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Urea derivatives of calix[4]arene *1,3-alternate*: an anion receptor with profound negative allosteric effect

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Abstract—The complexation behaviour of tetrakis(phenylureido)calix[4]arene in the *1,3-alternate* conformation has been studied using NMR titration experiments. It was found that this receptor with two possible binding sites exhibits a strong negative allosteric effect which leads to the exclusive complexation of only one anion. © 2001 Elsevier Science Ltd. All rights reserved.

Calix[4]arenes, well-known macrocyclic molecules with almost unlimited derivatisation potential, possess a unique three-dimensional structure with outstanding shaping possibilities.[1] During last decade these compounds have been widely used in supramolecular chemistry as building blocks or molecular scaffolds for the construction of receptors towards ions or neutral molecules.[2] While the complexation of cations[1–3] has been studied very intensively, the application of calixarenes for anion complexation remains relatively unused. Thus, several calixarene derivatives bearing activated amides[4] as hydrogen bonding units have been reported to interact with anions. Similarly, calix[4]arenes with two ureas or thioureas exhibit[5] a complexation ability towards anions, while the *cone* conformation bearing four urea units on the upper rim tends to give rise to the formation of intermolecular hydrogen bonds.[6] This phenomenon, the formation of dimeric structures, obviously adversely affects the complexation properties towards anions. In this communication we report the first synthesis and study of complexation abilities of a tetraureido calix[4]arene derivative immobilised in a *1,3-alternate* conformation.

The synthesis of derivative **5** is depicted in Scheme 1. *tert*-Butylcalix[4]arene **1** was immobilised in the *1,3-alternate* conformation by alkylation[7] with PrI/Cs_2CO_3 in acetone to yield derivative **2** (41%). *ipso*-Nitration[8] with 100% HNO_3 in a CH_2Cl_2/CH_3COOH mixture (80% yield) and subsequent reduction (98%) of the tetranitrocalix[4]arene **3** using $SnCl_2 \cdot 2H_2O$ in refluxing ethanol[9] gave the appropriate tetra-amino derivative[10] **4** in high yield. Reaction with phenyl isocyanate[11] in CH_2Cl_2 at room temperature led to the tetraureidocalix[4]arene **5** in 50% yield. Similarly, diureidocalix[4]arene **8**[12] and the corresponding benzoylamino derivative **9** were prepared via the diamino precursor **7** according to Scheme 2.

Tetraureido derivative **5** represents a receptor with two possible binding sites due to the preorganisation of the *1,3-alternate* conformer, supposing the simultaneous and cooperative effect of two urea units during the binding. The complexation ability of this compound was measured by standard ^{1}H NMR titration experiments ($CHCl_3$:CH_3CN = 4:1 v/v) using a constant calixarene concentration (0.5–2.0 mM) and increasing concentrations of the appropriate anion to obtain different host/guest ratios (0.1–20).[13] Addition of NBu_4Cl to the solution of **5** results in large down-field shifts of both urea -NH- signals (ca. 2 ppm), indicating strong binding of Cl^- via hydrogen bonds (Fig. 1). Similarly, large complexation induced chemical shifts were observed upon addition of NBu_4Br or NBu_4I.

It seems to be obvious that the complexation of spherical anions could occur at both anion binding positions of receptor **5**, however, the measuring of the complex stoichiometry revealed a different situation. The Job plot procedure unambiguously confirmed the exclusive formation of only 1:1 complexes with halides. Table 1 shows the corresponding association constants for this process. It is clear that the association constants for halides indirectly follow the diameter of the anions: K_{Cl} (4660 M^{-1})>K_{Br} (1450 M^{-1})>K_I (570 M^{-1}) which reflects the size recognition ability of receptor **5**. On the other hand, the complexation (1:1 complexes) of the dihydrogenphosphate ($K_{H_2PO_4}$ = 2610 M^{-1}),

