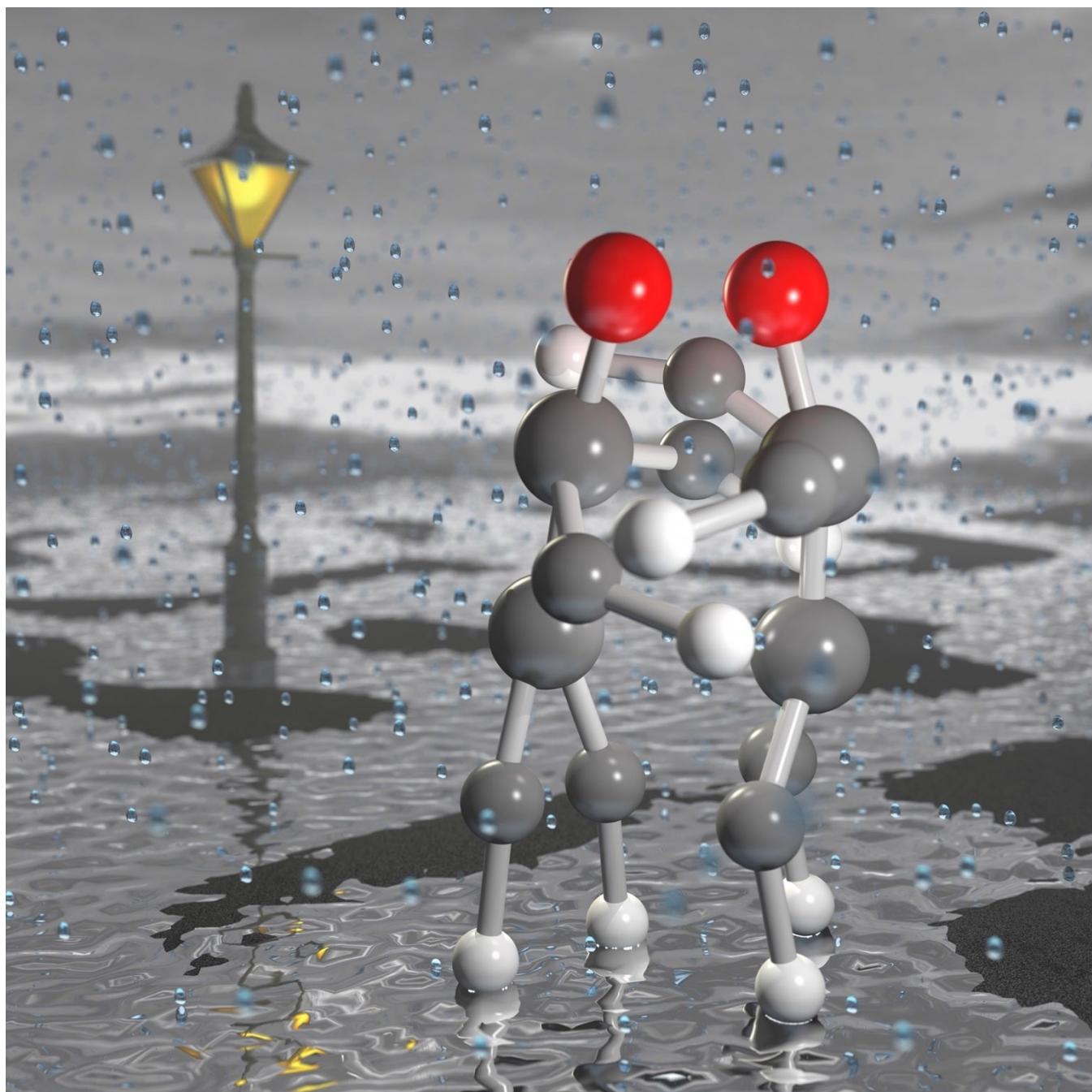




# When Molecules Meet in Water—Recent Contributions of Supramolecular Chemistry to the Understanding of Molecular Recognition Processes in Water

Stefan Kubik<sup>\*[a]</sup>

*In memory of François Diederich*



Molecular recognition processes in water differ from those in organic solvents in that they are mediated to a much greater extent by solvent effects. The hydrophobic effect, for example, causes molecules that only weakly interact in organic solvents to stay together in water. Such water-mediated interactions can be very efficient as demonstrated by many of the synthetic receptors discussed in this review, some of which have substrate affinities matching or even surpassing those of natural

binders. However, in spite of considerable success in designing such receptors, not all factors determining their binding properties in water are fully understood. Existing concepts still provide plausible explanations why the reorganization of water molecules often causes receptor-substrate interactions in water to be strongly exothermic rather than entropically favored as predicted by the classical view of the hydrophobic effect.

## 1. Introduction

Structurally and electronically complementary molecules that meet in solution stay together for a while. An important parameter determining the stability of complexes formed in this way is the nature of the intermolecular interactions, with strong ionic interactions potentially affording more stable complexes than weaker types of interactions.<sup>[1]</sup> Although deviations from this trend caused by effects such as multivalency<sup>[2]</sup> or cooperativity<sup>[3–5]</sup> are possible, the intrinsic strength of the primary interactions is generally considered to be a decisive factor for the efficiency with which two or more binding partners interact.

Another factor is the solvent in which complex formation takes place.<sup>[6]</sup> Since all types of noncovalent interactions feature a pronounced electrostatic component, complex stability decreases as the relative permittivity of the solvent increases. In addition, the solvation of the binding partners, especially that of the interacting functional groups, leads to a further reduction of complex stability since the energetic gain of complex formation is partially offset by the energy required to remove solvent molecules from the regions of the molecules that come into contact. As a consequence, complexes that are stable in a nonpolar environment can become almost nonexistent in a polar solvent in which solvation is strong.

