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Binding of neutral molecules by *p*-nitrophenylureido substituted calix[4]arenes

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ABSTRACT

Although originally designed for anion recognition, bis(*N′*-*p*-nitrophenylureido)calix[4]arenes immobilised in the 1,3-*alternate* conformation can act as receptors for small neutral molecules, such as sulfoxides and ketones. Their binding ability was studied both in solution and in the solid state using the combination of UV/vis, NMR, and X-ray crystallography.

1. Introduction

Calix[*n*]arenes, macrocyclic compounds with well-established chemistry enabling their easy/targeted derivatisation, are used frequently as molecular scaffolds for the design of various ligands and receptors.[1] As documented by numerous reviews and books published recently,[2] anion recognition represents an important part of supramolecular chemistry and many types of anion receptors were described. Among them the calix[4]arene-based receptors for anion recognition represent a well-established research area.[3]

Our recent research has been oriented to anion recognition using urea substituted calixarenes or thiacalixarenes. The introduction of amide or urea/thiourea moieties onto the calixarene skeleton enables the design of neutral anion receptors preorganised for complexation via directional hydrogen bonding from the –NH– functions. Based on our investigations we have developed the series of bis(ureido)calix[4]arenes in the *cone* or in the 1,3-*alternate* conformations.[4] During our complexation studies we have noticed that in some cases the binding of anions in more polar solvents, such as DMSO-d_6, is diminished and the interactions with neutral molecules (dimethyl sulfoxide) were observed instead of anion binding.

The recognition of neutral molecules by artificial receptors is a hot topic in supramolecular chemistry.[5] Moreover, neutral molecules like DMSO or DMF are important for their potential medicinal and environmental risks.[6] Hence, their recognition and sensing would be of great interest. The design of receptors suitable for the recognition of neutral molecules is rather challenging. Contrary to the complexation of charged molecules (cations, anions) one have to use only relatively weak non-covalent interactions as the strong electrostatic forces are usually worthless. On the other hand, highly directional hydrogen bonding arrays of urea functions combined with a suitably preorganised calixarene moiety may lead to efficient recognition of neutral molecules both in the solution and in the solid state.

Due to their unique three-dimensional shapes calixarenes are well known for their inclusion properties towards neutral molecules.[1] Especially, when they are preorganised in the *cone* conformation, calix[4]arenes posses a cavity capable of forming host–guest complexes using the π–π, CH–π or hydrophobic interactions. Interestingly, almost nothing is known about the binding ability of the corresponding 1,3-*alternate* conformers. In this paper we report the binding affinity of the upper-rim ureido-substituted calix[4]arenes towards selected sulfoxides and ketones.

2. Results and discussion

We have shown in our previous papers[4f,g] that the diureido derivatives immobilised in the *cone* or the 1,3-*alternate* conformations **1**–**4** are good anion receptors acting through the hydrogen bonding interactions of ureido functions. The binding constants were usually measured using NMR titration experiments in a $CDCl_3/CD_3CN$=4:1 v/v mixture. When facing the solubility

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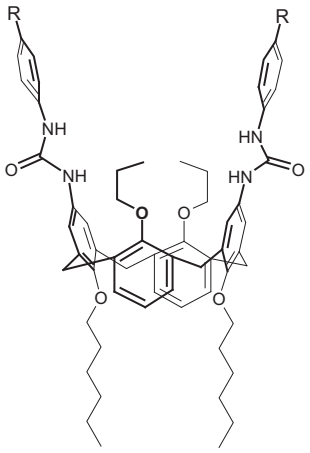
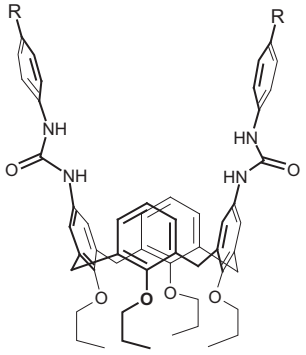
problems in case of nitroderivatives **1** or **3**, the addition of DMSO-d_6 as co-solvent led to the decrease of the corresponding complexation constants due to the competitive binding of DMSO. Thus, changing the solvent mixture to $CDCl_3$/DMSO-d_6 in the case of receptor **1** led to a measurable complexation of deuterated dimethyl sulfoxide.



