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Recognition of Ionic Guests by Ionic β-Cyclodextrin Derivatives

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Abstract: Inclusion compounds of cationic, anionic, and neutral *p*-substituted derivatives of *tert*-butylbenzene complexed in β-cyclodextrin and its ionic 6-mono and 6-hepta derivatives were systematically investigated by isothermal titration calorimetry (ITC). All inclusion compounds showed 1:1 stoichiometry with binding constants ranging from 10 to $3\times10^6\,\text{M}^{-1}$. The binding free energies could be subdivided into apolar and electrostatic contributions. The electrostatic interactions could be quantitatively described by Coulomb's law by taking into account the degree of protonation of hosts and guests, the orientations of the guests within the hosts, and ion shielding as described by the Debye–Hückel–Onsager theory. The orientations of the guests within the cyclodextrin cavities were determined by ROESY NMR spectroscopy.

Keywords: calorimetry · cyclodextrins · host–guest systems · molecular recognition · supramolecular chemistry

Introduction

Design, synthesis, and characterization of highly specific artificial receptors are among the main tasks of supramolecular chemistry.[1–4] Among other hosts, cyclodextrins (CDs), which are 1→4 α-linked cyclic oligomers of anhydroglucopyranose, have attracted particular interest since they are readily available and soluble in aqueous media.[5] All CDs have an internal cavity that is mainly hydrophobic and allows the binding of hydrophobic guest molecules. A large number of hydrophobic or amphiphilic guests can be complexed inside this cavity; indeed, binding data are available for numerous host–guest complexes, known as inclusion compounds, involving CDs.[6] Inclusion of guests in CDs and CD derivatives facilitates many applications,[7–10] such as solubilization[11] and targeting of pharmaceuticals,[12–14] dispersion of cosmetics,[15] catalysis,[16] and chromatographic separations.[17,18]

The driving forces for the formation of CD inclusion compounds are mainly nondirectional interactions such as hydrophobic and van der Waals interactions.[19,20] The dominance of solvatophobic interactions is evident in the fact that the inclusion of guests in CDs occurs preferentially in aqueous solution. The addition of small amounts of organic solvents to aqueous solutions is enough to render inclusion compounds significantly less stable.[19] The magnitude of hydrophobic interactions is determined mainly by the hydrophobic surface area of the guest. Binding free energies $\Delta G°$ of β-CD inclusion compounds involving several homologous series of guests become more negative by $2.8\pm0.6\,\text{kJ mol}^{-1}$ per methylene group.[6,21] We investigated the influence of *para* substituents at benzoic acid on the stabilities of β-CD inclusion compounds and found that binding free energy $\Delta G°$ decreased significantly from $-6.9\,\text{kJ mol}^{-1}$ for benzoic acid to $-24.3\,\text{kJ mol}^{-1}$ for *p-tert*-butylbenzoic acid, that is, $4.3\,\text{kJ mol}^{-1}$ per C atom.[22] Thus, a benzene ring alone seems to be too small to fill the β-CD cavity. The additional *tert*-butyl group elongates the hydrophobic part of the guest and makes it large enough to fill the β-CD cavity completely.

Additional polar groups must be attached to the CD ring to improve binding selectivity. A great variety of CD derivatives carrying one or more substituents at the primary or secondary positions has been synthesized.[23] Many of these CD derivatives showed improved molecular recognition. For

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example, 6-monoamino-β-CD and 6-*O*-carboxymethyl-β-CD show stronger chiral selectivity for amino acids than native β-CD.[24–27] Disubstituted β-CD derivatives performed even better.[28] The "three-point rule" states that at least three directed interactions between host and guests are prerequisites for noticeable chiral discrimination.[29] In addition, hepta-6-,[24] hepta-2,3-di-,[30] hepta-2,6-di-,[31] and hepta-2,3,6-trisubstituted[32–34] β-CD derivatives have been synthesized. In particular, hepta-6-*S*-6-deoxy-β-CD derivatives,[35–38] which are readily synthesized from heptakis-6-iodo-6-deoxy-β-CD and functional thiols, show interesting binding properties. They can form supramolecular structures including molecular capsules[39,40] and nanotubes.[31] Recently, we demonstrated the superior binding properties of hepta-6-*S*-6-deoxy-β-CD derivatives towards the drug camptothecin, which is used for cancer treatment.[38]

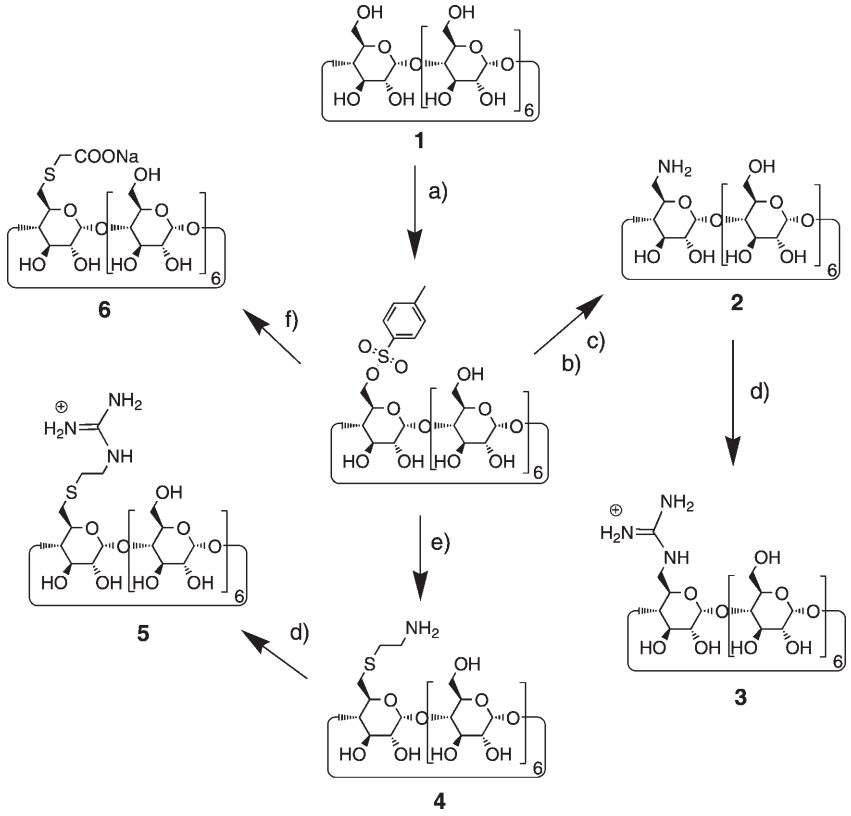
The contribution of Coulomb interactions to the binding of charged drug molecules by statistically substituted sulfobutyl ether β-CD derivatives has already been demonstrated.[41] Although extensive binding data are available on these and other β-CD derivatives, a quantitative understanding of specific interactions between charged hosts and guests is still lacking.[6,27,42] This understanding is very important for the design of highly selective artificial receptor molecules.[43,44]

We have now investigated the molecular recognition of cationic, anionic, and neutral *tert*-butylbenzene derivatives by a series of 13 charged mono-6- and hepta-6-substituted β-CD derivatives. The *tert*-butylphenyl group was chosen because of its high binding affinity towards the β-CD cavity.[22] For a quantitative description of the host–guest systems we collected a broad array of binding data, in addition to data on the protonation equilibria of hosts and guests and data on the orientations of the guests within the hosts. These data allowed us to distinguish between apolar binding, due to hydrophobic and van der Waals interactions within the cavity, and electrostatic interactions between functional groups on host and guest.

