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Unusual stoichiometry of urea-derivatized calix[4]arenes induced by anion complexation

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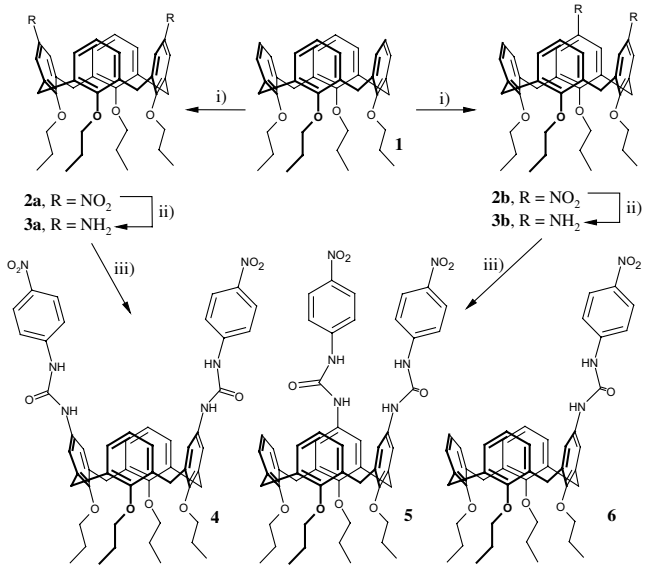
Abstract—Calix[4]arenes bearing two *p*-nitrophenyl-ureido functions at the upper rim are effective anion binders. The stoichiometry of complexation depends on the substitution pattern (distal vs proximal) and anion concentration. While the distally substituted receptor forms 1:1 complexes with anions, the corresponding proximal derivative prefers the 2:1 stoichiometry (calixarene:anion) under identical conditions.

Calix[4]arene derivatives[1] are extensively utilized as molecular scaffolds for the design and construction of elaborated supramolecular systems, including anion receptors.[2] We previously reported on the synthesis of calix[4]arenes bearing two phenylurea[3] and tetraphenylporphyrinurea[4] functions at the upper rim and their binding affinity towards selected anions (halogens, carboxylates). The binding is governed by hydrogen bonding between the urea-hydrogen atoms and anions.[5] During our ongoing research on the modulation of the strength of the interaction by substituent effects we designed novel receptors **4** and **5**. Here we report how the substitution pattern of the upper rim and the insertion of the nitro group affect the binding affinity towards anions and the stoichiometry of complexes including the first example of anion-induced calixarene dimerization.

The synthesis of the receptors (Scheme 1) started from tetrapropoxyderivative **1** immobilized in the cone conformation. Nitration with 100% HNO_3 according to a known procedure[6] yielded the mixture of regioisomers **2a** and **2b**. They were separated and reduced[7] to the corresponding diamines **3a** and **3b**. In the final step, the reaction of **3a** and **3b** with *p*-nitrophenyl isocyanate



Scheme 1. Reagents and conditions: (i) 100% HNO_3/DCM/AcOH, **2a** (30%) + **2b** (27%); (ii) $SnCl_2 \cdot 2H_2O$/EtOH, reflux, **3a** (87%), **3b** (81%); (iii) *p*-nitrophenyl isocyanate/THF, **4** (75%), **5** (71%), **6** (77%).

led to **4** and **5** in high yields (>70%), respectively. The model receptor **6** with one ureido function was synthesized using the same synthetic strategy. The structures of all compounds were confirmed by ^1H, ^{13}C NMR, IR and MS spectroscopy and elemental analysis.[8]

Keywords: Calixarene; Anion complexation; Dimerization; Receptor.
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Table 1. Binding constants[9] K_{11} (M^{-1}) in CH_2Cl_2 at 298 K