1: R = NO_2
2: R = H



3: R = NO_2
4: R = H

Based on these preliminary results we performed the binding experiments with receptors **2** and **4** (model compound without the nitro groups in the *para*-positions of ureido phenyl) and **1** and **3** (*cone* analogue) towards dimethyl sulfoxide in $CDCl_3$. The results are collected in Table 1. It is obvious that the presence of the electron-withdrawing NO_2 group leads to more acidic ureido NH protons. Consequently, the NO_2 substituted compounds (**1** and **3**) are stronger receptors for neutral DMSO than the corresponding analogues with unsubstituted phenyl rings (**2** and **4**). While the receptors in the *cone* conformation are almost exclusively used for the binding of neutral compounds, receptor **1** in the 1,3-*alternate* conformation has a higher binding affinity towards DMSO when compared with the *cone* analogue **3**. This rather unexpected fact initiated further investigation of the binding ability of receptor **1** towards neutral guests both in solution and in the solid state.

Table 1
Binding constants K [mol^{-1} dm^3] of receptors **1**–**4** towards DMSO (^{1}H NMR titration, 300 MHz, $CDCl_3$, 298 K)

Receptor	K [mol^{-1} dm^3]
1	33±6
2	5±1
3	16±1
4	3±1

The ^{1}H NMR titration experiments were performed using a constant calixarene host concentration (0.5–2.0 mM) and an increasing concentration of appropriate guest to obtain different host : guest ratios (1:1–300). The results obtained are summarised in Table 2. The titration curves (Fig. 1) suggest the formation of complexes of 1:1 stoichiometry with the strongest binding of diphenyl sulfoxide (K=70±8 mol^{-1} dm^3).[7] Regardless of the high steric hindrance of bis(isopropyl) sulfoxide, the molecule is bound comparably to DMSO (compare runs 1 and 4, Table 2) while the binding constant for cyclic tetrahydrothiophene-1-oxide (run 3) is very low (K=8±4 mol^{-1} dm^3). As the sulfoxide SO bond is known for its high polarity (thus suitable for hydrogen bonding) we wondered if the substitution of SO by common carbonyl C=O bond could lead to a similar binding phenomenon. As follows from Table 2, ketones also showed measurable interactions with ureido functions with the exception of sterically hindered analogue *i*-Pr–CO–*i*-Pr. In agreement with the lower polarity of the C=O bond, the corresponding binding constants of ketones are always lower than those of sulfoxides (see runs 1–4 and 5–8, Table 2).

Table 2
Binding constants K [mol^{-1} dm^3] of receptor **1** towards selected neutral guests (^{1}H NMR titration, 300 MHz, $CDCl_3$, 298 K)

Run	Guest	K [mol^{-1} dm^3]
1	CH_3–SO–CH_3	33±6
2	Ph–SO–Ph	70±8
3	–$(CH_2)_4$–SO–[a]	8±4
4	*i*-Pr–SO–*i*-Pr	39±15
5	CH_3–CO–CH_3	5±1
6	Ph–CO–Ph	11±1
7	–$(CH_2)_4$–CO–[a]	7±2
8	*i*-Pr–CO–*i*-Pr	n.b.[b]

[a] Cyclic molecule.
[b] No binding observed.