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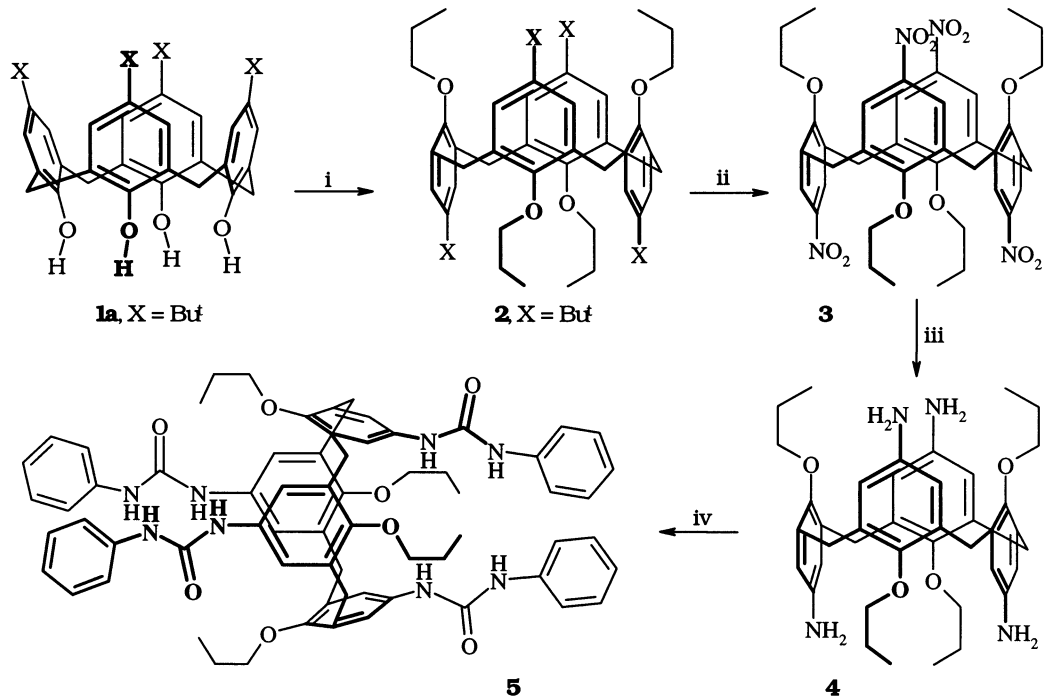
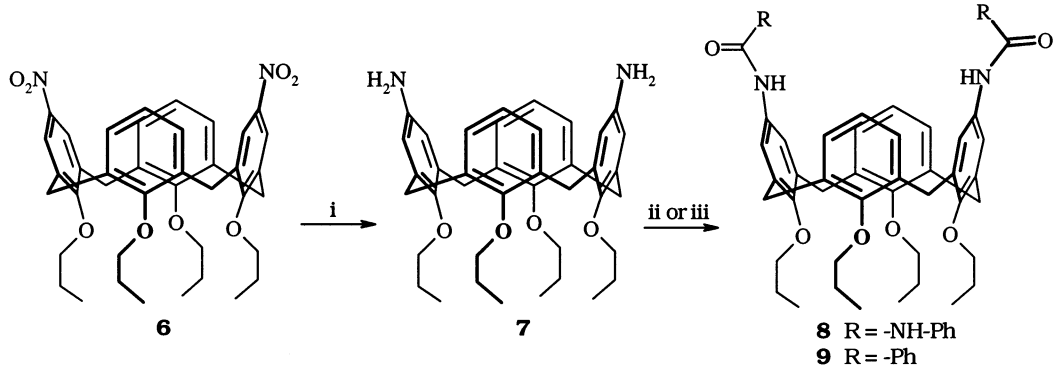
acetate ($K_{MeCO_2} = 2100\ M^{-1}$) or benzoate ($K_{PhCO_2} = 1800\ M^{-1}$) anions does not show any distinctive selectivity, presumably as a consequence of the almost equal steric requirements of these anions.