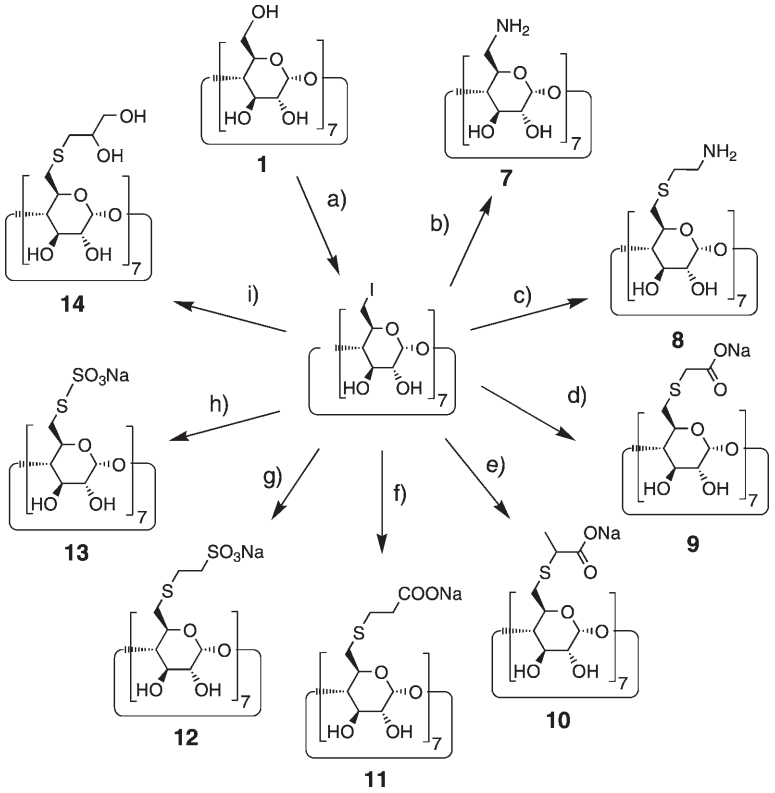
Results

Synthesis of hosts and guests: Monosubstituted derivatives **2**–**6** of β-CD (**1**) were synthesized by nucleophilic displacement reactions starting from 6-*O*-tosyl-β-CD[45] (Scheme 1). 6-Amino-6-deoxy-β-CD (**2**) was synthesized via 6-azido-6-deoxy-β-CD.[46] Reactions of 6-*O*-tosyl-β-CD with 2-aminoethanethiol and 2-mercaptoacetic acid yielded mono-[6-deoxy-6-(2-aminoethylsulfanyl)]-β-CD (**4**) and mono-[6-deoxy-6-(2-sulfanyl acetic acid)]-β-CD (**6**), as described recently.[38]

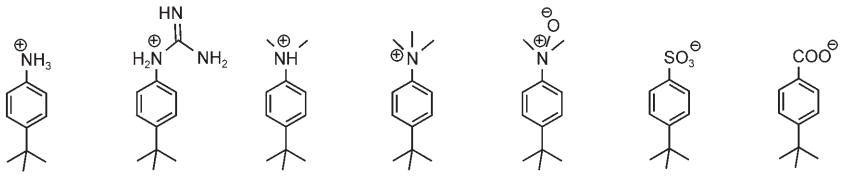
In addition, both amino derivatives **2** and **4** were converted to the corresponding guanidinium salts **3** and **5** by reaction with 1*H*-pyrazole-1-carboxamidine hydrochloride, in analogy to a published procedure.[47,48] Analogous cationic (**7**, **8**), anionic (**9**–**13**), and neutral (**14**) heptasubstituted β-CD derivatives were synthesized by nucleophilic displacement reactions of heptakis(6-iodo-6-deoxy)-β-CD with NaN_3 followed by Staudinger reduction,[49] and with functional thiols or thiosulfate (Scheme 2) by a previously described procedure.[38] We were unable to completely convert hepta-amino compounds **7** and **8** to the corresponding heptaguanidinium compounds.[48] For the synthesis of cationic guests (Scheme 3), 4-*tert*-butyl-aniline was protonated with HCl to give **15**, which was converted by reaction with 1*H*-pyrazole-1-carboxamidine hydrochloride to guanidinium derivative **16**, and by reaction with methyl iodide to trimethylammonium iodide **18**. Anionic sulfonate **20** was obtained by sulfonation of *tert*-butylbenzene, and neutral *N*-oxide **19** was syn-



Scheme 1. Synthesis of mono substituted β-CD derivatives. a) TosCl, NaOH, ACN/H_2O; b) NaN_3, H_2O; c) PPh_3, DMF, NEt_3; d) 1*H*-pyrazole-1-carboxamidine hydrochloride, DMF; e) 2-aminoethanthiol, NH_4HCO_3, DMF/H_2O; f) 1. methyl ester of 2-mercaptoacetic acid, NEt_3, DMF; 2. NaOH.



Scheme 2. Synthesis of heptasubstituted CD derivatives. a) 1. PPh_3, I_2, DMF; 2. CH_3ONa, CH_3OH; b) 1. NaN_3, DMF; 2. PPh_3/DMF, NH_3 or Raney Ni/H_2/H_2O; c) 2-aminoethanethiol, NH_4HCO_3, DMF/H_2O; d) 1. methyl ester of 2-mercaptoacetic acid, NEt_3, DMF; 2. NaOH; e) 1. methyl ester of 2-mercaptopropanoic acid, NEt_3, DMF; 2. NaOH; f) 1. methyl ester of 2-mercaptoacetic acid, NEt_3, DMF; 2. NaOH; g) 1. 2-mercaptoethanesulfonate, NEt_3, DMSO; 2. NaOH; h) 1. $Na_2S_2O_3$, NEt_3, DMSO; 2. NaOH. i) 3-mercaptopropane-1,2-diol, NEt_3, DMF.



Scheme 3. Amphiphilic guests for β-CD and its derivatives.

thesized by H_2O_2 oxidation of commercially available tertiary amine **17**.