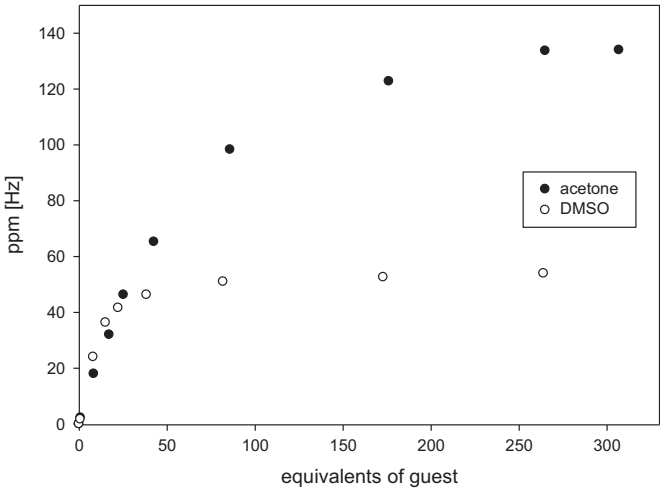
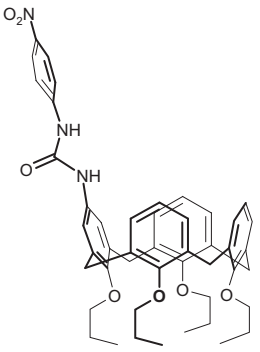


Figure 1. ^{1}H NMR titration curve for **1** with acetone (black circles) and DMSO (white circles), (300 MHz, 298 K, $CDCl_3$).

Although the interactions of the 1,3-*alternate* conformers with neutral molecules are obviously weak, the complexation phenomenon itself is interesting and rather unexpected. While the *cone* conformers have been mainly used for the binding of neutral molecules so far, our findings indicate the potential usefulness of the calix[4]arenes in the 1,3-*alternate* conformation[8] for the design and construction of neutral molecular receptors.



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The *p*-nitrophenyl group is a chromophore, hence, this structural motif in receptors **1** and **3** allowed us to perform complementary UV/vis titration experiments (Fig. 2a and b). The binding was clearly evidenced by a red shift of the *p*-nitrophenyl absorption band after the addition of increasing concentrations of DMSO. Titration experiments resulted in a well-defined isosbestic point suggesting the 1:1 binding stoichiometry. It cannot be confirmed by job's analysis because of low binding constants. Thus, the obtained sets of recorded absorption spectra were globally analyzed by the non-linear least-squares method assuming the 1:1 stoichiometry. The results are comparable with those obtained by NMR titration experiments showing that the receptor **1** (K=56 mol^{-1} dm^3) has a greater affinity towards DMSO than the receptor **3** (K=12 mol^{-1} dm^3). The model receptor **5**[4c] with one *p*-nitrophenylureido group on the upper rim has only one binding site for DMSO and undergoes similar spectral changes with a well-defined isosbestic point (K=24 mol^{-1} dm^3).