Based on these arguments, molecular recognition processes in water, with its high permittivity and the pronounced hydrogen bond donor and acceptor properties of water molecules,<sup>[7,8]</sup> should be particularly inefficient, which, in reality, is not the case. Not only have certain synthetic receptors long been known to work in water,<sup>[9]</sup> but the entire biochemical machinery, which relies heavily on noncovalent interactions between the various biomolecules, functions (and has evolved) in this solvent. Water can even mediate interactions between apolar

molecules that are not prone to interact in other environments if the reorganization of the water molecules that accompanies the association of the solutes is thermodynamically favorable. Molecular recognition in water is thus intricately linked to the peculiar properties of water molecules and water in the bulk.

Liquid water is highly cohesive, for example, as reflected in its high melting and boiling points, its surface tension, and heat capacity.<sup>[7,8]</sup> At the molecular level, these properties are due to the extensive interactions between the water molecules in the liquid state, each of which forms on average 3.6 hydrogen bonds to its immediate neighbors.<sup>[10]</sup> The incorporation of a solute into this network not only requires the formation of a cavity, but also the rearrangement of a certain number of hydrogen bonds. While new hydrogen bonds can potentially be formed to a polar solute, accommodating an apolar solute in the water matrix requires reorganizing hydrogen bonds to compensate for bonds that are given up when forming the cavity. Accordingly, the extent and outcome of the response of the water network depend characteristically on the solute's size, polarity and shape.<sup>[11,12]</sup> Furthermore, the transition from the state in which solutes are individually hydrated to the state in which they form a complex is normally associated with the release of water molecules, since the solvent-exposed surface area of the complex is smaller than the sum of the surface areas of the individual complex components. Thus, water molecules are reincorporated into the water matrix during complex formation with thermodynamic consequences that are much more pronounced than those in other solvents. These water-mediated binding processes are associated with the term hydrophobic effect,<sup>[13,14]</sup> whereby a distinction is often made between the classical and the nonclassical hydrophobic effect, depending on whether complex formation is dominated by entropy or enthalpy.<sup>[15]</sup>

For the understanding of recognition processes in water it is therefore not sufficient to only focus on the binding partners; one must also consider the effect of complex formation on the solvent. Not all relevant principles are fully understood yet,<sup>[16]</sup> although receptors are studied in water for many years. Examples are cyclodextrins,<sup>[17,18]</sup> macrocyclic polyamines,<sup>[19–22]</sup> and cucurbiturils.<sup>[23,24]</sup> Some aspects of supramolecular chemistry in water are therefore known for some time,<sup>[9,25]</sup> but with the increasing interest in developing receptors for practical applications,<sup>[26–29]</sup> many of which require functioning systems in water, the interest in deciphering the principles of molecular recognition in water has grown considerably.

In this review, a number of recent developments are highlighted with a particular focus on host-guest chemistry,

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while self-assembly in water will not be treated.<sup>[30,31]</sup> Emphasis is placed on providing insight into current views on how the hydration of the binding partners and the complex, as well as the reorganization of water molecules during complex formation affect binding. The respective discussion will remain qualitative, however, and readers interested in thorough thermodynamic treatments of the respective aspects are referred to more specialized reviews.<sup>[32,33]</sup> Receptors engaging in coordinative interactions with the substrate are not considered because the covalent nature of these interactions causes complex formation to be not very susceptible to solvent effects.

## 2. Ionic Interactions

### 2.1. Some Remarks About Ion Hydration

While interactions of ions in the gas phase can approach the strength of covalent bonds, the high relative permittivity of water ( $\epsilon = 78$ ) weakens these interactions by almost two orders of magnitude. In addition, ions are often strongly hydrated in water as reflected in pronounced negative Gibbs free energies of hydration.<sup>[34]</sup> The removal of solvation shells during complex formation, even only partially, therefore comes at a significant energetic cost, which causes interactions between charged species in water to be not very efficient unless they are complemented by other types of interactions. Indeed, a single salt bridge in water was estimated to be only worth between 5 and 8  $\text{kJ mol}^{-1}$  (corresponding to  $\log K_a$  values of ca. 1),<sup>[1,35]</sup> and simple ions should therefore be fully dissociated at the millimolar concentrations commonly used in supramolecular chemistry.

At higher salt concentrations, ranging from molar concentrations to concentrations at which not enough water molecules are present to hydrate all the ions, ion pairing in water cannot be neglected, however.<sup>[36–38]</sup> The decreased reorientation dynamics of a small fraction of water molecules, which was observed by dielectric relaxation and femtosecond mid-infrared spectroscopy in various salt solutions containing biologically relevant cations and anions indicated, for example, that ion pairs exist in these solutions, in which a single solvent layer

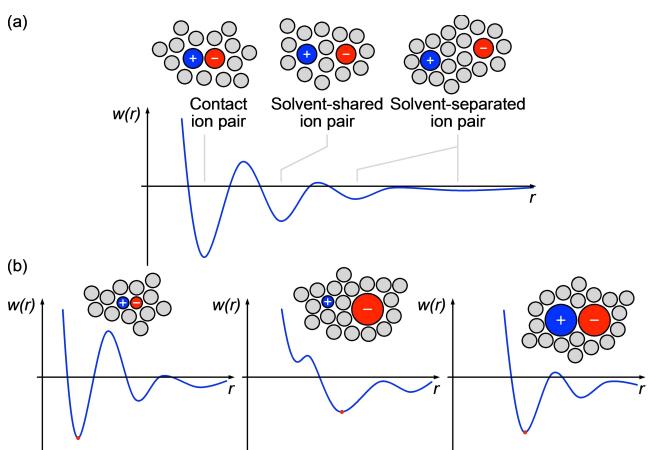


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(SIPs) or two intact solvation shells (2SIPs) separate the two ions.<sup>[38]</sup> Methods such as far-infrared absorption studies, X-ray absorption studies, and molecular dynamics simulations provided evidence also for the existence of contact ion pairs (CIPs), in which the cation and the anion are hydrated together. These three types of ion pairs differ energetically, as reflected in the free energy of bringing their constituents together to the respective distance  $r$  (Figure 1a).<sup>[8]</sup> The energetically most favorable situation is usually the CIP, unless the cation and the anion differ considerably in size. In this case, the arrangements of water molecules in the solvation shells of the two ions are incompatible because the small ion is efficiently hydrated, while the water molecules around the larger ion are more loosely arranged. As a consequence, SIPs become energetically more favorable than CIPs or 2SIPs (Figure 1b).