The protonation constants of polyamines **7** and **8**, polycarboxylates **9** and **11**, and amine oxide **19** were determined in aqueous solution by potentiometric titration. The pK_a values are listed in Table 1, and a representative species distribution diagram for polyamine **7** is shown in Figure 1. From these distribution curves the net charge numbers of a host z_h or guest z_g were calculated for our standard pH of 6.8 by summation of the contributions of the relevant charged species. The charge numbers z_h are listed in Table 4 below. Interestingly, host **7** is not fully protonated at pH 6.8. The low charge number of $z_h = 6.2$ was attributed to Coulomb repulsion between adjacent cationic ammonium groups of host **7**, which leads to significant decay of pK_a values with increasing degree of protonation. This repulsive effect is less pronounced for host **8**, since the cationic groups are farther apart from each other due to the SCH_2CH_2 spacers. Guest **19** is neutral at pH 6.8 and cationic at pH 3.0.

Determination of binding thermodynamics between hosts and guests: Since all hosts **1**–**14**, guests **15**–**21**, and their inclusion compounds are extremely soluble in water, isothermal titration microcalorimetry was used to determine all thermodynamic binding parameters. Titrations were performed under standard conditions, normally at pH 6.8 with 50 mM buffer. Hosts **7** and **8** with seven amino groups were titrated with charged guests **16** and **20** under acidic conditions (pH 3.0) to force complete protonation of all amino groups. All titration curves were in good agreement with a 1:1 stoichiometry of host/guest in the inclusion compounds. Binding constants K, molar binding free energies $\Delta G°$, and molar binding enthalpies $\Delta H°$ (Tables 2 and 3) were obtained by nonlinear regression of the titration curves. Although the hydrophobic parts of all guests **15**–**21** are the same, binding constants varied over five orders of magnitude, from 20 to 3×10^6 L mol^{-1}. In each case, conditions for the measurement were optimized to achieve maximum accuracy. The $\Delta G°$ values showed only a slight dependence on pH for those cases in which the protonation states of host and guest were

Table 1. pK_a values derived from potentiometric titration.

Compound	pK_a[a]
7	9.50(1), 8.89(1), 8.33(1), 8.07(1), 7.57(1), 7.35(1), 6.75(1)
8	9.99(1), 9.45(1), 9.05(1), 8.72(1), 8.32(1), 7.96(1), 7.37(1)
9	6.10(2), 5.32(2), 4.91(3), 4.37(3), 4.04(3), 3.50(2), 3.01(2)
11	6.49(1), 5.69(1), 5.25(1), 4.75(1), 4.31(1), 3.78(1), <3
19	4.30(1)

[a] $pK_{a,i}$ ($= -\log K_{a,i}$, $K_{a,i} = [H_{n-i}L] \times [H] \times [H_{n-i+1}L]^{-1}$, 25.0 °C, 0.10 M KCl). Uncertainties (3σ) are given in parentheses.

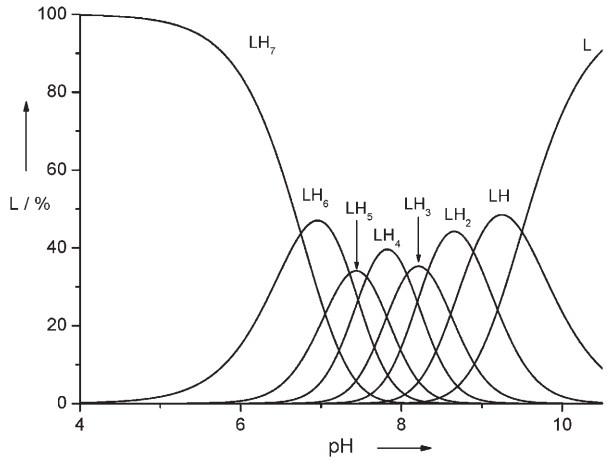


Figure 1. Distribution of protonated species for host **7** (L) as a function of pH, as determined by potentiometric titration. Calculations were carried out with the deprotonation constants listed in Table 1.

Table 2. Molar binding free energies $\Delta G°$ for the inclusion of various guests in β-CD **1** and in 6-amino-6-deoxy-β-CD **2** as determined by ITC at $T=25\,°C$.

Guest	pH	$\Delta G°$ [kJ mol^{-1}] in host **1**	$\Delta G°$ [kJ mol^{-1}] in host **2**
15	3.0	−22.03 ± 0.03	−19.29 ± 0.05
16	6.8	−21.71 ± 0.03	−19.75 ± 0.04
17	3.0	−22.08 ± 0.04	−19.30 ± 0.20
18	6.8	−22.25 ± 0.03	−20.11 ± 0.05
19	6.8	−22.27 ± 0.04	−19.92 ± 0.03
19	3.0	−21.06 ± 0.02	−18.64 ± 0.02
20	6.8	−23.19 ± 0.03	−22.99 ± 0.02
20	3.0	−23.12 ± 0.05	−23.25 ± 0.11
21	6.8	−24.03 ± 0.07	−23.41 ± 0.15

Table 3. Molar binding free energies $\Delta G°$ for the inclusion of cationic guest **16**, anionic guest **20**, and neutral guest **19** in various CD derivatives, as determined by ITC at $T=25\,°C$.

Host	pH	$\Delta G°$ [kJ mol^{-1}] with guest **16**	$\Delta G°$ [kJ mol^{-1}] with guest **20**	$\Delta G°°$ [kJ mol^{-1}] with guest **19**
1	6.8	−21.71 ± 0.03	−23.19 ± 0.03	−22.27 ± 0.04
2	6.8	−19.75 ± 0.04	−19.4 ± 0.04	−19.92 ± 0.04
3	6.8	−20.80 ± 0.03	−24.34 ± 0.03	−21.21 ± 0.04
4	6.8	−22.30 ± 0.03	−24.86 ± 0.05	−22.28 ± 0.05
5	6.8	−22.60 ± 0.12	−24.42 ± 0.02	−22.61 ± 0.05
6	6.8	−23.05 ± 0.05	−22.23 ± 0.13	−22.36 ± 0.04
7	3.0	−8.93 ± 0.08	−22.55 ± 0.06	−10.66 ± 0.17
8	3.0	−23.10 ± 0.04	−37.27 ± 0.23	−25.57 ± 0.09
9	6.8	−34.57 ± 0.24	−21.65 ± 0.05	−25.61 ± 0.04
10	6.8	−32.39 ± 0.24	−20.17 ± 0.03	−23.23 ± 0.03
11	6.8	−32.73 ± 0.08	−21.68 ± 0.04	−24.60 ± 0.09
12	6.8	−32.89 ± 0.21	−21.00 ± 0.07	−25.61 ± 0.04
13	6.8	−26.10 ± 0.08	−14.86 ± 0.06	−18.40 ± 0.11
14	6.8	−26.57 ± 0.05	−25.00 ± 0.03	−25.61 ± 0.07

not influenced by pH. The $\Delta G°$ values of the inclusion complex of *tert*-butylbenzenesulfonic acid **20** and **1** were the same for pH 6.8 and pH 3. On the other hand, when the protonation state of the guest was influenced by pH, $\Delta G°$ varied considerably with pH. *tert*-Butyl-*N*,*N*-dimethylaniline *N*-oxide **19** ($pK_a=4.3$) showed a significantly higher complex stability at pH 6.8 than at pH 3: $\Delta G°=-22.27\,kJ\,mol^{-1}$ versus $-21.06\,kJ\,mol^{-1}$, respectively (Table 2). This reflects the fact that it changes from neutral at pH 6.8 to cationic at pH 3.