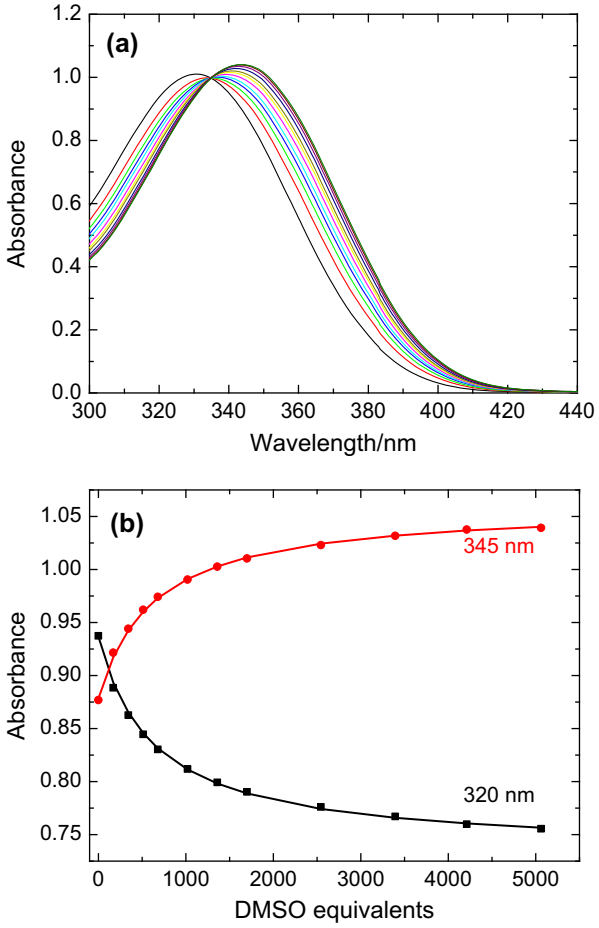

Figure 2. (a) UV/vis titration experiments and (b) binding isotherms of receptor **1** (c_0=3.3×10^{-5} M) after addition of DMSO (0–0.167 M) in $CHCl_3$ recorded at 320 nm and 345 nm. The solid lines represent the least-squares fit to the experimental data.

To gain a deeper understanding of the binding phenomenon receptor **1** was also studied in the solid state. Unfortunately, all our attempts at growing single crystals from DMSO failed.[9] On the other hand, the crystallization from an acetonitrile solution led to crystals suitable for the X-ray analysis. It was found that two solvent molecules are included within the crystal lattice while the cavity of the calixarene is surprisingly occupied by water molecule (originally present in MeCN). Water is fixed almost symmetrically in the middle of the cavity by two hydrogen bonds between the

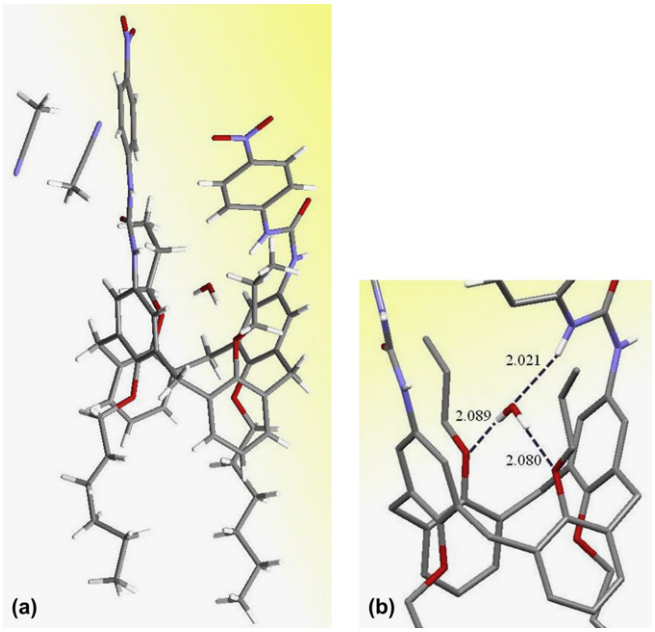

Figure 3. (a) The X-ray structure of complex **1**·H_2O·2CH_3CN. (b) Close-up of water binding, distances given in Å, hydrogen atoms of calixarene skeleton were deleted for better clarity.

oxygen atoms of two distal propoxy groups and water hydrogens (H···O distances are 2.08 Å and 2.09 Å). The third hydrogen bond is formed between the –NH– group of one ureido unit and the oxygen atom in water (H···O distance is 2.02 Å). As the second ureido function is not involved in the binding, the overall molecular symmetry is disturbed and the *p*-nitrophenyl group is bent over the calixarene cavity (Fig. 3). In the crystal packing the individual calixarene molecules are interconnected to each other via a complex system of hydrogen bonds where both ureido moieties are involved in the hydrogen bond bridges. Albeit the binding mode of water in the complex does not utilise both ureido functions, the binding motif indicates the ability of the 1,3-*alternate* conformation to interact with small neutral molecules via hydrogen bonding interactions.