Indeed, salts containing a combination of a large and a small ion are more water-soluble than salts containing only large or only small ions. This observation led Collins to formulate the *law of matching water affinities*,<sup>[39,40]</sup> which predicts that the pairing of two small or two large oppositely charged ions is energetically favorable. In the case of small ions, the energetic gain of ion pairing more than compensates the energetic cost of partially desolvating them, while the energetic cost of desolvating two large ions is compensated by the formation of new water-water interactions. The hydration shells of ions that differ considerably in size do not match, however, and ion pairing is therefore less efficient.

The widely used strategy in supramolecular chemistry to overcome the intrinsic weakness of a single salt bridge in water involves arranging multiple charged groups around the cavity of a receptor. These groups not only ensure water solubility, but also cause an increased local concentration of charges around the binding site. Accordingly, a substrate experiences a similar situation within the cavity of a charged host as in a



**Figure 1.** (a) PMF curve describing the distance dependence of the free energy of bringing two oppositely charged ions together from a large distance. Minima in the curve, representing solvent-separated, solvent-shared, and contact ion pairs, are marked. Water molecules are depicted as grey spheres without specifying the effect of the ions on the orientation of the water molecules in the solvation shells. (b) PMF curves of ion pairs containing two small, two large, and one small and one large ion.

concentrated salt solution, thus potentially allowing ion pairing to contribute to complex stability.

## 2.2. Charged Receptors for (Oppositely) Charged Substrates

Among the few receptors that mainly use ionic interactions for substrate binding are the tetraammonium hosts **1a,b** (Figure 2) developed a while ago by Schmidtchen.<sup>[41,42]</sup> These cage-type receptors feature four quaternary ammonium centers at the corners, which render them water-soluble and fourfold positively charged, independent of the pH. They bind halides and other inorganic anions, but with not very pronounced affinities. Both **1a** and **1b** most strongly bind to bromide, for example, with a  $\log K_a$  value of 2.5 ( $\Delta G^0 = -14.3 \text{ kJ mol}^{-1}$ ).<sup>[41]</sup> These complexes are thus somewhat less stable than predicted based on Schneider's increment of 5–8  $\text{kJ mol}^{-1}$  per salt bridge.<sup>[43,44]</sup> Ion pairing alone therefore seems to be insufficient to realize strong binding in water.

The comparison of the binding properties of receptors **2** and **3** supports this assumption.<sup>[45]</sup> While the tetraprotonated form of **2** binds adenosine triphosphate (ATP) with a  $\log K_a$  of 3.8, no interaction between **3** and ATP was detected under the same conditions, in spite of the same charge state of both receptors and the even higher charge density of **3**. Obviously, **3** and ATP are so well hydrated and the charges so well screened in water that ionic interactions are negligible between the two ions at the distance at which they can approach each other. The tetraprotonated form of **2**, on the other hand, can approach the oxygen atoms of ATP at a much smaller distance. As a consequence, electrostatic interactions become significant stronger or, in another terminology,  $\text{H}_4\text{2}^{4+}$  can form four charge-assistant hydrogen bonds to the triphosphate group of ATP. High anion affinity is, indeed, a general feature of such polyammonium receptors. Many other examples exist, rendering these compounds one of the largest and structurally diverse receptor classes for anions in water.<sup>[19–22,27]</sup>

While early investigations mainly focused on elucidating how structural aspects and the degree of protonation influence anion affinity and selectivity, interesting catalytic properties,<sup>[46]</sup> and bioactivities were later discovered,<sup>[27]</sup> including the potential to treat Leishmaniasis, a widespread parasitic disease.<sup>[47]</sup> With respect to the topic of this review it is worth noting that the anion binding of polyammonium receptors, including the receptors developed by Schmidtchen, is usually strongly

exothermic,<sup>[42,48]</sup> which is a thermodynamic signature that is characteristic for many host-guest interactions in water.

Charge-assisted hydrogen bonds are also operative in Schmuck's guanidiniocarbonyl pyrrole (GCP)-based receptors, which primarily serve to bind carboxylates or phosphates.<sup>[27,49]</sup> A guanidinium moiety serves in these systems as the primary binding site that in itself has unusual properties in water.<sup>[50]</sup> Guanidinium ions are protonated at pH values up to 12 due to their high  $pK_a$ , for example, and feature a seam of hydrogen bond donors along the edge of their planar structure. In contrast to spherical ammonium ions, hydrating water molecules therefore mainly encircle the edge of the ion, leaving the more hydrophobic surfaces somewhat exposed. Accordingly, guanidinium ions can stack in water to afford dimers, in which the Coulomb repulsion is overcompensated by dispersion interactions and solvent effects.<sup>[51]</sup> This pairing of like-charged ions could explain why arginine-rich peptides readily penetrate cell membranes.<sup>[52]</sup> In addition, the ability of guanidinium ions to pair with both hydrophobic and hydrophilic groups in proteins, including the guanidinium groups in the side chain of arginine residues, is the reason why they efficiently denature proteins.

