

(THIO)UREA-FUNCTIONALIZED CAVITANDS AS EXCELLENT RECEPTEORS FOR ORGANIC ANIONS IN POLAR MEDIA

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Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday.

Ureidocavitand **1** and thioureidocavitand **2** bind in CH_3CN organic anions such as acetate, propionate, butyrate, etc. with K values of $2-8 \times 10^5 \text{ l mol}^{-1}$ and $2-9 \times 10^6 \text{ l mol}^{-1}$, respectively, as was determined with isothermal microcalorimetry (ITC). Bringing together four (thio)urea binding sites on a molecular platform gives rise to about 2000 times higher binding constants, compared with those of the corresponding single binding sites. Glucose- and galactose-containing thioureidocavitands **5** and **6** bind acetate in 1:1 CH_3CN /water with a K -value of $2.15 \times 10^3 \text{ l mol}^{-1}$.

Keywords: Anions; Binding constants; Cavitands; Microcalorimetry; Receptors; Glycosides; Carboxylates; Recognition.

Recognition of anions by synthetic receptors, which mimics non-covalent interactions in nature, represents an important area in supramolecular chemistry¹. Urea and thiourea moieties are well known binding sites for anions². To enhance the sensitivity and the selectivity for the recognition of organic anions³, they have been attached to a variety of scaffolds, viz. calix-arenes⁴, azamacrocycles⁵, saccharides⁶, organometallic complexes⁷, crown ethers⁸, and heterocycles⁹, as well as incorporated in cyclophanes¹⁰ or dendritic wedges¹¹. For instance, acetate recognition has been reported for mono- and bis(thio)urea-appended calixarenes. Stibor et al. found that a 1,3-alternate calix[4]arene urea receptor binds acetate ($K \approx 4000 \text{ l mol}^{-1}$ in $\text{CDCl}_3/\text{CD}_3\text{CN}$ 4:1) with a profound allosteric effect¹². The groups of Beer¹³ and Ungaro^{4c} published ditopic calix[4]arene receptors in which an acetate counter-ion is bound by (a) (thio)urea moiety(ies).

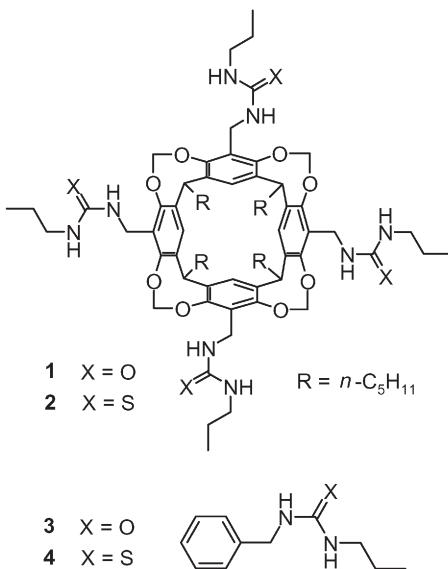
Recently, we reported that (glycocluster) cavitand-based anion receptors, having four thiourea moieties, complex inorganic anions with a preference

for chloride¹⁴. In this paper we describe the excellent complexation behavior of cavitand (thio)urea receptors toward a variety of organic anions.

RESULTS AND DISCUSSION

Self-Association of the Hosts

(Thio)ureidocavitands **1** and **2** undergo 1:1 self-association similarly to that of the corresponding tetraurea calixarene derivatives¹⁵. The nanoelectrospray ionization (nanoESI) mass spectra showed distinct peaks for 1:1 capsules + Na⁺. The formation of higher aggregates could not be detected. In addition, the formation of unspecific dimers can be excluded, since the ¹H NMR spectra show *C*₄ symmetry. ¹H NMR dilution experiments gave for **2@2** a *K* value of $7.0 \pm 0.2 \times 10^4$ l mol⁻¹ in CD₃CN; changing the concentration from 1.5 to 0.01 mmol l⁻¹, the NH shifted from δ 6.47 to 6.95 and the ArCH₂ from δ 4.31 to 4.47. ITC dilution experiments showed that the association is a strongly entropy-driven exothermic process ($K_{\text{diss}} = 1.46 \pm 0.05 \times 10^{-5}$ mol l⁻¹; $K = 6.85 \pm 0.2 \times 10^4$ l mol⁻¹, $\Delta G = -6.59$ kcal mol⁻¹, $\Delta H = -2.90$ kcal mol⁻¹, $\Delta S = 12.4$ cal mol⁻¹ K⁻¹). Ureidocavitand **1** has a less pronounced tendency to self-assemble ($K = 4600$ l mol⁻¹ in CD₃CN)¹⁶.