Influence of the functional groups on guests 15–21 on binding free energy $\Delta G°$: Although native β-CD **1** is uncharged, it can recognize the charge of a guest, as shown in Table 2 and Figure 2. The binding free energies of the anionic guests

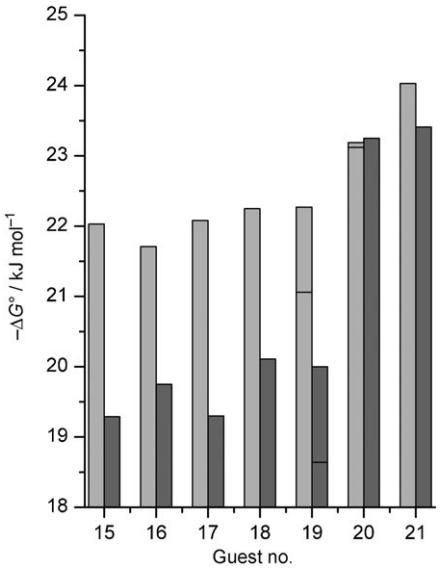


Figure 2. Molar binding free energies for β-CD (light gray) **1** and mono-6-amino-β-CD **2** (dark gray) for various guest molecules **15**–**21**; pH values as specified in Table 2.

21 ($\Delta G°=-24.03\,kJ\,mol^{-1}$) and **20** ($\Delta G°$ $-23.19\,kJ\,mol^{-1}$) were more negative than those of cationic guests **16** ($\Delta G°$ $-21.71\,kJ\,mol^{-1}$) and **15** ($-22.03\,kJ\,mol^{-1}$), even though the strength of hydrophobic interactions between host and guest should be very similar in both cases. The value of the binding free energy of neutral guest **19** in host **1** fell in the middle of the range between the values of the cationic and anionic guests.

Charge recognition was even more pronounced for cationic β-CD derivative **2**, as shown in Table 2. Again, all cationic guests **15**–**18** showed similar binding free energies for host **2**. The $\Delta G°$ values of the anionic guests **21** and **20** were similar as well, but much more negative (by $\Delta\Delta G°\sim4\,kJ\,mol^{-1}$) than the values for the cationic guests. Since the $\Delta G°$ values were rather similar for various guests of the same charge, further ITC measurements were performed with three representative guests rather than the entire panel. Because of their greater solubility in water, guests **16**, **19**, and **20** with guanidinium, amine *N*-oxide and sulfonate groups, respectively, were chosen as cationic, neutral, and anionic reference compounds for investigation of polar interactions between hosts and guests (see Table 3). The $\Delta G°$ values of the

charged guests **16** and **20** have a much broader range (−9 to −37 kJ mol^{-1}) than those of neutral guest **19** (−11 to −26 kJ mol^{-1}).

Influence of functional groups on hosts 1–14 on apolar binding: The binding free energies $\Delta G^{\circ\circ}$ for neutral guest **19** at pH 6.8 was mainly attributed to apolar binding due to hydrophobic and van der Waals interactions between the guest and the β-CD cavity. Apolar binding free energies $\Delta G^{\circ\circ}$ of hosts **1–14** are summarized in Table 3. Heptakis-6-deoxy-6-thioether derivatives **8–12** and **14** showed the highest $\Delta G^{\circ\circ}$ values of around −25 kJ mol^{-1}, followed by mono thioethers **4–6** ($\Delta G^{\circ\circ} \approx -22$ kJ mol^{-1}), which have values close to that of native β-CD ($\Delta G^{\circ\circ} = -22.3$ kJ mol^{-1}). Much smaller values were observed for the mono-6-deoxy-6-ammonium **2** and mono-6-deoxy-6-guanidinium derivatives **3** ($\Delta G^{\circ\circ} \approx -21$ kJ mol^{-1}), and especially for hepta-6-deoxy-6-amino derivative **7** ($\Delta G^{\circ\circ} \approx -11$ kJ mol^{-1}). These different binding free energies can be correlated with the hydrophobicity of the atoms attached to the C-6 positions on the β-CD scaffold of the hosts. The atomic increments for the calculation of log *P* values (where *P* is the octanol/water partition coefficient) were taken as measures of these hydrophobicities: OH, −1.4; S, −0.4; NH_3^+, −4.6.[50,51] They clearly reflect the greater hydrophobicity of the sulfur linker and the much lower hydrophobicity of the ammonium group compared to the hydroxyl group. The influence of hydrophilic end groups on the host seems to level off with increasing spacer length, since binding free energies of derivatives **8**, **11**, **12**, and **14** with C_2 spacers are very similar despite their different end groups. Consequently, only atoms close to the hydrophobic part of the guest contribute to apolar binding.

Quantification of electrostatic interactions between functional groups: Binding data for charged guests **16** and **20** with various hosts **1–14** (see Table 3) were collected to investigate electrostatic interactions. Binding constants and binding free energies are strongly dependent on the combination of functional groups on host and guest. For example, the binding constant *K* of cationic guest **16** in cationic host **7** is as low as 21 M^{-1}, while that of anionic guest **20** in cationic host **8** is as high as 3.6×10^6 M^{-1}, close to binding constants of natural receptors.[4]

For a more detailed data analysis, electrostatic interactions $\Delta\Delta G^{\circ}$ were estimated for all hosts **1–14** from the differences between the binding free energies of the charged guests (**16**, **20**) and the binding free energy of neutral guest **19** according to Equation (1); they are summarized in Table 4. Both attractive interactions (negative values) and repulsive interactions (positive values) were found. Neither interaction was symmetrical. For each host, for example, **9**, the attractive interaction with $\Delta\Delta G^{\circ} = -8.96$ had a higher absolute value than the repulsive interaction with $\Delta\Delta G^{\circ} = 3.96$. This finding may be explained by the fact that the orientation of the guest inside the CD cavity is influenced by interactions of functional groups. The guest may avoid repulsive forces and orient its functional group towards the secondary rim of β-CD. As a result, the increased distance between the charged groups reduces the electrostatic repulsion energy. Measurements of the NOE were performed to test this hypothesis.