When pairing with oppositely charged oxoanions such as carboxylates, guanidinium groups form two parallel hydrogen bonds as shown schematically in Figure 3. The respective ion pairs are not very stable in water, however, as already pointed out by Collins.<sup>[39]</sup> Arginine residues in proteins are therefore often located in regions of the folded peptide backbone where the permittivity is lower, resulting in more efficient guanidinium-anion interactions.<sup>[53]</sup> For similar reasons, there are only a few synthetic guanidinium-based anion receptors that are active in water, and most of them contain more than one guanidinium group.<sup>[54,55]</sup> The efficiency of Schmuck's GCP-based receptors is due to a network of highly efficient charge-assisted hydrogen bonds in which the pyrrole unit is also involved (Figure 3). The simple self-complementary GCP derivative **4** thus dimerizes in water, forming a complex with a  $\log K_a$  of 2.2.<sup>[56]</sup> The possibility to further modulate substrate binding by structural variation of the substituents in the 5-position of the pyrrole ring, as shown schematically in Figure 3, renders the GCP group a versatile building block for the development of receptors, chemosensors, gene transfection agents, and for realizing various types of self-assembled architectures in water.<sup>[49]</sup>

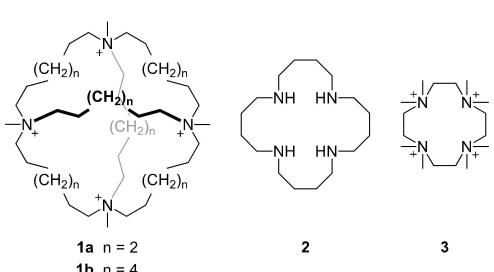


Figure 2. Structures of receptors **1a–c**, and **2–3**.

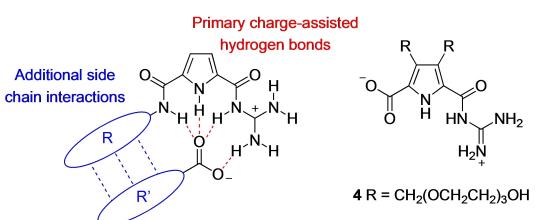


Figure 3. Schematic illustration of the hydrogen bonding pattern in the complex between a GCP group and a carboxylate (left) and structure of the self-complementary GCP derivative **4** (right).

Further cyclic and acyclic receptors with charged groups along the binding site are shown in Figures 4 and 5. The octaanionic  $\gamma$ -cyclodextrin derivative **5**, known as sugammadex and sold under the trade name Bridion<sup>TM</sup>, is used to treat side effects of steroid-derived anesthetics such as rocuronium **6**.<sup>[57]</sup> The mode of action involves sequestering rocuronium by

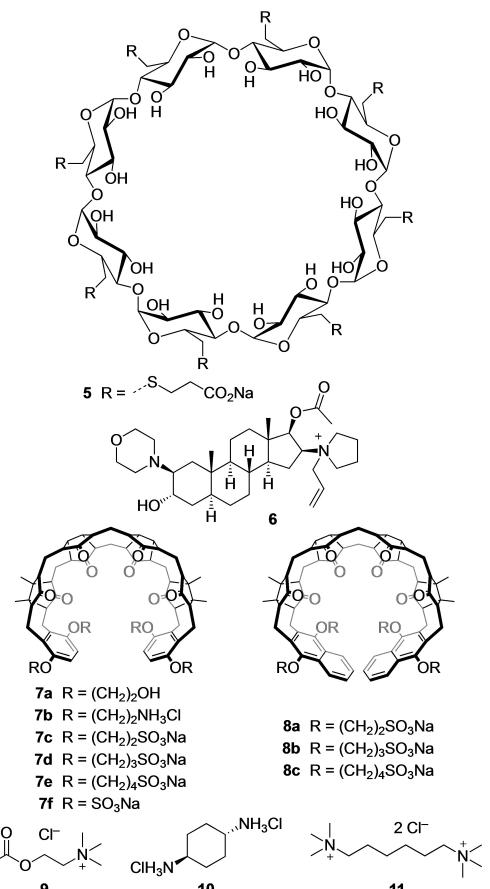


Figure 4. Structures of receptors **5**–**8** and selected guests.

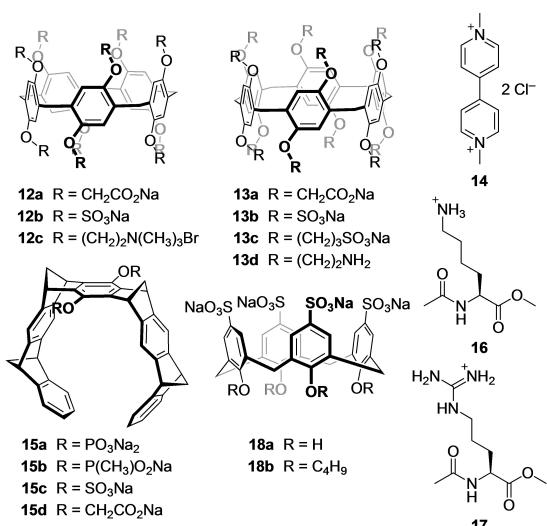


Figure 5. Structures of receptors **12**–**18** and selected guests.

complexation, thereby preventing it from interacting with its biological target. The high  $\log K_a$  of the respective complex of **7.3** can partly be attributed to ionic interactions between the carboxylate groups along the cyclodextrin ring and the rocuronium ammonium group.<sup>[58]</sup>

The Isaacs group has shown that acyclic cucurbiturils (aCBs) bind rocuronium and related steroid-derived drugs with an affinity that is on par with or even higher than that of sugammadex.<sup>[59]</sup> These receptors can therefore also be used as sequestration agents, not only for neuromuscular blockers but also for various drugs of abuse.<sup>[57,60]</sup> In addition, they improve the solubility and bioactivity of hydrophobic pharmaceuticals, potentially allowing their use in drug formulations.<sup>[61]</sup>