The fact that receptor **5** is unable to bind a second anion is interesting and a rather unpredictable phenomenon. The distance between both complexation sites is more than 11 Å, which does not justify an explanation based solely on possible repulsive interactions between two negatively charged sites. Rather, this could be ascribed to a strong negative allosteric effect induced by the change of conformation. The binding of the first anion leads to outstretching of the two ureido clefts engaged in the complexation to adjust to the ideal mutual distance needed for hydrogen bonding (Fig. 2). As a consequence the two propoxy groups on the opposite site of the *1,3-alternate* receptor **5** become closer to each other thus disturbing the geometry suitable for binding of a second anion.

To gain a deeper insight into the complexation process, the model compound **8** bearing only two ureido units was used for a complexation study. Again, in all cases only formation of a 1:1 complex was observed (Job plot). As follows from Table 1, the association constants towards selected anions are almost identical with those of receptor **5**, which indicates similar binding modes for both compounds. In other words, the binding circumstances of the disubstituted *cone* derivative **8** strongly resembles that of the *1,3-alternate* tetrasubstituted derivative **5**. Namely, two suitably preorganised ureido groups create simultaneous hydrogen



Scheme 1. (i) PrI, $CsCO_3$, acetone, reflux (41% yield); (ii) 100% HNO_3, CH_2Cl_2/CH_3COOH, rt (80%); (iii) $SnCl_2 \cdot 2H_2O$, ethanol, reflux (98%); (iv) Ph-N=C=O, CH_2Cl_2, rt (50%).



Scheme 2. (i) $SnCl_2 \cdot 2H_2O$, ethanol, reflux; (ii) Ph-N=C=O, CH_2Cl_2, rt (63%); (iii) PhCOCl, CH_2Cl_2, Et_3N (40%).