3. Conclusions

In conclusion, the bis(*N*′-*p*-nitrophenylureido)-calix[4]arenes immobilised in the 1,3-*alternate* conformation, originally designed for anion recognition, have been studied as receptors for small neutral molecules, such as sulfoxides and ketones. Although the corresponding binding constants are small, the complexation phenomenon indicates potential applications of the 1,3-*alternate* conformation in the design of new molecular receptors.

4. Experimental

4.1. Synthesis

The synthesis of all four ligands **1**–**4** (Fig. 1) was already published by our group and compounds were prepared according to known procedures.[4f,g]

4.2. NMR titration experiments

The ^{1}H NMR titration experiments were performed using a constant calixarene host concentration (0.5–2.0 mM) and increasing concentration of appropriate guest to obtain different

host : guest ratios (1:1–300) in $CDCl_3$ as solvent using a Varian Gemini 300 spectrometer (300 MHz, 298 K). The corresponding binding constants (Table 1 and 2) were calculated using the original non-linear regression curve-fitting program.[7]

4.3. UV/vis titration experiments

Binding experiments were performed in $CHCl_3$ at room temperature (25±2 °C). Typically 3.3×10^{-5} M **1** in $CHCl_3$ was titrated with DMSO up to 0.2 M concentration. The recorded sets of the absorption spectra were globally analyzed using the Specfit program (v. 3.0, Spectrum Software Associates) to get the corresponding binding constants. Estimated error is 15%.