To elucidate the effect of the charged groups on complex stability, the receptor properties of a series of aCB derivatives were compared.<sup>[62]</sup> A trend suggesting that complex stability benefits from ionic interactions is the increase of cation affinity when going from a neutral water-soluble aCB (**7a**)<sup>[63]</sup> to one with two sulfonate groups<sup>[64,65]</sup> and finally to one with four negatively charged groups.<sup>[62]</sup> Unsurprisingly, the cationic aCB **7b** has the lowest cation affinity,<sup>[63]</sup> but binds anionic substrates such as ATP.<sup>[66]</sup> The distance of the sulfonate groups from the cavity opening also influences binding strength, but the effects are often not very pronounced and easy to rationalize. Among the aCBs **7c**–**e** and **8a**–**c**, containing substituents with ethylene, propylene, and butylene chains in the substituents, for example, the ones with propylene chains often possess comparable or even higher cation affinities than the analogs with longer or shorter chains (Table 1). Accordingly, the distance of the sulfonate groups from the cavity opening is not the only factor determining binding strength.<sup>[67]</sup>

The aCB **7f** with sulfate groups directly attached to the aromatic units binds dicationic substrates stronger by factors ranging between 6 and 12 in 20 mM aqueous phosphate buffer (pH 7.4) than aCBs with flexible substituents.<sup>[68]</sup> In the case of guests with two quaternary ammonium head groups, the affinity of **7f** is even 75 times higher than that of **7c**. Accordingly, bringing the negatively charged groups closer to the binding sites helps, but the much larger effect observed for quaternary ammonium ions compared to other cations indicates that electrostatics alone cannot explain all of the observed effects. The greater ease with which the larger cations are dehydrated likely plays an additional role. In addition, the pronounced exothermicity typically associated with complex

Table 1. Stability constants  $\log K_a$  of the complexes of selected aCB derivatives and their corresponding guests.

Receptor	$\log K_a$ values of complexes with <sup>[a]</sup>			
	9	10	11	6
<b>7d</b> <sup>[b]</sup>	4.4	6.3	8.0	6.9
<b>7f</b> <sup>[b]</sup>	5.4	6.5	9.8	8.8
<b>8a</b> <sup>[c]</sup>	5.2	6.3	n.a. <sup>[d]</sup>	9.0
<b>8b</b> <sup>[c]</sup>	5.3	6.4	n.a.	9.8
<b>8c</b> <sup>[c]</sup>	4.8	6.0	n.a.	9.1

[a] 20 mM Aqueous phosphate buffer, pH 7.4, 25 °C; [b] from Ref. [68];

[c] from Ref. [67]; [d] n.a. – not available.

formation suggests that ionic interactions are not the only driving force of binding.

Like acBs, pillararenes also allow arranging charged groups at both cavity openings.<sup>[69]</sup> Such pillararenes are not only water-soluble, but also exhibit pronounced affinities for oppositely charged guests. For example, the pillar[5]arenes **12a** (Figure 5) with 10 carboxylate groups and **13a** with 12 carboxylate groups bind paraquat **14** in water with  $\log K_a$  values of 4.9<sup>[70]</sup> and 8.0,<sup>[71]</sup> respectively. In an independent study,  $\log K_a$  values of 6.9 and 8.2 were determined for the same complexes by using isothermal titration calorimetry.<sup>[72]</sup> The paraquat complex of the corresponding pillar[7]arene with 14 carboxylates even has a  $\log K_a$  of 9.5.<sup>[73]</sup> Although the better fit of the guest in the larger cavities could be partly responsible for this trend, an additional factor is likely the reinforcement of complex stability with increasing number of negative charges in the host.

In a systematic study, Isaacs and co-workers compared the cation affinities of the carboxymethylated pillararenes **12a** and **13a** with those of pillararenes containing sulfonate and sulfate groups.<sup>[72]</sup> They were particularly interested in the receptor properties of the pillararenes **12b** and **13b** (Figure 5) with the anionic groups in the immediate vicinity of the cavity openings as in **7f**. It turned out that both of these pillararenes have extraordinarily high cation affinities, much higher than **12a**, **13a**, or the sulfonated pillararene **13c** with the anionic groups arranged at a larger distance from the cavity (Table 2). No improvement of cation affinity was observed when further enlarging the ring, in turn increasing the number of negatively charged substituents, which suggests that binding is only partly due to ionic interactions. A particularly pronounced improvement of cation affinity was observed for guests containing quaternary ammonium ions, mirroring to some extent the effect observed for **7f**. For these guests, cation affinity approaches the picomolar range, explaining why **12b** and **13b** were named Pillar[n]MaxQ.<sup>[72]</sup> For all studied receptors, complex formation is again strongly exothermic with a smaller but favorable entropic term.

By arranging cationic instead of anionic substituents along the cavities of pillararenes, the binding of anionic substrates can be achieved. These substituents thus overcompensate the intrinsic preference of the electron-rich aromatic moieties surrounding the pillararene cavity to interact with cations through cation-π interactions. In the respective complexes, an example is the 1-octylsulfonate complex of **12b**, the apolar part

of the guest is included into the cavity while the anionic head group is arranged close to the cationic groups in the substituents.<sup>[74]</sup> The pillar[6]arene **13d** interacts efficiently with dicarboxylic acids and the amino acids glutamic acid and aspartic acid in water.<sup>[75]</sup>

Another family of receptors with charged groups at both cavity openings is based on the molecular tweezers developed by Klärner and Schrader.<sup>[76]</sup> The respective receptors **15a-d** (Figure 5) have a high affinity for the positively charged groups in the side chains of lysine and arginine, also when exposed on protein surfaces, which leads to interesting biological activities. These tweezers can modulate the abnormal protein aggregation associated with diseases such as Alzheimer's and Parkinson's disease, for example, and destroy enveloped viruses, including HIV, Ebola, and Zika viruses, rendering them highly promising supramolecular drug candidates.<sup>[76]</sup>