Complexation Studies

The complexation behavior of (thio)ureidocavitands **1** and **2** towards formate, acetate, propionate, butyrate, valerate, benzoate, and lactate (tetrabutylammonium salts) in CH_3CN (or CD_3CN) was studied. In all cases, 1:1 complexation was clearly observed in the electrospray ionization (ESI) negative-ion-mode mass spectra. Peaks of complexes of the 1:1 self-assembled capsules with an anion were not present. The formation of 1:1 capsules containing two anions (overall 2:2 stoichiometry) can be excluded, since in the ESI-MS spectra the corresponding doubly charged species were not detected.

^1H NMR spectroscopy evidently showed the formation of host-guest complexes. In a few cases, pronounced shifts of the guest hydrogens are observed (Table I). Both dilution and titration experiments in the cases of acetate and propionate and hosts **1** and **2** did not give rise to chemical shift changes of the encapsulated guests, indicating a slow process on the ^1H NMR time scale. In addition, upon dilution the ratio of the intensities of signals of the host and bound guest did not change, which indicates a strong binding.

The four convergent (thio)urea binding sites can provide eight NH protons. The complexation of thioureidocavitand **2** with acetate was studied with molecular modeling (Quanta 97, CHARMM 24.0), which showed that all eight NH protons are involved in the complexation of the carboxylate forming hydrogen bonds¹⁷, and the methyl group pointing into the cavitand. The included anion can adopt two orientations depending on the size of the substituent attached to the carboxylate function. In principle, it

TABLE I

^1H NMR data of the CH_3 protons of free and complexed carboxylates (tetrabutylammonium salts) in hosts **1** and **2** in CD_3CN

Entry	Guest	^1H NMR chemical shifts		
		CH_3 of free guest	1 @guest	2 @guest
1	Acetate	1.65	-2.14	-2.00
2	Propionate	0.95	-2.96	-3.02
3	Butyrate	0.86	-0.38 ^a	-1.26 ^a
4	Valerate	0.88	0.81	0.81

^a Very broad signals.

can point outside (*out*-isomer) or inside (*in*-isomer) the cavity. From the large negative chemical shift values in the cases of acetate and propionate (Table I), it is clear that they prefer the formation of *in*-isomers. Apparently, the alkyl chains well fit in the cavity of the cavitand, which is, due to the anisotropy effect, reflected in large upfield shifts (for acetate $\Delta\delta \approx 3.7$). Butyrate cannot already be efficiently accommodated in the cavity; therefore, it appears as very broad signals¹⁸. Increasing the alkyl chain to valerate gives rise to the formation of an *out*-isomer. The C₄-valerate chain is too large for the cavitand cavity. In the ¹H NMR spectrum, there is only a small shift from δ 0.86 to 0.81 for the terminal methyl group upon complexation. NOESY ¹H NMR spectra of the acetate and propionate complexes of hosts **1** and **2** reveal cross-peaks between the guest and the cavitand (ArH, O₂CH^HH) and the presence of small cross-peaks between the *in*- and *out*-isomers (Fig. 1). Unfortunately, the signal of the *out*-isomer ($\delta \approx 1.95$) is hidden under that of CHD₂CN. However, based on the integrals of the peaks of the *in*-isomer and those of a few signals of the hosts in 1:1 complexes, the amount of *out*-isomer in both cases is only 5–7%. A corresponding experiment in CDCl₃ showed the same behavior and the presence of a small peak for the *out*-isomer at δ 2.05 (*in*-isomer: -2.04, free acetate: 1.97). In both solvents the chemical shift of the acetate *out*-isomer is at lower field than that of the unbound acetate, which is probably due to the more electron-withdrawing environment upon complexation.