Anion[a]	**4**	**5**[b]	**6**
Cl^-	$>10^6$	$\geqslant 10^5$, $\beta_{21} \geqslant 10^{11}$	5.3×10^4
Br^-	$>10^6$	$\beta_{21} \geqslant 10^{10}$	1.2×10^4
I^-	1.7×10^5	5×10^3, $\beta_{21} = 5\times10^9$	1.2×10^3
NO_3^-	4.1×10^5	1×10^4, $\beta_{21} \geqslant 10^{10}$	6.9×10^3
BzO^-	$>10^6$	1×10^5, $\beta_{21} \geqslant 10^{10}$	6.2×10^5
AcO^-	$>10^6$	$\beta_{21} \geqslant 10^9$	4.3×10^5

[a] Anions were used as tetrabutylammonium salts. Estimated error is 15%.

[b] In all cases the Job plots indicate the stoichiometry of 2:1.

The binding affinity of **4**–**6** towards selected anions of spherical (Cl^-, Br^- and I^-), triangular (NO_3^-) and other (BzO^-, AcO^-) shapes was studied in CH_2Cl_2 and $CDCl_3$ using UV–vis and ^1H NMR titrations, respectively. As the binding constants were too large to be measured accurately by NMR spectroscopy, our conclusions are based on comparative UV–vis titration experiments (Table 1). The binding was clearly evidenced by a red shift of the nitrophenyl absorption band after the addition of increasing concentrations of anions. In all cases the binding stoichiometry was determined by Job's analysis.

The diametrically functionalized receptor **4** has a high affinity towards all anions (Table 1). In most cases the corresponding binding isotherms exhibit a sharp saturation beyond the molar concentration ratio **4**:anion = 1:1 indicating the stoichiometry of the complexes to be 1:1 and the binding constants above $10^6\ M^{-1}$ (Fig. 1). The stoichiometry was confirmed by Job's plots constructed from UV–vis and ^1H NMR data. The chemical shifts of the NH hydrogens indicated favourable hydrogen bonding between anions and the urea hydrogen atoms. Comparison of **4** with the model compound **6** documents the importance of multipoint interactions on the efficiency of the binding. From large differences, for example, $K_{Cl}^{\mathbf{4}} > 10^6$ versus $K_{Cl}^{\mathbf{6}} = 5.3\times10^4\ M^{-1}$, it is evident that the cooperative effect of two ureas contributing four hydrogen bonded interactions, is much more efficient. In addition, the interaction between NH and anions is much stronger when compared to the structurally equivalent calix[4]arene–porphyrins[4] or calix[4]arene–benzenes[3] since the nitro group on the benzene ring makes the ring electron deficient thus increasing the hydrogen bond donating capability of the NH groups. For example, the substitution of the porphyrin unit in **6** for *p*-nitrophenyl strengthens the binding constant from 6.3×10^3 to $5.3\times10^4\ M^{-1}$ for Cl^-.[4]

The high affinity of benzoates and acetates towards **6** (Table 1) means that the two-urea receptor **4** can bind two anions, each anion by the separate urea moiety. These complexes **4**·(anion)$_2$ are observed with an excess of anions and are indicated by an additional red shift of the absorption band from 360 nm, belonging to **4**·(BzO^-), to 378 nm (Fig. 2). Evidently, the binding mode also affects the spectral features of the complexes. The complex **6**·(BzO^-) is characterized by the absorption band at 380 nm while the complex of the same stoichiometry **4**·(BzO^-), with anion bound by two ureas, has the band at 360 nm. The absorption band of **4**·(BzO^-)$_2$ is located at 378 nm, similar to **6**·(BzO^-), confirming that ureas of **4** are involved in the binding of separate anions.