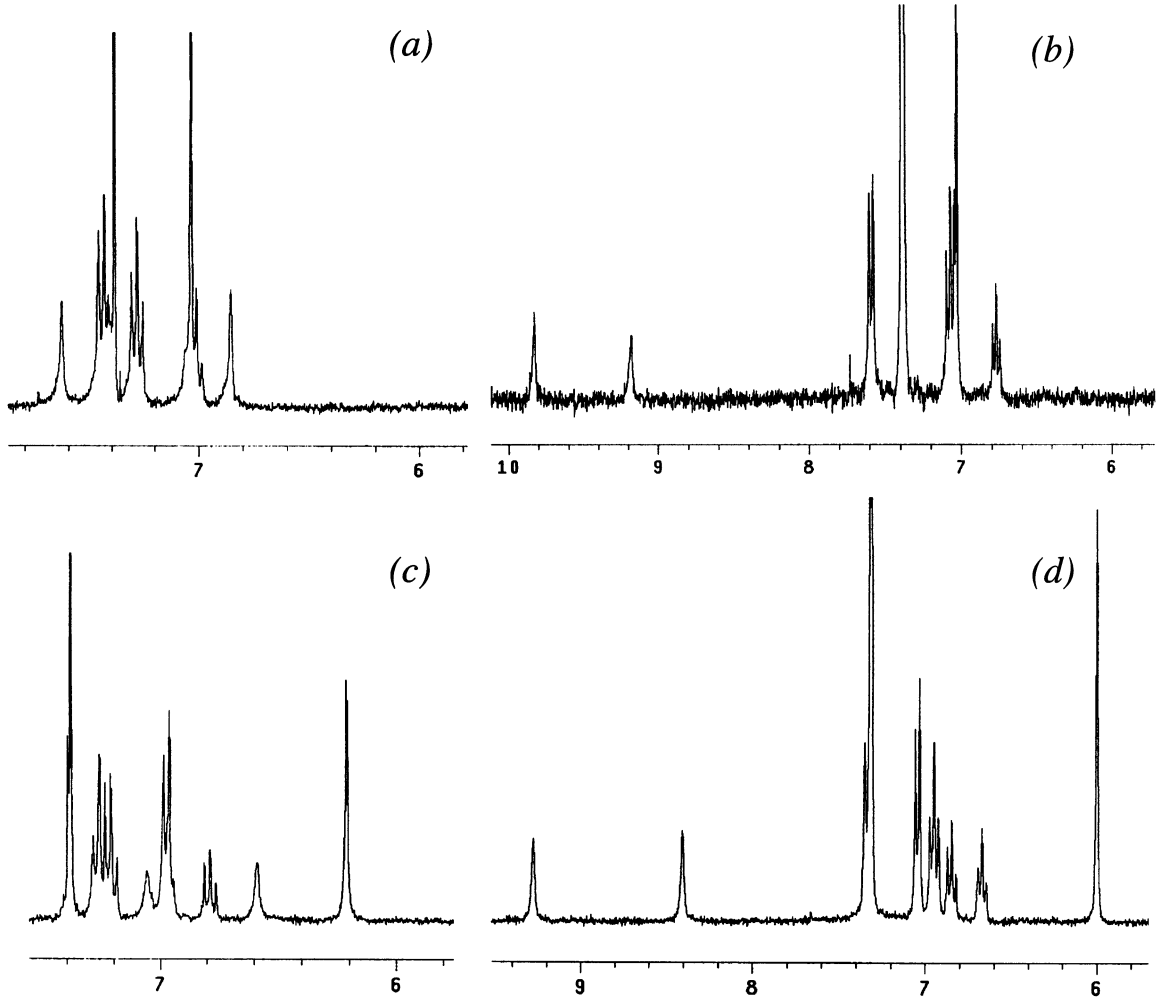


Figure 1. Partial ^{1}H NMR spectra (300 MHz, 298 K) in $CDCl_3$:CD_3CN = 4:1 v/v: (a) free **5**; (b) **5** after addition of NBu_4Ac (3 equiv.); (c) free **8**; (d) **8** after addition of NBu_4Ac (3 equiv.).

bonds to achieve efficient complexation of the anion. The only significant difference was observed in the case of tetrabutylammonium benzoate. While compound **5** exhibits almost the same complexation constant (K_{PhCOO} = 1800 M^{-1}) as that for acetate (K_{MeCOO} = 2100 M^{-1}), in the case of **8** the complexation constant for benzoate is much more than one order of magnitude higher (K_{PhCOO} = 161 000 M^{-1}). A reasonable explanation could be based on the additional interactions between the aromatic parts of the benzoate and calixarene moieties. These interactions are obviously excluded in receptor **5** due to the steric hindrance of the inverted propoxysubstituted aromatic rings. Another model compound, diamide **9**, was used to demonstrate the importance of urea units for the strength of the interactions. As follows from Table 1, the presence of two amide groups results in a dramatic reduction of the complexation ability of derivative **9**.

Table 1. Complexation constants of receptors **5**, **8** and **9** towards selected anions (^{1}H NMR, $CDCl_3$: CD_3CN = 4:1 v/v, 25°C, 300 MHz)

Anion	K_C [mol^{-1} ΣI]		
	5	**8**	**9**
Chloride	4660 ± 190	4640 ± 490	[a]
Bromide	1450 ± 95	1370 ± 160	–
Iodide	570 ± 90	710 ± 190	–
$H_2PO_4^-$	2610 ± 300	2300 ± 480	4.3 ± 1.1
Acetate	2110 ± 200	3940 ± 1180	–
Benzoate	1800 ± 700	161 000 ± 45 000	–

[a] No changes in NMR spectra were observed.

In conclusion, the novel tetraureido calix[4]arene receptor **5** with the *1,3-alternate* conformation, albeit preorganised for multiple binding, was proven to complex exclusively only one anion with a distinctive size selectivity towards halides. As was demonstrated using model compounds, this phenomenon is attributable to a strong negative allosteric effect operating in the receptor molecule during the complexation process.

