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# Phenylurea-equipped *p-tert*-butylthiacalix[4]arenes as the synthetic receptors for monocharged anions

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New *p-tert*-butylthiacalix[4]arenes linked with phenylurea fragments can serve as synthetic receptors for fluoride, acetate or dihydrogen phosphate anions depending on the conformation of the macrocycle (*cone*, *1,3-alternate*) and the number of substituents.

Molecular design of selective complexing agents for anionic substrates is one of the most rapidly developing areas in supramolecular chemistry.[1] Calixarenes and thiacalixarenes are widely used as molecular building platforms for creating hosts for specific types of guests.[2–9] It is well known that compounds containing amide, urea and thiourea moieties interact with anions through hydrogen bonding between the NH protons and the corresponding anion.[10–15] The effectiveness of such interactions, *i.e.*, the binding of receptor to a substrate, can be enhanced by increasing the number of specific spatial binding sites, as it is in dendrimer-like compounds.[16] Thus, we have proposed to combine the prospects of a thiacalixarene platform (existence in several configurations, the spatial orientation of substituents and the macrocyclic structure) and the ability of the urea moieties to interact with some anions.

Previously, we have shown that the variation of the length of the bridge connecting the phthalimide and macrocyclic fragments made it possible to synthesize thiacalix[4]arene derivatives containing from one to four phthalimide groups.[17] In this study, new phenylurea-linked thiacalix[4]arenes were synthesized (Scheme 1, Table 1) and their complexing properties towards some single charged anions were studied.

According to $^1$H-$^1$H NOESY NMR data, the presence of cross peaks between the protons of the spatially close *tert*-butyl groups and the propylidene fragment of compound **2** and their absence in the case of compound **3** confirm the *1,3-alternate* and *cone* conformation for the macrocycles **2** and **3**, respectively.

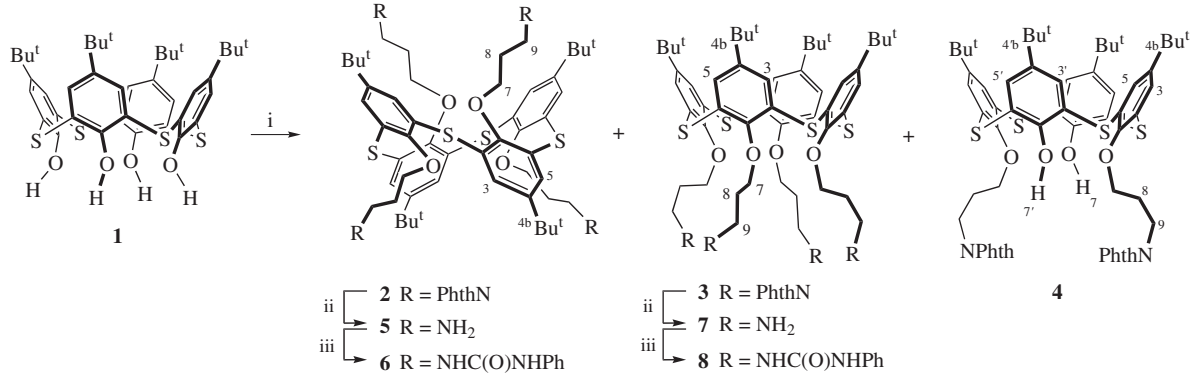
Note that the formation of the *cone* stereoisomer **3** herein observed is not typical of thiacalix[4]arene chemistry. More commonly, *1,3-alternate* stereoisomers do form and no template effect of alkali metal cations is observed.[18–20] In this study, template effect of sodium cation occurred in MeCN and the *cone* stereoisomer **3** was isolated in 53% yield, with the reaction passing through the partially alkylated intermediate **4**. In acetone which is a poorer solvent towards $Na_2CO_3$,[21] the reaction did not proceed.

**Table 1** Yields of compounds **2**–**4**.

| Base | Solvent | | | | | |
|---|---|---|---|---|---|---|
| | Acetone | | | Acetonitrile | | |
| | Product | *t*/h | Yield (%) | Product | *t*/h | Yield (%) |
| $Na_2CO_3$ | no reaction | | | **3** | 100 | 53 |
| | | | | **4** | 60 | 72 |
| $K_2CO_3$ | **2** | 20 | 51 | **2** | 20 | 50 |
| $Cs_2CO_3$ | **2** | 20 | 70 | **2** | 20 | 72 |