The quantification of binding affinity showed that the affinity in terms of  $\log K_a$  of **15a** to the protected amino acid Ac-Lys-OMe (**16**) in 200 mM phosphate buffer (pH 7.6) amounts to 4.8. Under the same conditions, Ac-Arg-OMe (**17**) is bound with a slightly reduced  $\log K_a$  of 4.2, which was attributed to the lower charge density of the guanidinium group in the side chain of arginine in comparison to the ammonium group in lysine. The cation affinity of the tweezers **15b** and **15c**, which contain singly charged residues, is lower than that of **15a**, and **15d**, whose anionic groups are arranged at a larger distance to the cavity opening, has the lowest cation affinity in this series. Tweezers with only one negatively charged substituent also bind cations much less strongly than **15a**. All of these trends suggest that ionic interactions contribute to the cation affinity of these receptors.

Unlike the receptors presented so far, sulfonated calixarenes such as **18a** have cone-like shapes, conformationally stabilized by a ring of hydrogen bonds between the phenolic OH groups. The deprotonation of the first OH group is associated with a  $pK_a$  of 3.3,<sup>[77]</sup> and such calixarenes are therefore overall fivefold negatively charged in water at physiological pH. Accordingly, a substrate included into the cavity is not only surrounded by the four anionic substituents but also arranged close to a phenolate oxygen atom. The effect of this group on cation complexation was assessed by comparing the affinities for the trimethylanilinium (TMA) cation at pH 6.0 and 2.0.<sup>[78]</sup> At the acidic pH, where all phenol oxygen atoms are protonated, the TMA complex of **18a** is less stable by a factor of almost 6 than at pH 6.0, indicating that the negative charge at the lower rim indeed improves cation affinity (pH 6.0:  $\log K_a = 5.3$ , pH 2.0:  $\log K_a = 4.5$ ). The pH-independent cation affinity of the corresponding butylated anionic calix[4]arene **18b** is consistent with this assumption. This receptor binds TMA less efficiently than **18a** ( $\log K_a = 3.0$ ), which was attributed to the effect of the butyl groups on the calixarene conformation: while **18a** favors the cone conformation, which is well suited for the incorporation of quaternary ammonium ions, alkylated calix[4]arenes adopt the pinched cone conformation in which two opposing aromatic subunits are oriented close to one another in an almost parallel manner.<sup>[78]</sup> This arrangement is not well suited for the binding of spherical guests.

**Table 2.** Stability constants  $\log K_a$  of the complexes of selected pillararene derivatives and their corresponding guests.

Receptor	$\log K_a$ values of complexes with <sup>[a]</sup>			
	14	10	11	6
<b>12a<sup>[b]</sup></b>	6.9	n.a. <sup>[c]</sup>	7.1	n.a.
<b>12b<sup>[b]</sup></b>	8.2	n.a.	12.0	5.6
<b>12c<sup>[b]</sup></b>	5.3	n.a.	5.6	n.a.
<b>13a<sup>[b]</sup></b>	7.5	7.2	7.8	6.2
<b>13b<sup>[b]</sup></b>	10.8	8.3	11.1	11.8

[a] 20 mM Aqueous phosphate buffer, pH 7.4, 25 °C; [b] from Ref. [72];

[c] n.a. – not available.

Sulfonatocalix[4]arenes interact with a variety of biomolecules and pharmaceutically active compounds, allowing their use in medicinal applications.<sup>[79]</sup> In addition, **18a** can be used for sensing purposes and has been shown to mediate the detoxification of viologen derivatives.<sup>[80]</sup> The Hof group furthermore demonstrated that **18a** possesses a pronounced affinity for trimethyllysine, a lysine derivative with a trimethylated amino group in the side chain. This amino acid is bound with a  $\log K_a$  of 4.6 in 40 mM phosphate buffer at pH 7.4,<sup>[81]</sup> while the  $\log K_a$  of the lysine complex of **18a** amounts to 2.7 under the same conditions. Calixarene **18a** is therefore a valuable supramolecular tool to study the methylation of amino acid side chains during the posttranslational modification of proteins.<sup>[27]</sup> While the preferred binding of **18a** to quaternary ammonium groups could be due to a better fit of these groups into the calixarene cavity, allowing cation- $\pi$  interactions to contribute to complex stability, differences in the hydration of protonated and quaternary ammonium ions might also play a role (see above).

In a recent collaborative effort, the stabilities and binding modes of complexes of **7d**, **8b**, **15a**, and **18a** with arginine, lysine, and methylated derivatives of these amino acids were compared.<sup>[82]</sup> Consistent with previous results, the calixarene **18a** was found to bind the native amino acids only weakly, but complex stability improved progressively with increasing degree of methylation, reaching a  $\log K_a$  of 3.9 for trimethyllysine in 10 mM phosphate buffer at pH 7.4. The observed trends for the aCBs **7d** and **8b** were similar, but the overall affinities were at least one order of magnitude higher than those of **18a**. The tweezer **15a** exhibited a different selectivity, binding most strongly to the unmethylated amino acids. Ionic interactions alone do not explain these selectivities, since the charge state of all substrates was the same and the charge states of the receptors similar. Instead, structural parameters are more important such as the ability of aCBs and the tweezers to thread the guests through their cavities, thus allowing the host and guest to make extensive contact. By contrast, the cone-shaped structure of **18a** restricts the interactions to the cationic head groups of the guests.