Comparison of diametrically substituted **4** and proximally substituted **5** revealed that the substitution pattern of the calix[4]arene upper rim has dramatic consequences on the complexation stoichiometry. The absorption spectra of **5** show an isosbestic point until the molar ratio **5**:anion approximately reaches 2:1 followed by the appearance of a new band concomitant with a new isosbestic point (Fig. 3). It indicates that the complex stoichiometry is **5**$_2$·(anion), that is two receptor molecules are interconnected by an anion. The stoichiometry 2:1 is confirmed by Job's plots constructed using UV–vis and ^1H NMR experiments for all anions (Fig. 3). From the spectral features it can be deduced that the anion is bound within two urea moieties of the calixarene dimer. As suggested by Job's plots

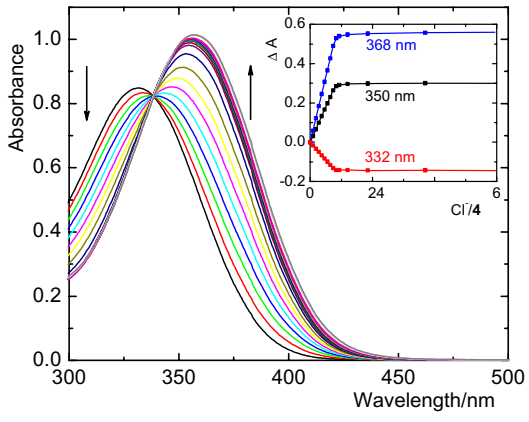

Figure 1. UV–vis titration of **4** (2.9×10^{-5} M) with Cl^- (up to 7.5×10^{-3} M) in CH_2Cl_2 reflecting the typical 1:1 stoichiometry of the complex. Arrows show changes due to increasing concentration of Cl^-. Inset: Binding isotherms at selected wavelengths. The solid lines represent connected experimental points for clarity.

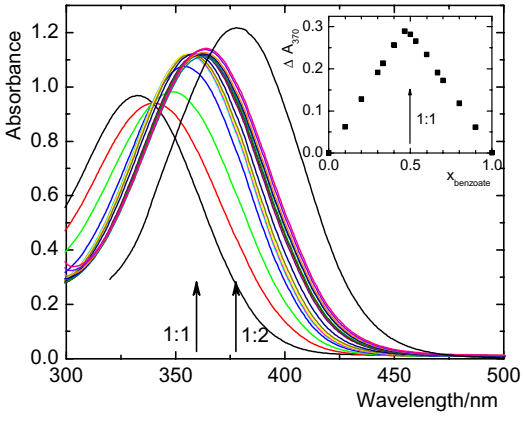

Figure 2. UV–vis titration of **4** (3.3×10^{-5} M) with BzO^- (to 1.3×10^{-2} M) in CH_2Cl_2. The complete formation of **4**·(BzO^-)$_2$ (i.e., 1:2) needs large excess of BzO^- (>0.1 M). Inset: Job's plot documenting that the stoichiometry at comparable concentrations of **4** and BzO^- is 1:1; constructed from absorbance changes at 370 nm, the sum of concentrations 3.0×10^{-5} M.

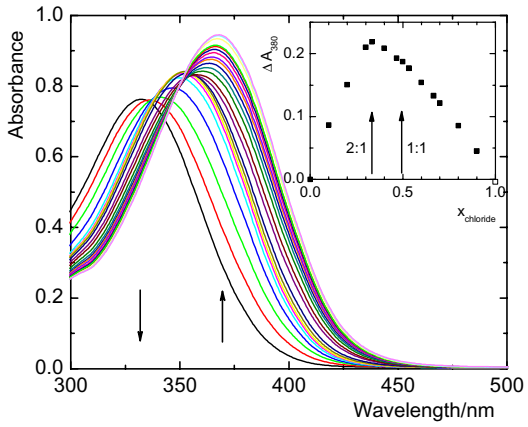

Figure 3. UV–vis titration of **5** (2.7×10^{-5} M) with Cl^- (0–1.2×10^{-2} M) in CH_2Cl_2. Arrows show changes due to increasing concentration of Cl^-. Inset: Job's plot documenting the formation of the 2:1 complex $(\mathbf{5})_2 \cdot Cl^-$. Plot was constructed from the absorbance changes at 380 nm using the sum of concentrations 2.9×10^{-5} M.

the complex $\mathbf{5}_2$·(anion) dissociates at an excess of anions to form the complex **5**·(anion) of the stoichiometry 1:1 (Fig. 3, inset). Since **5**·(anion) is spectrally very similar to **6**·(anion) or **4**·(anion)$_2$ rather than to **4**·(anion), the sterical reasons, and the similarity of K_{11} of **5** and **6** the binding pattern in **5**·(anion) can be most likely attributed to one urea–anion arrangement.