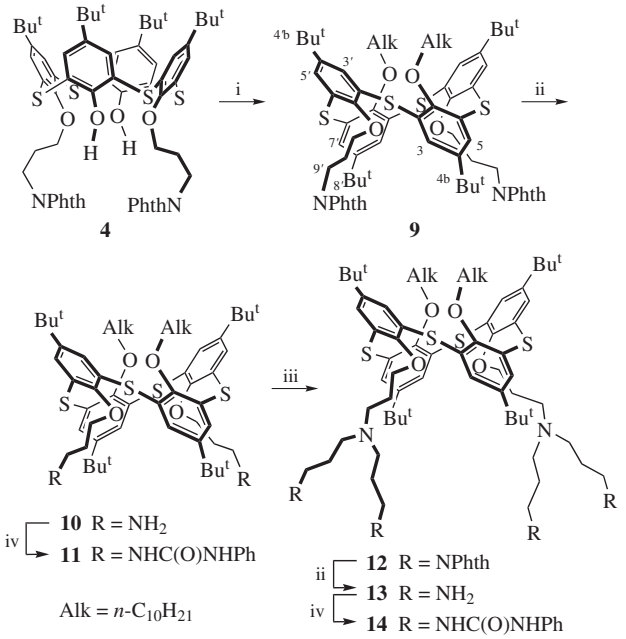
Hydrazinolysis of the phthalimido derivatives **2** and **3** gave amines **5** and **7**, respectively. Subsequent interaction of compounds **5** and **7** with phenyl isocyanate led to corresponding phenylurea derivatives **6** and **8**. According to 2D $^1$H-$^1$H NOESY NMR data, these transformations did not affect the conformation of the thiacalix[4]arene core.

Treatment of compound **4** with 1-bromodecane in acetone in the presence of cesium carbonate (Scheme 2) afforded tetrasubstituted thiacalix[4]arene derivative **9** in the *1,3-alternate* conformation. Its hydrazinolysis led to diamine **10**, which was then used in the synthesis of the first generation dendrimer-like compound **12** and corresponding phenylurea derivative **11**. The macro-




**1** **4**

**Scheme 1** *Reagents and conditions*: i, *N*-(3-bromopropyl)phthalimide, $M_2CO_3$, acetone or acetonitrile; ii, hydrazine hydrate, THF–EtOH; iii, PhNCO, THF.




**Scheme 2** *Reagents and conditions*: i, *n*-$C_{10}H_{21}Br$, $Cs_2CO_3$, acetone; ii, $N_2H_4 \cdot H_2O$, THF–EtOH; iii, *N*-(3-bromopropyl)phthalimide, $K_2CO_3$, acetone or acetonitrile; iv, PhNCO, THF.

cycle **12** was also subjected to hydrazinolysis followed by the treatment with phenyl isocyanate to furnish phenylureido derivative **14**.

The complexation properties of the synthesized *p-tert*-butylthiacalix[4]arenes containing phenylurea fragments was evaluated for a number of single charged anions ($F^-$, $Cl^-$, $Br^-$, $AcO^-$, $H_2PO_4^-$, $NO_3^-$) in chloroform with electron spectroscopy. The complexation of compound **6** could not be studied because of its low solubility. We initially determined the ability of the synthesized thiacalix[4]arene derivatives **8**, **11** and **14** to bind the tetrabutylammonuim cation of the salts *n*-$Bu_4NX$ ($F^-$, $Cl^-$, $Br^-$, $AcO^-$, $H_2PO_4^-$, $NO_3^-$) in $CDCl_3$ with molar ratios of 10:1, 1:1, 1:10 by $^1$H NMR spectroscopy and revealed no response to chemical shifts for *n*-$Bu_4N^+$ protons in the $^1$H NMR spectra in their presence. This indicates no interaction between thiacalix[4]arenes and tetrabutylammonuim cation.

By isomolar series method, the stoichiometry of the complexes was determined as 1:1. The association constant of the complexes was determined by the spectrophotometric titration (Table 2).† As could be seen from Table 2, the thiacalixarene **8** with four phenylurea fragments in the *cone* conformation binds a number of anions ($F^-$, $AcO^-$, $H_2PO_4^-$) with about the same efficiency. The maximum logarithm of the association constant value is observed for macrocycle **11** with acetate ion, and for compound **14** with the dihydrogen phosphate anion. As expected, the transition from the zero to the first generation derivative (macrocycles **11** and **14**) increases the number of the receptor fragments and hence the reception efficiency. However, the types of guests bonded change. Thiacalixarene **11** does not bind *n*-$Bu_4NBr$ and *n*-$Bu_4NNO_3$, and the host **14** *n*-$Bu_4NCl$ and *n*-$Bu_4NBr$.