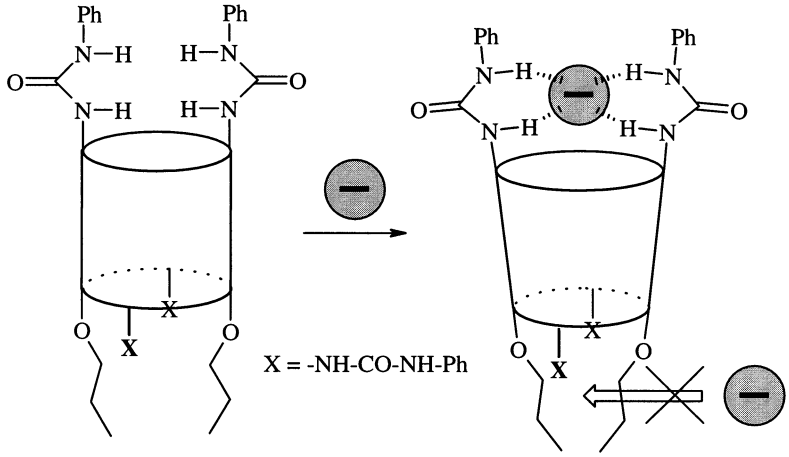


Figure 2. Exclusive formation of 1:1 complex in derivative **5**.

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10. *Procedure for the preparation of derivative* **5***:* To a stirred solution of tetra-amine **4** (100 mg, 0.15 mmol) in 6 ml of dry dichloromethane, phenylisocyanate (0.83 ml, 7.5 mmol, 50 equiv.) was added at room temperature. The clouded reaction mixture was stirred for 12 h and poured into methanol to produce a clear solution. The mixture was evaporated to dryness under a reduced pressure. The solid residue was dissolved in small amount of methanol and stored overnight in a freezer to yield 86 mg (50%) of derivative **5** (mp >350°C, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (brs, 4H, -NH-CO), 7.73 (d, 8H, $J=8.2$ Hz, H-arom), 7.35 (m, 8H, H-arom), 7.09 (t, 4H, $J=7.2$ Hz, H-arom), 6.99 (s, 8H, H-arom), 6.56 (brs, 4H, -NH-CO), 3.72 (t, 8H, $J=7.2$ Hz, O-CH_2-CH_2-), 3.47 (s, 8H, Ar-CH_2-Ar), 1.88 (m, 8H, O-CH_2-CH_2-), 1.04 (t, 12H, $J=7.2$ Hz, -CH_2-CH_3); MS ESI (CH_3CN/acetone+NaI): calcd 1128.55 (M^+), found 1151.6 $(M+Na)^+$. Anal. calcd for $C_{68}H_{72}N_8O_8$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.52; H, 6.31; N, 9.71.
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12. *Derivative* **8***:* Obtained similarly to compound **5**, yield (63%), mp 266–8°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 4H, H-arom), 7.25 (d, 4H, $J=7.7$ Hz, H-arom), 7.12 (d, 4H, $J=7.7$ Hz, H-arom), 7.04 (t, 2H, $J=6.8$ Hz, H-arom), 6.93 (t, 2H, $J=7.2$ Hz, H-arom), 6.00 (s, 4H, H-arom), 4.46 (d, 4H, $J=13.4$ Hz, Ar-CH_2-Ar_{ax}), 4.01 (t, 4H, $J=8.3$ Hz, O-CH_2-CH_2-), 3.67 (t, 4H, $J=6.6$ Hz, O-CH_2-CH_2-), 3.16 (d, 4H, $J=14.3$ Hz, Ar-CH_2-Ar_{eq}), 1.96–1.83 (m, 8H, O-CH_2-CH_2-), 1.11 (t, 6H, $J=7.5$ Hz, -CH_2-CH_3), 0.87 (t, 6H, $J=7.5$ Hz, -CH_2-CH_3); MS FAB calcd 860.41, found 861.8 $(M+H)^+$. Anal. calcd for $C_{54}H_{60}N_4O_6$: C, 75.32; H, 7.02; N, 6.51. Found: C, 74.98; H, 6.94; N, 6.56.
13. The stoichiometry of complexes and the complexation constants were calculated using the computer program OPIUM (Kyvala, M.) freely available at http://www.natur.cuni.cz/~kyvala/opium.html.