Table 4. Selectivities of hosts **1–14** as a function of spacer distance *r* and net charge z_h.

Host	$\Delta\Delta G^{\circ}$ [kJ mol^{-1}][a] with guest **16**	$\Delta\Delta G^{\circ}$ [kJ mol^{-1}][a] with guest **20**	r_S [nm][b]	z_h[c]
1	−0.92	0.56	–	0
2	−3.07	0.17	0.147	1
3	−3.13	0.42	0.250	1
4	−2.58	0.00	0.544	1
5	−1.82	0.00	0.657	1
6	−0.69	0.13	0.537	−1
7	−11.89	1.73	0.233	6.2
8	−11.70	2.47	0.544	6.8
9	−8.96	3.96	0.537	−6.8
10	−9.17	3.06	0.537	−7
11	−8.14	2.92	0.663	−6.6
12	−7.28	4.62	0.716	−7
13	−7.70	3.54	0.459	−7
14	−0.96	0.62	–	0

[a] Contributions of electrostatic interactions to binding free energy. [b] Spacer length. [c] Charge of the host.

$$\Delta\Delta G^{\circ} = \Delta G^{\circ} - \Delta G^{\circ\circ} \quad (1)$$

Influence of functional groups on hosts 1–14 on the orientation of the guest molecules: The orientation of the guest molecules in the CD host were determined by ROESY NMR spectroscopy. In all cases, strong ROESY cross-peaks were observed between the internal protons of the β-CD scaffold (H-3, H-5, H-6) and the two aromatic protons of guests **15–21**, that is, the hydrophobic portion of all guests was completely included within the CD host, except for inclusion compound **7·15**. Assignments of the NMR signals of the inclusion compounds of monosubstituted β-CD derivatives **2–6** were difficult in many cases because of the complexity of the host spectra caused by the missing C_7 symmetry. In the case of the cationic guest **15** in β-CD, the signals of H-3 and H-5 overlapped because they were shifted due to complexation; as a result, it was impossible to determine the molecular orientation. However, unambiguous results were obtained for homologous guest **15a**, which should be similar to guest **15**.

The relative ROESY intensities of six inclusion compounds as measures of the interatomic distances are shown in Figure 3. The orientation of a guest was defined on the basis of the ROESY intensities between outer protons H-6 and H-3 of the host and the outer protons of the guest, H-*tert*-butyl, and the protons *ortho* to the functional group, H-*o*. As a convention, the CD cone was always depicted with the primary side up to facilitate comparison of the guest orientations. If the functional group of the guest was pointing towards the primary side of CD, it was said to be oriented upwards, and downwards in the opposite case. Upward orientations were found for inclusion compounds **1·20**, **4·20**,

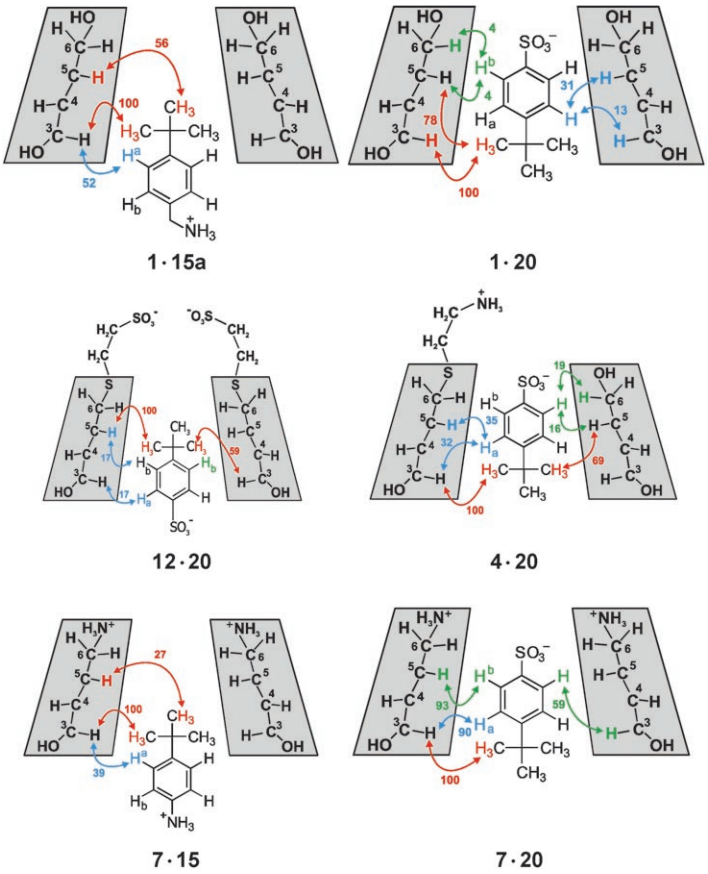


Figure 3. Relative ROESY NMR intensities [%] for various host–guest complexes. The strongest signal was set to 100%.

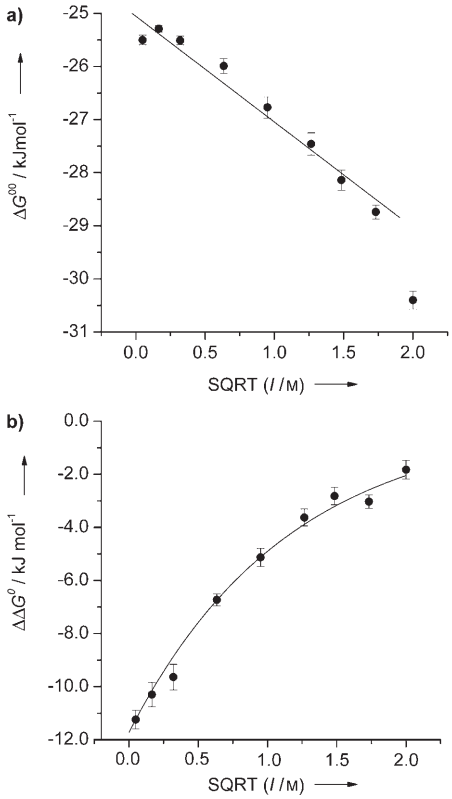


Figure 4. Influence of ionic strength I on a) apolar binding free energy of neutral guest **19** $\Delta G^{\circ\circ}$, and b) contribution of electrostatic interactions to binding free energy $\Delta\Delta G^{\circ}$ of anionic guest **20** for heptacationic host **8**. The curve was calculated according to Debye–Hückel–Onsager theory [Eqs. (2)–(4) with $r_{eff}=0.23$ nm].

7·20, and downward orientations were determined for **1·15a**, **12·20**, and **7·15**. These findings clearly support our previous hypothesis that attractive interactions lead to upward orientation and repulsive ones to downward orientations.