To the best of our knowledge anion-induced dimerization has not been reported in the calixarene chemistry so far. Surprisingly, the formation of $\mathbf{5}_2$·(anion) is observed for all studied anions irrespective of their geometry (Table 1). It is known that tetraurea calix[4]arenes form dimeric capsules with a suitable guest included[10a] and some bis(ureido)calix[4]arenes give a hydrogen bonded dimer in the pinched cone conformation.[10b] The analysis of the upfield shift of the urea hydrogens of **4** or **5** in ^{1}H NMR dilution experiments provides dimerization constants below 200 M^{-1} indicating that self-aggregation is negligible under UV–vis titration conditions (Fig. 4). The plausible explanation of dimerization consists of the anion templating effect and the

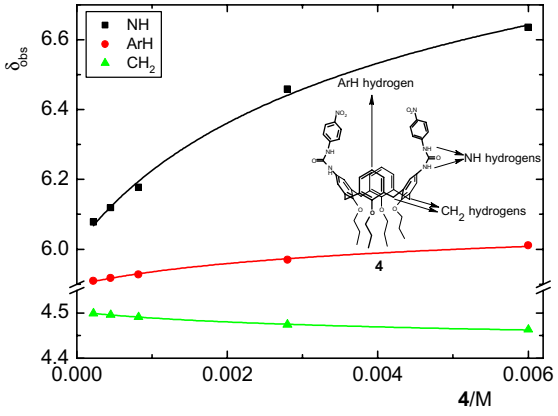

Figure 4. Dilution experiments with **4** in $CDCl_3$ at 298 K. The solid lines represent the least-squares fit to the experimental data;[11] K_D estimated from the curve fit is 90 M^{-1}.

dimer reinforcement via additional complementary hydrogen bonds of individual calixarenes.

In summary, we have demonstrated that calix[4]arenes are versatile synthons for the modular construction of anion receptors. The novel ureido derivatives **4**–**6** are effective binders both for spherical and for non-spherical anions such as NO_3^- and BzO^-, which implicate possible applications in future design of anion receptors. Our results point towards the importance of the location of the appropriate moieties in determining the structure of the complexes and affinity to anions.