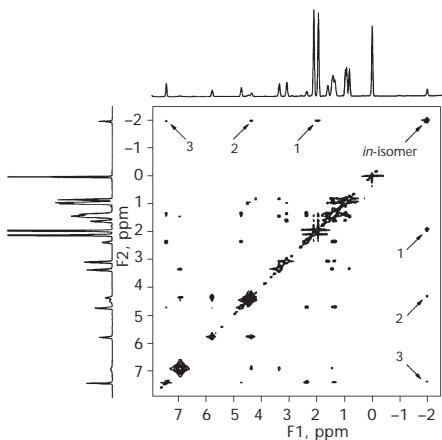


FIG. 1
NOESY (mixing time is 0.4 s) 2D ¹H NMR spectrum of complex **2**@OAc in CD₃CN: 1 is the cross peak between *in*- and *out*-isomers, 2 and 3 are the cross peaks of the CH₃ protons of the *in*-isomer and cavitand OCH'HO or ArH protons, respectively

Because of the very high binding affinity, NMR spectroscopy cannot be used for the *K*-value determination. Therefore, microcalorimetric (ITC) studies were carried out. The different binding constants and heat effects upon complexation are summarized in Table II. With ITC, in all cases a 1:1 stoichiometry was found for the binding. The complexation of organic anions by receptors **1** and **2** is an enthalpically driven process, while the entropy contribution is small. For a representative example of an ITC titration, see Fig. 2.

The entire process consists of two parts, viz. endothermic dissociation of **1@1** or **2@2** capsules and the exothermic formation of complexes with the anions (Fig. 3a). Figure 3b shows the changes in the concentration of all the components upon ITC titration. In general, the *K* values of the *in*-isomer complexes (e.g. acetate, propionate, butyrate) and the *out*-isomer complexes

TABLE II

K values and thermodynamic data of complexation of carboxylates by hosts **1** and **2** determined by ITC^a

Entry	Guest	Host 1			
		<i>K</i> , 1 mol ⁻¹	Δ <i>G</i> , kcal mol ⁻¹	Δ <i>H</i> , kcal mol ⁻¹	Δ <i>S</i> , cal mol ⁻¹ K ⁻¹
1	Formate	9.6×10^4	-6.80	-4.19	8.72
2	Acetate	8.0×10^5	-8.04	-9.85	-6.03
3	Propionate	4.0×10^5	-7.64	-8.42	-2.61
4	Butyrate	3.4×10^5	-7.54	-6.90	2.14
5	Valerate	2.0×10^5	-7.22	-7.19	0.08
6	Benzoate	4.1×10^4	-6.29	-5.15	3.82
Host 2					
7	Formate	5.3×10^5	-7.81	-4.73	10.32
8	Acetate	9.4×10^6	-9.51	-8.95	1.89
9	Propionate	7.4×10^6	-9.37	-8.98	1.31
10	Butyrate	4.7×10^6	-9.10	-8.61	1.65
11	Valerate	2.2×10^6	-8.66	-8.72	-0.22
12	Benzoate	5.0×10^4	-6.41	-3.52	9.68
13	Lactate	8.5×10^5	-8.08	-8.61	-1.79

^a The data are average values of two titrations; the error is <10%.

(e.g. valerate) are about 2–4 times higher, indicating the possible contribution of CH–π interactions in the former cases. Ureidocavitand **1** is about ten times weaker complexing agent than thioureidocavitand **2**, in line with the fact that urea ($pK_a = 26.9$) is a weaker acid than thiourea ($pK_a = 21.0$)¹⁹. The selectivity for acetate over benzoate, that can only give an *out*-isomer complex due to its size, is about 20 in the case of ureidocavitand **1**, while it increases to almost 180 in the case of thiourea analogue **2**. The thioureidocavitand receptor **2** has an excellent binding affinity to organic anions, which is, to the best of our knowledge, higher than those of known neutral anion receptors²⁰ and comparable with that of charged and organometallic anion receptors²¹.