Dependence of apolar binding and electrostatic interactions on salt concentration: To provide an additional test of our approach of dividing binding free energy into apolar binding and electrostatic interactions, we investigated the effect of salt. Differential salt effects on the two types of binding are conceivable: apolar binding could be strengthened by an increase in salt concentration, while electrostatic interactions should level off. Indeed, these contrasting effects have been reported in investigations of the effect of salt on the binding behavior of statistical β-CD sulfonates.[41] The dependence of the binding free energies on the ionic strength I of NaCl was measured for the heptacationic host **8** with neutral guest **19** and anionic guest **20**. As expected, increasing ionic strength I made the apolar binding free energy $\Delta G^{\circ\circ}$ more negative but the electrostatic part $\Delta\Delta G^{\circ}$ less negative (Figure 4). The influence of ionic strength I on electrostatic interactions was stronger than on the apolar binding.

Discussion

The potential of native β-CD to recognize charged guests was already suggested in the literature.[52] For instance, the β-CD inclusion compound of adamantane-1-carboxylate (ΔG° −25.7 kJ mol^{-1})[53] is more stable than that of adamantane-1-amine·HCl ($\Delta G^{\circ}=-22.5$ kJ mol^{-1}).[54] The preference of β-CD for anionic guests can be rationalized by electrostatic interactions between the intrinsic dipole moment of β-CD, parallel to the C_7 symmetry axis, and the charge of the guest. The dipole moment of β-CD was estimated to be 14–20 D in the crystalline state,[55] and 2.9–3.7 D in solution,[56] with the partial positive charge situated on the primary side. This dipole moment should control the orientation of an included dipolar guest. Indeed, anionic guests like benzoic acid, phenol,[57] and *tert*-butylbenzoic acid are oriented with their electronegative functional group upwards towards the primary side of β-CD, whereby dipole–dipole interactions are maximized.[58] Our ROESY results for β-CD inclusion compounds support an antiparallel alignment of the dipoles. Anionic guest **20** is oriented upwards in β-CD, while cationic guest **15a** is oriented downwards. The downward orientation seems to lead to weaker binding, possibly due to only partial space filling of the cavity. Nevertheless, these dipole–dipole

interactions are small (ca. 1 kJ mol^{-1}) and are neglected in the following discussion for the sake of simplicity.

Orientations of charged guests in charged hosts are predominantly controlled by Coulomb forces. An attractive interaction ($\Delta\Delta G° < 0$) forces the guest to adopt an upward orientation, while a repulsive one ($\Delta\Delta G° > 0$) leads to a downward orientation. This rule was generalized to all the inclusion compounds tested when calculating binding energies.

The measured $\Delta\Delta G°$ were correlated with Coulomb energies, calculated according to Equation (2). In these calculations, z_h and z_g are the charge numbers of host and guest, r is the intercharge distance, and $\varepsilon_r = 78.5$ the relative dielectric constant of water. The intercharge distance r was estimated by Equation (3) with $r_0 = 0.3$ nm equal to the internal radius of the β-CD cavity[59] for an upwards-oriented guest, and $r_0 = 1.0$ nm equal to the height of the CD cavity for a downward-oriented guest, and the length of the spacer group r_s (see Table 4) between C-6 and the ionic atom of hosts **2**–**13** was estimated by summation of increments for all bonds. The increments were calculated from the projections of the bond lengths parallel to the main direction of the spacer, assuming all-*trans* conformations (see Supporting Information). The shielding effect exerted by clouds of oppositely charged ions surrounding the interacting functional groups was quantitatively described by Debye–Hückel–Onsager theory.[60] We used a simplified formulation that has already been used to describe Coulomb interactions of proteins in aqueous salt solution, with the Debye length λ_D proportional to $I^{1/2}$ according to Equation (4) at $T = 298$ K.[61] It was assumed that the buffer ions cannot intrude into the CD cavity and that formation of an ion cloud is partially sterically hindered. Therefore we defined an effective length r_{eff} within which ion shielding occurs. This effective length was approximated by the spacer length r_s diminished by one bond length ($r_{eff} = r_s - 0.15$ nm), which led to the best fit. This calculated Coulomb energy E_{Coul} was plotted against the experimental electrostatic interactions $\Delta\Delta G°$ (Figure 5). Considering an ionic strength of $I = 0.2$ M for the buffer solution, the correlation was very good ($R = 0.97$) with a low standard deviation (SD = 1.3 kJ mol^{-1}). The slope of 1.0 within the experimental error verified our model. The negligible intercept for Coulomb energy $E_{Coul} = 0$ at $\Delta\Delta G° = -(0.5 \pm 0.3)$ kJ mol^{-1} demonstrates that the specificities $\Delta\Delta G°$ are due solely to Coulomb interactions.

$$E_{Coul} = \frac{N_A e^2}{4\pi\varepsilon_0\varepsilon_r}\frac{z_h z_g}{r} e^{-r_{eff}/\lambda_D} \quad (2)$$

$$r = r_0 + r_s \quad (3)$$

$$\lambda_D = \sqrt{\frac{\varepsilon_0\varepsilon_r k_B T}{2N_A e^2 I}} \quad (4)$$

The decay of the electrostatic interaction $-\Delta\Delta G°$ with increasing ion strength I (Figure 4b) was also quantitatively described by Debye–Hückel–Onsager theory. The best fit was found for $r_{eff} = 0.27$ nm, somewhat less than expected. The small value of r_{eff} was attributed to steric hindrance of ion-cloud formation within the constricted environment of the host. On the other hand, apolar binding increases linearly with the square root of ionic strength I. This is, to our knowledge, the first time this relationship has been reported. It may be due to an increase of the hydrophobic interaction caused by depletion of ions down to a thin layer close to the hydrophobic surface.[62,63]

In addition, electrostatic interaction enthalpies $\Delta\Delta H°$ were calculated by taking the binding enthalpies $\Delta H°$ for the cationic and anionic guests (**16** and **20**) and subtracting the binding enthalpies $\Delta H°°$ of the neutral guest (**19**). Surprisingly, only a very bad correlation ($r < 0.5$) was found with the Coulomb energies, which were calculated according to Equations (2)–(4). We have no explanation for this finding at present.

The well-known enthalpy–entropy compensation is valid only for the apolar binding free energies for neutral guest **19**, as shown in Figure 6. A straight line with reasonable correlation ($R = 0.93$) and standard deviation (SD = 0.8 kJ mol^{-1}) was found. The slope $A = 0.5$ was smaller than reported elsewhere.[6] On the other hand, correlation was in-

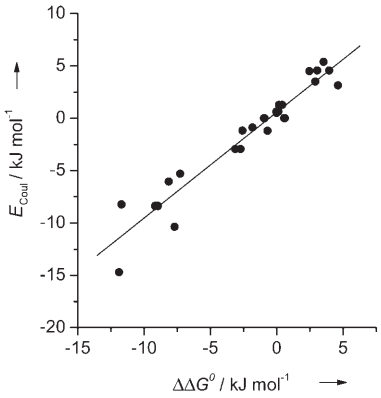


Figure 5. Coulomb energies E_{Coul}, calculated according to Equations (2)–(4), as functions of the measured electrostatic interactions $\Delta\Delta G°$.