Ionic interactions also contribute to the substrate binding of coordination macrocycles or cages. If the ligands are cationic or neutral or if their negative charges cannot overcompensate the positive charges of the metal ions, such coordination complexes are overall positively charged, causing them to preferentially interact with anions.<sup>[31]</sup> Examples are the coordination cages **19**<sup>[83]</sup> and **20**<sup>[84]</sup> (Figure 6) in which anion binding is furthermore reinforced by hydrogen bonding to donors in the ligands. By contrast, the overall neutral metallacrowns developed in the Severin group strongly interact with small alkali metal ions through ion-dipole interaction (Section 3.2),<sup>[85]</sup> and the 12-fold negatively charged coordination cage **21** developed by Raymond, in which six bis(catecholate) ligands are coordinated to four gallium(III) ions, possesses a pronounced affinity for ammonium and phosphonium ions in water.<sup>[86]</sup> Accordingly, the charge states of such coordination compounds control binding selectivity. In the case of **21**, large positive entropic terms of

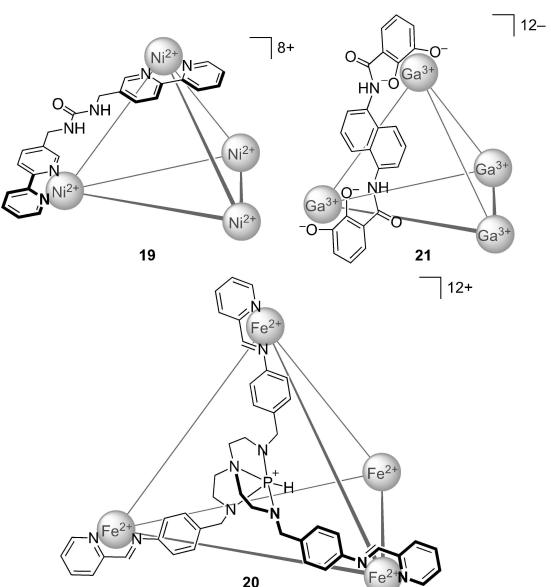


Figure 6. Structures of the coordination cages **19–21**.

complex formation suggest that binding benefits from the release of water molecules from the receptor cavity.<sup>[87]</sup>

These and further examples<sup>[88–93]</sup> illustrate that ionic interactions in water contribute to the stability of host-guest complexes. The high stabilities observed for certain complexes, the pronounced exothermicities associated with complex formation, and some binding selectivities indicate, however, that other types of interactions, including those mediated by the solvent, also influence binding, sometimes even to a larger extent than salt bridge formation.

### 2.3. Some Remarks About Salt Effects

There are additional aspects that influence the interaction of charged species in water. One of them is the effect of the often not innocent counterions that compete with the substrate for the receptor's binding site, thereby reducing the extent to which the receptor-substrate complex can be formed. In other words, the energetic gain of substrate binding is reduced by the energetic cost of counterion decomplexation, leading to an underestimation of complex stability in binding studies.

Such counterion effects should affect the affinity of all charged receptors, but they are best characterized for calixarenes such as **18a**.<sup>[94]</sup> This receptor binds alkali metal and alkaline earth metal ions in the form of 1:1 complexes. The complex with  $\text{Na}^+$ , the typical counterion of this sulfonatocalix[4]arene, has a  $K_a$  of  $85 \text{ M}^{-1}$  at pH 7.4, for example.<sup>[95]</sup> Complex stability increases with increasing ionic radius and charge of the cation. A slightly larger stability constant of  $183 \text{ M}^{-1}$  was obtained for the  $\text{Na}^+$  complex at pH 7.0 by using ITC, meaning that about 40% of the calixarene molecules contain a sodium ion at a concentration of 1 mM.<sup>[96]</sup> If additional buffer salts are present, the degree of complexation is significantly higher. Accordingly, counterions and

potential buffer cations directly influence the interaction of **18a** with any given substrate and if these effects are not considered when evaluating the results of binding studies, no reliable information about the true stability of the complex of interest can be obtained. Indeed, conflicting reports on the stability of some calixarene complexes likely originated from the different conditions under which the measurements were performed and/or the different binding models used to evaluate the results.<sup>[96]</sup> If counterion complexation is properly accounted for, however, the stability of a complex can be determined in a single titration.<sup>[97]</sup>

Counterion complexation of **18a** also influences the thermodynamic signature of substrate binding, which for many organic cations is strongly exothermic: the complexation of TMA is associated with a  $\Delta H^0$  of  $-28.9\text{ kJ mol}^{-1}$ , for example.<sup>[78]</sup> This exothermicity can partly be attributed to the release of  $\text{Na}^+$  ions from the calixarene cavities when replacing them with other guests, resulting in the enthalpically favorable but entropically unfavorable reintegration of the cations into the water matrix. The reverse reaction,  $\text{Na}^+$  complexation, is indeed endothermic and associated with a gain in entropy.<sup>[96]</sup> Cations from buffer salts may also be involved in these equilibria, in which case further effects on binding enthalpy and entropy can be expected.<sup>[98]</sup> Accordingly, it is often problematic to limit the discussion of the thermodynamics of complex formation in aqueous buffers to receptor-substrate interactions and solvation effects alone.<sup>[27]</sup>

Evidence for the pronounced effects of buffers on receptor-substrate interactions came from Gibb and co-workers who used the tetracationic cavitand **22** (Figure 7) as a model receptor.<sup>[99]</sup> Two aspects were studied in this context: the effects of the increasing ionic strength of the solution during the host-guest titration on the binding constants, and the effects of buffer salts. The results showed that binding models neglecting the increased screening of receptor charges when the salt concentration during the titration rises afford only approximate values for the actual binding strength, especially in the case of weakly bound ions. The competitive binding of buffers to the receptor produces, however, roughly twice the effect of screening. Accordingly, screening does not necessarily have to be considered for strong binders, but it cannot be neglected if the interaction is weak, in which case complex formation is also markedly affected by the competitive binding of other ions. The authors therefore stress that the influence of buffers in binding