The complexation of ureidocavitand **1** with lactate shows a deviating behavior. By ITC, a 1:2 host/anion stoichiometry was found with $K_1 = 4.5 \times 10^5 \text{ l mol}^{-1}$ and $K_2 = 2.1 \times 10^5 \text{ l mol}^{-1}$. ESI-MS measurements at a low cone voltage (16 V) revealed in the spectrum a small peak of the double-charged 1:2 complex.

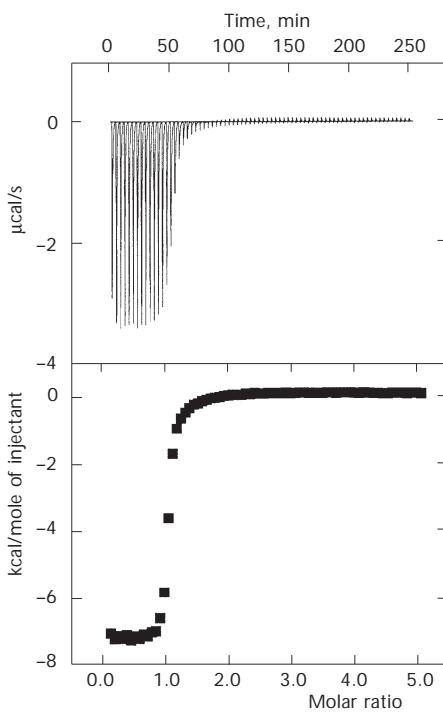


FIG. 2
Example of an ITC titration curve: thioureidocavitand **2** (0.2 mmol l^{-1}) with tetrabutylammonium valerate (4.5 mmol l^{-1})

The advantage of bringing together four (thio)urea binding sites on a molecular platform is clear from a comparison of the data of **1** and **2** with those of acyclic analogs, viz. 1-benzyl-3-propylurea (**3**) and 1-benzyl-3-propylthiourea (**4**): K (**3**@OAc) = 497 l mol⁻¹ ($\Delta G = -3.67$ kcal mol⁻¹, $\Delta H = -5.57$ kcal mol⁻¹, $\Delta S = -6.37$ cal mol⁻¹ K⁻¹); K (**4**@OAc) = 3.5×10^3 l mol⁻¹ ($\Delta G = -4.83$ kcal mol⁻¹, $\Delta H = -4.52$ kcal mol⁻¹, $\Delta S = 1.05$ cal mol⁻¹ K⁻¹). The corresponding cavitand-based receptors **1** and **2** bind about 1600 and 2700