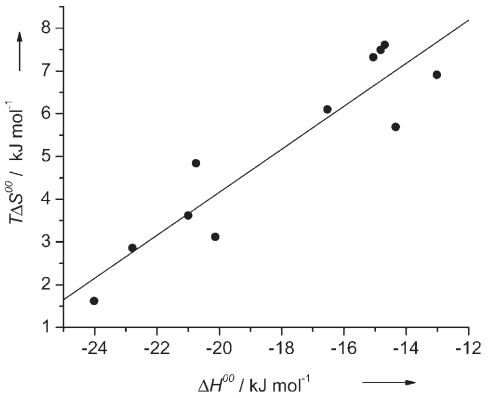


Figure 6. Plot of binding enthalpy $\Delta H°°$ versus entropy $T\Delta S°°$ for hosts **1**–**14** and neutral guest **19**.

significant ($R<0.5$) for both ionic guests **16** and **20**, in agreement with previously reported results.[64] This finding leads us to conclude that the enthalpy–entropy compensation principle mainly holds for apolar interactions. Coulomb interactions may influence solvation effects, especially by ions of the solvent, and thereby lead to more complicated situations.

Conclusion

Attachment of seven charged substituents at the primary rim of β-CD gives rise to highly potent host molecules. Strikingly, electrostatic repulsion between the charged substituents does not diminish apolar binding due to deformation of the CD cavity as described elsewhere.[30] This can be explained by the fact that stabilization by intramolecular hydrogen bonds at the secondary rim is retained for our compounds. These so-called flip-flop hydrogen bonds are known to stabilize the CD scaffold.[65,66]

Electrostatic interactions can be described in good approximation by Coulomb's law combined with Debye–Hückel–Onsager theory. These simple theories would fail unless the CD hosts of this study would not be quite rigid. Within the heptasubstituted CD derivatives, spacer groups are forced to point radially outwards because of the intramolecular repulsive forces between the charged end groups.

These results may help to design new cyclodextrin receptors with even higher binding constants. Furthermore, these binding data may also prove useful for parameterization of force fields to allow more accurate molecular dynamics calculations of CD inclusion compounds in water boxes.

Experimental Section

Materials: Compounds **15**, **17**, and **21** were purchased from Aldrich. β-CD was donated by Wacker. Synthesized host compounds were purified by nanofiltration by using a Berghof BM-5 membrane (molecular weight cutoff 500 Da) and Milli-Q water.

Synthetic procedures: Monosubstituted β-CD derivatives **2**–**6** were synthesized starting from 6-*O*-tosyl-β-CD[45] by displacement reactions with nitrogen and sulfur nucleophiles, as depicted in Scheme 1, by using standard procedures described previously.[38] Heptasubstituted β-CD derivatives **7**–**14** were synthesized starting from heptakis(6-iodo-6-deoxy)-β-CD[67] by displacement reactions with nitrogen and sulfur nucleophiles, as depicted in Scheme 2, by using standard procedures described previously.[38]

***N*-(6-deoxy-6-β-cyclodextrinyl)guanidinium chloride (3)**: Mono-[6-deoxy-6-amino]-β-CD **2** (1.13 g, 1.00 mmol) was dissolved in anhydrous DMF (15 mL). The mixture was stirred for 24 h at room temperature after addition of Hünig's base (0.17 mL, 1.0 mmol) and 1*H*-pyrazole-1-carboxamidine hydrochloride (0.13 g, 1.00 mmol). The solvent was evaporated and the product precipitated in acetone to give a white material (1.05 g, 0.89 mmol, 89%). ^{1}H NMR (500 MHz, D_2O/DSS): $\delta=3.40$–3.59 (m, 15H; H-2/2′/4/4′/6a′), 3.59–3.74 (m, 8H; H-5/5′/6b′), 3.74–3.90 (m, 19H; H-3/3′/6a/6b), 4.95–5.00 ppm (m, 7H; H-1/1′); ^{13}C NMR (125.71 MHz, D_2O/DSS): $\delta=44.07$ (C-6′), 61.86 (C-6), 73.93 (C-2/C-2′/C-5/C-5′), 75.09 (C-3), 83.04 (C-4), 84.83 (C-4′), 104.08 (C-1/C-1′), 159.58 ppm (C-7′); IR: $\tilde{\nu}=1020$, 1149 (s, C–C), 1359 (w), 1649 (w, N–H), 2916 (m, C–H), 3272 cm^{-1} (s, O–H); MS (ESI) *m/z*: 1175.4 [M+H$^+$]; elemental analysis calcd (%) for $C_{43}H_{73}N_3O_{28}\cdot$HCl·16$H_2O$: C 36.77, H 7.50, N 3.00; found: C 36.50, H 6.48, N 4.47.

***N*-(6-deoxy-6-β-cyclodextrinylsulfanylethyl)guanidinium chloride (5)**: Mono-[6-deoxy-6-(2-aminoethylsulfanyl)]-β-CD **4** (1.48 g, 1.24 mmol) was dissolved in anhydrous DMF (15 mL). The mixture was stirred for 24 h at room temperature after addition of Hünig's base (0.21 mL, 1.24 mmol) and 1*H*-pyrazole-1-carboxamidine hydrochloride (0.18 g, 1.24 mmol). The solvent was evaporated and the product precipitated in ethanol to give a white material (1.29 g, 1.04 mmol, 84%). ^{1}H NMR (500 MHz, D_2O/DSS): $\delta=2.85$ (m, 2H; H-7′), 3.29 (m, 2H; H-8′), 3.40–3.51 (m, 21H; H-2/2′/4/4′/5/5′), 3.63–3.83 (m, 21H; H-3/3′/6a/6b/6a′/6b′), 4.88–4.90 ppm (m, 7H; H-1/1′); ^{13}C NMR (125.71 MHz, D_2O/DSS): $\delta=37.98$ (C-7′), 38.50 (C-6′), 41.69 (C-8′), 61.24 (C-6), 73.19 (C-2/C-2′/C-5/C-5′), 74.28 (C-3), 82.38 (C-4), 85.51 (C-4′), 103.21 (C-1/C-1′), 157.91 ppm (C-9′); IR: $\tilde{\nu}=1020$, 1149 (s, C–C),1353 (w), 1650 (w, N–H), 2916 (m, C–H), 3269 cm^{-1} (s, O–H); MS (ESI): *m/z*: 1236.4 [M+H$^+$]; elemental analysis calcd (%) for $C_{45}H_{77}N_3O_{28}\cdot$HCl·10$H_2O$: C 40.77, H 7.47, N 3.17; found: C 40.28, H 6.69, N 2.70.