Acknowledgements

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8. Selected analytical data for **4**: Mp: 174–175 °C ($CHCl_3$–MeOH); ^{1}H NMR (300 MHz, $CDCl_3$–CD_3CN 4:1) δ 0.92 (t, J = 7.4 Hz, 6H, –CH_2CH_3), 1.07 (t, J = 7.4 Hz, 6H, –CH_2CH_3), 1.92 (m, 8H, –CH_2CH_3), 3.17 (d, J = 13.5 Hz, 4H, ArCH_2Ar), 3.72 (t, J = 6.6 Hz, 4H, –O–CH_2–), 3.96 (t, J = 8.0 Hz, 4H, –O–CH_2–), 4.46 (d, J = 13.50 Hz, 4H, Ar–CH_2–Ar), 6.27 (s, 4H, H-arom), 6.77 (t, J = 7.42 Hz, 2H, H-arom), 6.97 (d, J = 7.70 Hz, 4H, H-arom), 7.44 (d, J = 9.40 Hz, 4H, H-arom), 8.08 (d, J = 9.10 Hz, 4H, H-arom); MS (TOF ESI+) *m/z* (rel int.): 973 $[M+Na]^+$ (100), 989 $[M+K]^+$ (8); IR ($CHCl_3$) ν_{max} (cm^{-1}): 3404 (NH), 1676 (C=O), 1544, 1512, 1334 (NO_2); UV–vis (CH_2Cl_2) λ_{max} (nm): 332 (2.9×10^4 M^{-1} cm^{-1}). EA calcd for $C_{54}H_{58}N_6O_{10}$: C, 68.20; H, 6.15, N, 8.84%. Found C, 67.76; H, 6.07; N, 8.51%.
   Selected analytical data for **5**: Mp: 193–195 °C ($CHCl_3$–MeOH); ^{1}H NMR ($CDCl_3$:CD_3OD 5:1, 300 MHz): δ 0.90 (m, 12H, –CH_2–CH_3), 1.82 (m, 8H, –CH_2–CH_3), 3.02 (m, 4H, Ar–CH_2–Ar, eq.), 3.72 (m, 8H, –O–CH_2–), 4.35 (m, 4H, Ar–CH_2–Ar, ax.), 6.51 (m, 8H, H-arom), 6.63 (s, 2H, H-arom), 7.45 (d, 4H, J = 9.4 Hz, H-arom), 8.03 (d, 4H, J = 8.8 Hz, H-arom); MS (TOF ESI+) *m/z* (rel int.): 973 $[M+Na]^+$ (100), 989 $[M+K]^+$ (5); IR (KBr) ν_{max} (cm^{-1}): 3392 (NH), 1684 (C=O), 1552, 1508, 1330 (NO_2); UV–vis (CH_2Cl_2) λ_{max} (nm): 333 (2.8×10^4 M^{-1} cm^{-1}). EA calcd for $C_{54}H_{58}N_6O_{10}$: C, 68.20; H, 6.15, N, 8.84%. Found C, 68.55; H, 5.98; N, 8.60%.
   Selected analytical data for **6**: Mp: 135–138 °C ($CHCl_3$–MeOH); ^{1}H NMR ($CDCl_3$:DMSO-d_6 4:1, 300 MHz) δ 8.83 (s, 1H, –C(O)N*H*–), 8.02 (d, 2H, J = 9.2Hz, H-arom), 7.81 (s, 1H, –C(O)N*H*–), 7.49 (d, 2H, J = 9.1 Hz, H-arom), 6.66 and 6.40 (m, 11H, H-arom), 4.36 and 4.34 (2d, 4H, J = 13.2 Hz, Ar–CH_2–Ar), 3.80–3.66 (m, 8H, –O–CH_2–CH_2–), 3.06 and 3.04 (2d, 4H, J = 13.0 Hz, Ar–CH_2–Ar), 1.90–1.80 (m, 8H, –O–CH_2–CH_2–), 0.96–0.89 (m, 12H, –CH_2–CH_3). MS (ESI) (MeOH) *m/z*: 772 MH^+, 794 $(M+Na)^+$, 810 $(M+K)^+$. IR (KBr) ν_{max} (cm^{-1}): 3358 (N–H), 1666 (C=O), 1598 (N–H), 1555 $\nu_{assym.}$ (NO_2), 1512 $\nu_{assym.}$ (NO_2), 1464 $\nu_{assym.}$ (NO_2), 1331 $\nu_{sym.}$(NO_2); UV–vis (CH_2Cl_2) λ_{max} (nm): 330 (1.6×10^4 M^{-1} cm^{-1}). EA calcd for $C_{47}H_{53}N_3O_7$: C, 73.17; H, 6.92, N, 5.44. Found C, 72.71; H, 6.77; N, 5.21%.
9. 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. The titration data obtained for **5** were analyzed using a model where both 2:1 (β_{21}/M^{-2}) and 1:1 (K_{11}/M^{-1}) complexes are present. The obtained binding constants were used for the simulation of the spectra of the 1:1 complexes and cross-checked with the spectra obtained at large excess of anions (>0.1 M). The best agreement with experimental spectra was obtained for the binding constants indicated in Table 1.
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