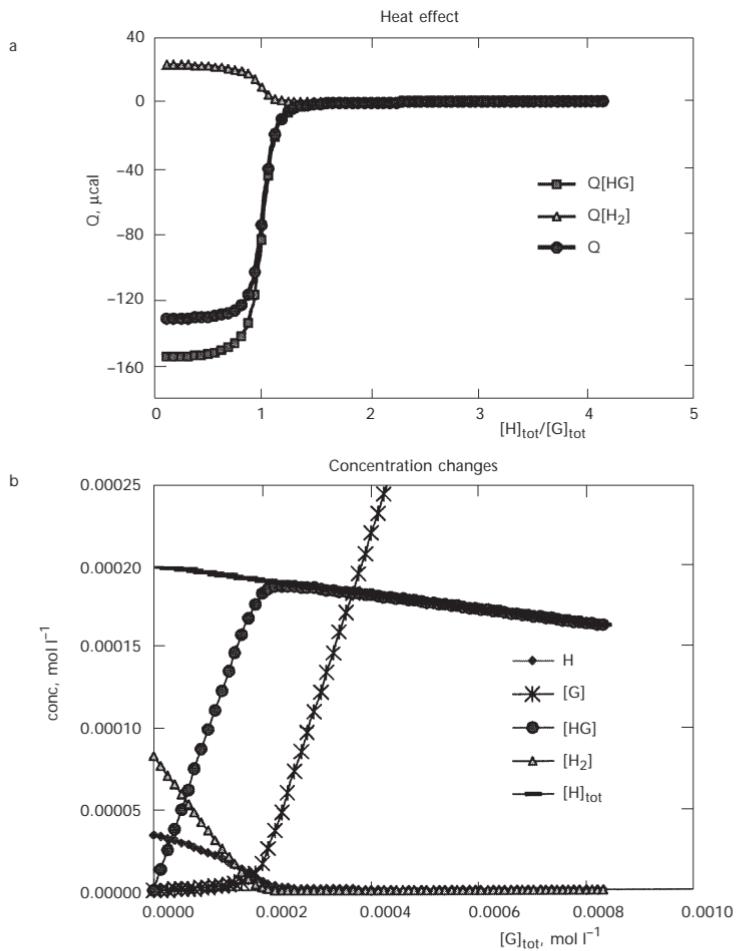


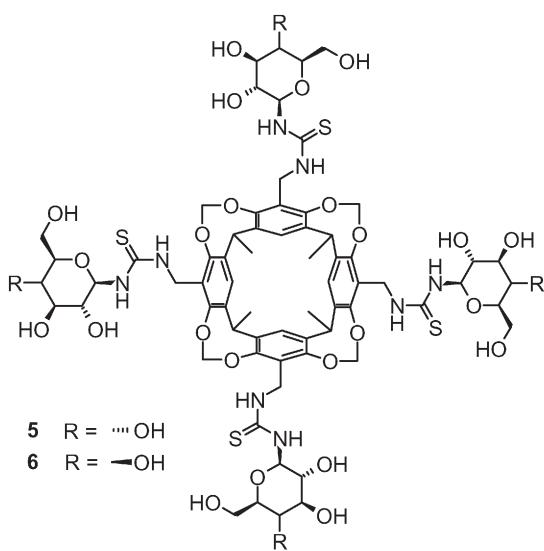
FIG. 3

a Heat effects (Q , heat effect monitored upon the titration; $Q[\text{H}_2]$, heat of the dissociation of the self-assembly; $Q[\text{HG}]$, heat of the complex formation; $Q = Q[\text{H}_2] + Q[\text{HG}]$) and b concentration changes of the components upon ITC titration of thioureidocavitand **2** (0.2 mmol l⁻¹) with tetrabutylammonium valerate (4.5 mmol l⁻¹) in CH_3CN

times stronger, respectively. In general, binding with these cavitand-based ionophores is considerably stronger than with the structurally related, although more flexible, calix[4]arene counterparts. This may be caused by the fact that the rigid cavitand-based ionophores cannot form intramolecular hydrogen bonds¹⁴.

Acetate Recognition in Aqueous Media

The complexation affinity of the corresponding glucose- and galactose-containing thioureidocavitands **5** and **6** to acetate was studied by ITC in the more polar $\text{CH}_3\text{CN}/\text{water}$ 1:1 mixture. In both cases, a K value of $2.15 \pm 0.4 \times 10^3 \text{ l mol}^{-1}$ ($\Delta G = -4.54 \text{ kcal mol}^{-1}$, $\Delta H = 0.69 \text{ kcal mol}^{-1}$, $\Delta S = 17.57 \text{ cal mol}^{-1} \text{ K}^{-1}$) was obtained. Upon increasing the solvent polarity, thermodynamic parameters change considerably – the process becomes endothermic and entropically driven, in contrast to the enthalpically driven complexation of acetate by hosts **1** and **2** in CH_3CN .



In conclusion, we have demonstrated that thioureidocavitands are among the strongest receptors for organic anion recognition with K values up to $9.4 \times 10^6 \text{ l mol}^{-1}$ in CH_3CN .

