kalchenko. *Tetrahedron* **63**, 11451 (2007).
25. O. I. Kalchenko, A. V. Solovyov, S. A. Cherenok, N. F. Starodub, V. I. Kalchenko. *J. Incl. Phenom. Macrocycl. Chem.* **46**, 19 (2003).
26. O. I. Kalchenko, J. Lipkowski, V. I. Kalchenko, M. A. Vysotsky, L. N. Markovsky. *Chromatogr. Sci.* **36**, 269 (1998).
27. O. Kasyan, O. Mikhailenko, A. Drapailo, M. Kornilov, V. Kalchenko. *Moldavian-Polish-Ukrainian Symposium on Supramolecular Chemistry*. Chisinau, R. Moldova, Book of Abstracts, p. 17 (2005).
28. F. Hof, S. L. Craig, C. Nuckolls, J. Rebek Jr. *Angew. Chem., Int. Ed.* **41**, 1488 (2002).
29. O. Kasyan, V. Kalchenko, M. Bolte, V. Böhmer. *Chem. Comm.* 1932 (2006).
30. W. Zielenkiewicz, A. Marcinowicz, J. Poznański, S. Cherenok, V. Kalchenko. *J. Incl. Phenom. Macrocycl. Chem.* **55**, 11 (2006).
31. W. Zielenkiewicz, A. Marcinowicz, S. Cherenok, V. Kalchenko, J. Poznański. *Supramol. Chem.* **18**, 167 (2006).
32. O. Kalchenko, J. Poznański, A. Marcinowicz, S. Cherenok, A. Solovyov, W. Zielenkiewicz, V. Kalchenko. *J. Phys. Org. Chem.* **16**, 246 (2003).
33. O. Kalchenko, A. Marcinowicz, J. Poznański, S. Cherenok, A. Solovyov, W. Zielenkiewicz, V. Kalchenko. *J. Phys. Org. Chem.* **18**, 578 (2005).
34. A. I. Vovk, V. I. Kalchenko, S. O. Cherenok, V. P. Kukhar, O. V. Muzychka, M. O. Lozynsky. *Org. Biomol. Chem.* **2**, 3162 (2004).
35. V. I. Boyko, A. Shivanyuk, V. V. Pyrozhenko, R. I. Zubatyk, O. V. Shishkin, V. I. Kalchenko. *Tetrahedron Lett.* **47**, 7775 (2006).
36. A. V. Yakovenko, V. I. Boyko, O. Danylyuk, K. Suwinska, J. Lipkowski, V. I. Kalchenko. *Org. Lett.* **9**, 1183 (2006).
37. S. Cherenok, A. Vovk, I. Muravyova, A. Shivanyuk, V. Kukhar, J. Lipkowski, V. Kalchenko. *Org. Lett.* **8**, 549 (2006).
38. Yu. Shirshov, B. Snopok, O. Rengevich, V. Kalchenko, A. Coleman. *Frontiers of Multifunctional Nanosystems*, E. Buzaneva, P. Scarf (Eds.), pp. 347–368, Kluwer Academic, Dordrecht (2002).
39. V. I. Kalchenko, I. A. Koshets, E. P. Matsas, O. N. Kopylov, A. V. Solovyov, Z. I. Kazantseva, Yu. M. Shirshov. *Mater. Sci.* **20**, 73 (2002).
40. D. Filenko, Z. Kazantseva, K. Ivanova, O. Rabinovych, A. Kukla, Yu. Shirshov, V. Kalchenko, I. Rangelow. *Proceedings of the IEEE Sensors 2004 Conference*, p. 669, Vienna, Austria (2004).
41. D. Filenko, T. Gotszalk, Z. Kazantseva, O. Rabinovych, I. Koshets, Yu. Shirshov, V. Kalchenko, I. Rangelow. *Sens. Actuators, B* **111–113**, 264 (2005).