**Table 2** Logarithms of association constants ($\lg K_{ass}$) of the complexes of thiacalixarenes synthesized and single charged anions.

| Compound | Anion | | | | | |
|---|---|---|---|---|---|---|
| | $F^-$ | $Cl^-$ | $Br^-$ | $H_2PO_4^-$ | $AcO^-$ | $NO_3^-$ |
| **8** | 4.83±0.25 | 3.41±0.17 | —[a] | 4.01±0.51 | 4.44±0.45 | — |
| **11** | 3.26±0.09 | 3.16±0.30 | — | 3.44±0.31 | 4.18±0.40 | — |
| **14** | 4.12±0.20 | — | — | 4.91±0.14 | 4.20±0.24 | 3.95±0.58 |

[a] No changes in UV spectra.

Compounds **8** and **14** have the same number of the binding sites. This allowed us to estimate the influence of the tertiary nitrogen atoms (compound **14**) on the complexation properties of a thiacalixarene. Lower association constants for fluoride ion and no affinity toward other halides in the case of thiacalixarene **14** are possibly caused by electrostatic repulsion of the lone pair of electrons of the tertiary amine group and the corresponding anions.

The high value of the complexation constant in the case of macrocycle **14** with dihydrogen phosphate anion is probably due to the interaction of $H_2PO_4^-$ with the phenylurea moieties and amine groups of the receptor (Figure 1). Possibly, the interaction of the dihydrogen phosphate anion protons with amine groups of the receptor reduces the intramolecular repulsion of the lone pairs of the latter one. This leads to the optimal spatial arrangement of the phenylurea fragments while a guest is bonded. The proposed structure of the thiacalixarene **14** and $H_2PO_4^-$ complex (Figure 1) was confirmed by $^1$H NMR spectroscopy. Downfield shift of 0.5 ppm and broadening of proton signals referred to the dihydrogen phosphate anion, as well as downfield shift of 0.2 ppm for methylene protons signals [$(CH_2)_3N$] indicate the involvement of the macrocycle amine group in the guest binding. The observed upfield 0.3 ppm change in signal position for *ortho*-protons of the phenyl substituent at the urea fragment during the interaction of compound **14** and $H_2PO_4^-$ confirms the binding of the anion by the urea fragment. Thus, the $^1$H NMR spectral data are in good agreement with the scheme proposed for the binding of compound **14** to the dihydrogen phosphate anion. The guest protons interact with the tertiary amine group of a host and the oxygen atoms with phenylurea fragments (Figure 1).

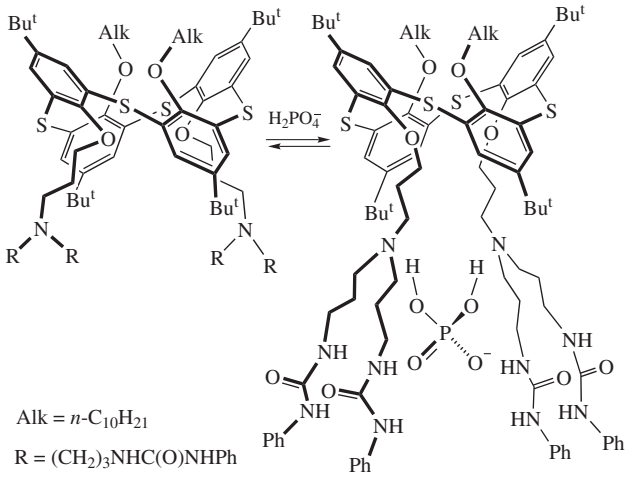



**Figure 1** Possible scheme for the formation of the thiacalixarene **14** and $H_2PO_4^-$ complex.

† The studies of the receptor properties of the thiacalix[4]arene derivatives **6**, **8**, **11**, **14** were carried out in $CHCl_3$ (analytical grade). UV spectra were recorded on the Perkin Elmer spectrophotometer Lambda 35.

*Determination of the stoichiometry of the complexes by isomolar series.* A series of experiments with a constant total concentration of a guest and host ($1\times10^{-6}$ mol dm$^{-3}$) and the varying guest/host ratio was carried out according to the standard method.[22]

*Determination of association constants lg $K_{ass}$ using electron spectroscopy.* The experiment was performed in chloroform with the $1\times10^{-6}$ mol dm$^{-3}$ concentration of a receptor. The efficiency of anion binding was determined by addition of 200-fold excess of corresponding tetrabutylammonium salt. The concentration of the anion was varied from $1\times10^{-6}$ to $2\times10^{-4}$ mol dm$^{-3}$. The stability constant was calculated by standard methods. The average value was estimated for three independent experiments with a standard deviation of ±3%.[22]

In summary, three new synthetic receptors have been constructed as hosts for single charged anions using *p-tert*-butylthiacalix[4]arene as a macrocyclic building platform and urea fragments as the binding sites.

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*Online Supplementary Materials*

Supplementary data associated with this article (syntheses and characteristics of compounds **2**–**14**) can be found in the online version at doi:10.1016/j.mencom.2013.01.015.

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