4.4. X-ray crystallography

4.4.1. Crystallographic data for $C_{60}H_{70}N_6O_{10}\cdot 2CH_3CN\cdot H_2O$. M=1135.37, orthorhombic system, space group $P2_12_12_1$, a=11.8319(1) Å, b=14.3658(2) Å, c=36.3764(4) Å, Z=4, V=6183.07(12) Å^3, D_c=1.220 g cm^{-3}, μ (Mo Kα)=0.084 mm^{-1}, crystal dimensions of 0.25×0.32×0.38 mm. Data were collected at 150(2) K on a Nonius KappaCCD diffractometer with graphite monochromated Mo Kα radiation. The structure was solved by direct methods[10] using the CRYSTALS suite of programs[11] and anisotropically refined by full matrix least-squares on F value to final R=0.0382 and R_w=0.0448 using 6014 independent reflections (Θ_{max}=25.020°) and 802 parameters. The position of disordered groups was found from the electron density maps. Disordered fragments were then placed in appropriate positions, and all distances between neighbouring atoms and angles were fixed. Site occupancies were refined for the different parts with same thermal parameters for the same atoms in the various fragments. At the end of refinement, site occupancies were fixed and hydrogen atoms were placed in calculated positions.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.08.006. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. For books on calixarenes see: (a) Gutsche, C. D. *Calixarenes: An introduction*, 2nd ed.; The Royal Society of Chemistry, Thomas Graham House: Cambridge, 2008; (b) *Calixarenes in the Nanoworld*; Vicens, J., Harrowfield, J., Backlouti, L., Eds.; Springer: Dordrecht, 2007; (c) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001; (d) Mandolini, L.; Ungaro, R. *Calixarenes in Action*; Imperial College: London, 2000; (e) Gutsche, C. D. In *Calixarenes revisited: Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998; Vol. 6.
2. For recent reviews/books on anion-recognition see: (a) Sessler, J. L.; Gale, P. A.; Cho, W. S. *Anion Receptor Chemistry*; The Royal Society of Chemistry: Cambridge, 2006; (b) *Recognition of Anions*; Vilar, R., Ed.; Springer GmbH: Berlin, 2008; (c) *Anion Sensing, Topic in Current Chemistry*; Stibor, I., Ed.; Springer: Berlin, 2005; Vol. 255; (d) Amendola, V.; Fabbrizzi, L. *Chem. Commun.* **2009**, 513–531; (e) Cametti, M.; Rissanen, K. *Chem. Commun.* **2009**, 2809–2829; (f) Gale, P. A.; Garcia-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151–190; (g) Gale, P. A.; Beer, P. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516; (h) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., Garcia-Espana, E., Eds.; Wiley-VCH: New York, NY, 1997.
3. For review on calixarene-based anion receptors see: (a) Matthews, S. E.; Beer, P. D. *Calixarenes* **2001**, 421–439 (see Ref. 1c); (b) Lhoták, P. *Top. Curr. Chem.* **2005**, *255*, 65–96 (see Ref. 2c); (c) Matthews, S. E.; Beer, P. D. *Supramol. Chem.* **2005**, *17*, 411–435; (d) Kalchenko, V. I. *Pure Appl. Chem.* **2008**, *80*, 1449–1458.
4. For some recent examples of urea-substituted calixarene-bases receptors from our group see: (a) Dudic, M.; Lhoták, P.; Stibor, I.; Lang, K.; Prosková, P. *Org. Lett.* **2003**, *5*, 149–152; (b) Zlatuskova, P.; Stibor, I.; Tkadlecová, M.; Lhoták, P. *Tetrahedron* **2004**, *60*, 11383–11390; (c) Lang, K.; Curinová, P.; Dudic, M.; Prosková, P.; Stibor, I.; Stastny, V.; Lhoták, P. *Tetrahedron Lett.* **2005**, *46*, 4469–4472; (d) Lhoták, P.; Svoboda, J.; Stibor, I. *Tetrahedron* **2006**, *62*, 1253–1257; (e) Kroupa, J.; Stibor, I.; Pojarova, M.; Tkadlecova, M.; Lhotak, P. *Tetrahedron* **2008**, *64*, 10075–10079; (f) Stibor, I.; Budka, J.; Michlová, V.; Tkadlecová, M.; Pojarová, M.; Curínová, P.; Lhoták, P. *New J. Chem.* **2008**, *32*, 1597–1607; (g) Curínová, P.; Stibor, I.; Budka, J.; Sykora, J.; Lang, K.; Lhoták, P. *New J. Chem.* **2009**, *33*, 612–619.
5. (a) Brotin, T.; Dutasta, J. P. *Chem. Rev.* **2009**, *109*, 88–130; (b) Coquiere, D.; Le Gac, S.; Darbost, U.; Seneque, O.; Jabin, I.; Reinaud, O. *Org. Biomol. Chem.* **2009**, *7*, 2485–2500; (c) Rudkevich, D. M. *Eur. J. Org. Chem.* **2007**, *20*, 3255–3270; (d) Mateos-Timoneda, M. A.; Kerckhoffs, J. M. C. A.; Crego-Calama, M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3248–3253; (e) Cram, D. J.; Cram, J. M. In *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1994.
6. (a) Jacob, S. W.; de la Torre, J. C. *Pharmacol. Rep.* **2009**, *61*, 225–235; (b) Herbold, B.; Haas, P.; Seel, K.; Walber, U. *Mutat. Res., Genet. Toxicol. Environ. Mutagen.* **1998**, *412*, 167–175.
7. The biding constants were calculated using the computer program OPIUM (Kyvala M.) freely available at: http://www.natur.cuni.cz/~kyvala/opium.html. All our attempts to measure the stoichiometry of complexes using Job plot analysis have failed as the small complexation constants did not lead to well resolved maximum in the corresponding plots. Anyhow, the complexation curves gave the best fit using 1:1 stoichiometry.
8. For complexation of neutral molecules (gases) by the cavity of 1,3-*alternates* see Ref. 5c.
9. For X-ray structures of diarylurea–DMSO complexes see Etter, M. C.; Urbakzyk-Lipkowska, Z.; Zia-Ebrahimi, S. M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415–8426.
10. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
11. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.