EXPERIMENTAL

¹H NMR spectra were recorded on a Varian Unity Inova (400 MHz) spectrometer. Tetramethylsilane (TMS) was used as internal standard. Acetonitrile-*d*₃ was purchased from Aldrich and stored for at least 2 days over molecular sieves before use. The ESI-MS experiments were carried out with a Micromass LST ESI-TOF instrument. The solutions were introduced at a flow rate of 20 μ l min⁻¹ for 2 min (120 scans). The standard spray conditions: negative ion mode, capillary voltage 2500 V, sample cone voltage 30–50 V, desolvation gas flow 250 l h⁻¹, source temperature 100 °C, desolvation temperature 100 °C.

(Thio)urea cavitands **1**²², **2**^{14b}, 1-benzyl-3-propylurea²³ **3**, 1-benzyl-3-propylthiourea²⁴ **4** and glycoside thiourea cavitand derivatives^{14b} **5**, **6** were prepared according to literature procedures. Tetrabutylammonium salts of organic acids were either purchased from Aldrich and Acros Organics or prepared from the corresponding acids and tetrabutylammonium hydroxide²⁵. All the salts were dried in a freeze dryer for at least 3 days before use.

Determination of *K* Values of Self-Association of the Hosts

The ¹H NMR titration curves were modeled using a non-linear regression analysis. Modeling of the ¹H NMR data was performed using an Excel program based on standard equations that consider self-association²⁶.

Isothermal Titration Calorimetry Experiments

The ITC titration experiments were performed using a Microcal VP-ITC microcalorimeter with a cell volume of 1.4115 ml (cell temperature 25 °C, reference power 16.3 μ cal s⁻¹, stirring speed 310 RPM, auto ITC equilibration option, low feedback mode gain, volume of injectant 4 μ l (73 injections) or 5 μ l (59 injections), duration of injection 20 s, spacing 210 s, filter period 5 s). The host concentrations range from 0.04 to 7 mmol l⁻¹, depending on the value of the binding constant. The guest (tetrabutylammonium salt) concentration is 15–25 times higher than the corresponding host concentration. Excel non-linear regression analysis models for the treatment of ITC data are based on equations that include complexation and self-association equilibria, dilution of the solution upon injections, and the heat effect of the guest solution dilution.

The concentrations of all the components during an ITC titration were calculated by the iterative solution of the following set of equations that consider the self-association equilibrium, the 1:1 complexation equilibrium, and both of them.



a) Self-association:

$$[H_2] = K_s[H]^2 \quad (3)$$

$$[H] = \frac{[H]_{\text{tot}-i}}{1 + 2K_s[H]} \quad (4)$$

b) 1:1 complexation equilibria:

$$[H] = \frac{[H]_{\text{tot}-i}}{1 + K[G]} \quad (5)$$

$$[G] = \frac{[G]_{\text{tot}-i}}{1 + K[H]} \quad (6)$$

$$[HG] = K[H][G] \quad (7)$$

c) Self-association and 1:1 complexation equilibria involve Eqs (3), (6), (7) and (8),

$$[H] = \frac{[H]_{\text{tot}-i}}{1 + K[G] + 2K_s[H]}, \quad (8)$$

where $[H]$, $[G]$, $[HG]$, $[H_2]$ are the concentrations of host, guest, host-guest complex and self-assembly, respectively; $[H]_{\text{tot}-i}$ and $[G]_{\text{tot}-i}$ are corrected for dilution total concentrations of host and guest following the i -th injection; K_s and K are the self-association and 1:1 binding constant. All the concentrations were corrected for the dilution during the ITC titration process²⁷. The heat effect of complexation was calculated using the standard equation from the MicroCal VP-ITC manual. In the case of anion complexation by (thio)ureidocavitands, the sum of the heat effects of two processes (Fig. 3a) was calculated. Subtraction of the residual heat effect caused by the heat of dilution and deaggregation of guests in CH_3CN or subtraction of the data of dilution of the guest solution in CH_3CN /water 1:1 was carried out.

The fitting was carried out by varying K_s , K , ΔH , the residual heat effect, and the concentration of the solution of the guest added (concentration variations of <10% relative to the 1:1 stoichiometry were accepted).

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