1-(4-*tert*-Butylphenyl)guanidine (16): 4-*tert*-Butylaniline (2.0 g, 13.4 mmol) was dissolved in anhydrous DMF (5 mL). The mixture was stirred for 48 h at room temperature after addition of 1*H*-pyrazole-1-carboxamide hydrochloride (2.17 g, 14.7 mmol). The solvent was evaporated and the residue was washed with diethyl ether, dissolved in water, and extracted with diethyl ether. The aqueous phase was lyophilized to give the white product (2.14 g, 11.2 mmol, 70%). ^{1}H NMR (500 MHz, D_2O/DSS): $\delta=1.32$ (s, 9H; H-6), 7.28 (d, $^3J=8.83$ Hz, 2H; H-2), 7.85 ppm (d, $^3J=8.51$ Hz, 2H; H-3); ^{13}C NMR (125.71 MHz, D_2O/DSS): $\delta=32.84$ (C-6), 36.57 (C-5), 128.35 (C-2), 129.52 (C-3), 133.30 (C-1), 149.22 (C-4), 154.40 ppm (C-7); MS (ESI): *m/z*: 192.2 [M+H$^+$].

4-*tert*-Butyl-*N*,*N*-dimethylaniline *N*-oxide (19): 4-*tert*-Butyldimethylaniline (0.5 g, 2.82 mmol) was dissolved in methanol (5 mL), hydrogen peroxide (30%, 1.15 mL) was added dropwise, and the mixture was stirred for seven days at room temperature. After addition of a catalytic amount of Pd/C, the mixture was filtered through Celite to give the colorless product (0.23 g, 1.18 mmol, 42%) after evaporation of the solvent. ^{1}H NMR (500 MHz, D_2O/DSS): $\delta=1.31$ (s, 9H; H-6), 3.60 (s, 6H; H-7) 7.62 (d, $^3J=8.51$ Hz, 2H; H-3), 7.80 ppm (d, $^3J=8.51$, 2H; H-2); ^{13}C NMR (125.71 MHz, D_2O/DSS): $\delta=32.98$ (C-6), 36.62 (C-5), 64.21 (C-7), 121.65 (C-2), 129.10 (C-3), 152.36 (C-1), 155.71 ppm (C-4); MS (ESI): *m/z*: 194.2 [M+H$^+$]; elemental analysis calcd (%) for $C_{12}H_{19}NO\cdot H_2O$: C 68.21, H 10.02, N 6.63; found: C 68.72, H 9.91, N 6.25.

4-*tert*-Butylbenzenesulfonic acid (20): 4-*tert*-Butylbenzene (5.37 g, 40.0 mmol) was cooled to 0°C and oleum (1.62 mL, 40.0 mmol) was added dropwise. The mixture was stirred for 3 h at room temperature, water was added (20 mL), and the solution was neutralized with Amberlite IRA-402. The solution was lyophilized to give the white product (1.21 g, 5.68 mmol, 14%). ^{1}H NMR (500 MHz, D_2O/DSS): $\delta=1.32$ (s, 9H; H-6), 7.62 (d, $^3J=8.83$, 2H; H-2), 7.74 ppm (d, $^3J=8.51$ Hz, 2H; H-3); ^{13}C NMR (125.71 MHz, D_2O/DSS): $\delta=32.97$ (C-6), 36.91 (C-5), 121.65 (C-2), 129.10 (C-3), 152.36 (C-1), 155.71 ppm (C-4); MS (ESI): *m/z*: 213.0 [M+H$^+$]; elemental analysis calcd (%) for $C_{10}H_{13}O_3SNa\cdot H_2O$: C 47.23, H 5.95; found: C 46.63, H 6.25.

Potentiometric measurements and calculation of pK_a values: The titration experiments were performed as described previously[68] (25.0°C, 0.1 M KCl) by using a Metrohm 665 piston burette, a Metrohm 6.0262.100 glass electrode with an incorporated Ag/AgCl reference, and a Metrohm 713 pH/mV meter. Data acquisition and addition of the titrant (0.1 M KOH) were controlled by a PC.[69] The total concentration of the various polybases was always 0.5 mM. The two polyamines **7** and **8** were used as hydrochlorides, and the polycarboxylates **9** and **11** as sodium salts together with eight equivalents of HCl to ensure complete protonation at the beginning of the experiment. Potentiometric data were evaluated with the computer program HYPERQUAD.[70] All protonation constants were calculated as concentration constants, pH was defined as $-\log[H^+]$, and the fixed value p$K_w=13.78$ was used.[71] For each system, at least four titration experiments were performed, and in the final evaluation two curves of each system were combined into one data set and evaluated together.

ITC measurements: Isothermal microcalorimetric titrations were performed at 25.0 °C with an AutoITC isothermal titration calorimeter (MicroCal Inc., Northampton, USA) with 1.414 mL of sample and reference cells. The reference cell was filled with distilled water. Prior to the measurements, samples of hosts and guests were brought to pH 6.8 by titration with small amounts of aqueous HCl or NaOH and lyophilized afterwards. The sample cell was degassed and filled with a 1 mM solution of the respective host in 50 mM phosphate buffer (pH 6.8) and constantly stirred at 450 rpm. A 13 mM solution of the guest in the same buffer was automatically added by syringe in 20 separate injections of 12.5 μL. The resulting 20 heat signals were integrated to yield the mixing heats, which were corrected by the corresponding dilution enthalpies of the guest, which had been measured separately. The host–guest titration curve (molar heats vs. molar ratio guest/host) was fitted by nonlinear regression with the program Origin 7.0 for ITC. For each inclusion compound, the host–guest stoichiometry was found to be 1:1. The binding constant K and the molar binding enthalpy $\Delta H°$ were obtained as fitting parameters, from which the binding free energy $\Delta G°$ and binding entropy $\Delta S°$ were derived. The titration was repeated 2–3 times with concentrations of $[\text{host}] = 10/K$ and $[\text{guest}] = 130/K$ to achieve optimal accuracy. For small binding constants ($K < 2500\ \text{L mol}^{-1}$), concentrations were limited to [host] = 4 mM and [guest] = 40 mM.

NMR measurements: All ^{1}H NMR experiments were carried out in deuterium oxide at 25 °C on a Bruker Avance 500 spectrometer at 500.00 MHz. ROESY experiments were performed on 15 mM solutions of hosts and guests in 0.05 M phosphate buffer solutions by using the Bruker standard routine "roesyph." The data consisted of NS = 32 scans collected over 2048 complex points with a spectral width (SW) of 4005 Hz. A mixing time (P15) of 300 ms, a repetition delay (D1) of 2 s, an acquisition time of 0.167 s, and a 90° pulse width (P1) of 7.95 μs at PL1 = −2 dB power attenuation were used.

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