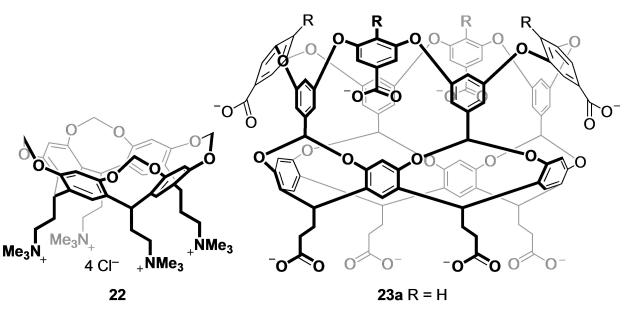


Figure 7. Structures of receptors **22** and **23a, b.**

studies has to be considered, even of buffers that are typically assumed inconspicuous in biochemical studies.

Screening and competitive binding are only two effects of ionic species that can affect binding equilibria. Another effect was already described at the end of the 19<sup>th</sup> century by Franz Hofmeister, who studied the influence of salts on the solubility of proteins. Hofmeister found that certain salts precipitate egg white protein from the aqueous solution (salting-out) while others increase protein solubility (salting-in).<sup>[100]</sup> This work led to separate sequences in which cations and anions are ranked according to their salting-in and salting-out capabilities (Figure 8). In the case of anions, which usually have stronger effects than cations, small ions with a high charge density reside at the salting-out end of the so-called Hofmeister series and large, charge-dispersed, and weakly hydrated ions at the opposite end. Subsequent work revealed correlations between the position of ions in the Hofmeister series and their effects on many bulk properties of water,<sup>[101]</sup> demonstrating that the salt properties discovered by Hofmeister are of general relevance. Unfortunately, there is still no simple and universal concept that explains all of the observed phenomena.<sup>[16,102,103]</sup>

Models explaining the Hofmeister series initially concentrated on the effects of ions on the water structure. That electronic effects cause the water molecules in the first solvation shell to direct their oxygen atoms toward a cation, while the reverse arrangement is preferred in the case of an anion is obvious. In addition, ions also influence the number and dynamics of hydrogen bonds between the surrounding water molecules, as shown by various experimental techniques and molecular dynamics simulations.<sup>[36–38,104]</sup> Whether these effects extend beyond the first solvation shell is, however, an open question.<sup>[37]</sup> A parameter associated with the effect of an ion on the surrounding water molecules is the ion's structural entropy,<sup>[37]</sup> with positive values of  $\Delta S_{\text{struc}}$  indicating that the order around the ion decreases due to a loss of hydrogen bonds. Conversely, negative  $\Delta S_{\text{struc}}$  values suggest that water structuring occurs in the solvation shell. Structural entropy thus indicates that ions can act as structure-makers ( $\Delta S_{\text{struc}} < 0$ ) or structure-breakers ( $\Delta S_{\text{struc}} > 0$ ),<sup>[37]</sup> at least in the first solvation shell. Alternatively, the terms "kosmotropes" or "chaotropes" are used for structure-makers and structure-breakers, respectively, although these terms were originally introduced to describe the salting-out and salting-in properties of ions,<sup>[105]</sup> and it is therefore not generally accepted to use them in other contexts.<sup>[16,25]</sup> A selection of  $\Delta S_{\text{struc}}$  values is collected in Table 3 together with  $\Delta G_{\text{HB}}$ , a parameter that specifies how many hydrogen bonds are lost (negative value) or gained (positive value) when the respective ion is dissolved in water.<sup>[37]</sup> Table 3 shows that, at least for anions, there is a correlation between the  $\Delta S_{\text{struc}}$  values and the position of the ion in the Hofmeister series.

Anions:	$\text{SO}_4^{2-}$	$\text{H}_2\text{PO}_3^-$	$\text{F}^-$	$\text{HCO}_3^-$	$\text{Cl}^-$	$\text{Br}^-$	$\text{NO}_3^-$	$\text{I}^-$	$\text{ClO}_4^-$	$\text{SCN}^-$
<b>Salting-out ions</b>					<b>Salting-in ions</b>					
Cations:	$\text{K}^+ \sim \text{Na}^+$	$\text{Cs}^+$	$\text{Li}^+$	$\text{NH}_4^+$	$\text{Li}^+$	$\text{Mg}^{2+}$	$\text{Ca}^{2+}$			

Figure 8. Hofmeister series for anions and cations.<sup>[37]</sup>

**Table 3.** Water structural entropy  $\Delta S_{\text{struc}}$  and net effects of hydrogen bonds in surrounding water molecules ( $\Delta G_{\text{HB}}$ ) for a selection of cations and anions differing in their ionic radii  $r$ .

Ion	$r/\text{pm}^{\text{[a]}}$	$\Delta S_{\text{struc}}/\text{JK}^{-1}\text{mol}^{-1}\text{[c]}$	$\Delta G_{\text{HB}}^{\text{[d]}}$
<b>cations</b>			
$\text{Li}^+$	59	-52	0.35
$\text{Na}^+$	102	-14	-0.04
$\text{K}^+$	138	47	-0.65
$\text{Rb}^+$	149	52	-0.70
$\text{Cs}^+$	170	68	-0.86
$\text{NH}_4^+$	148	5	-0.22
$\text{NMe}_4^+$	280	41	-0.59
$\text{NBu}_4^+$	413	-144 <sup>[d]</sup>	1.30
<b>anions</b>			
$\text{SO}_4^{2-}$	230	-94 <sup>[b]</sup>	0.78 <sup>[b]</sup>
$\text{HPO}_4^{2-}$	200	-57	0.41
$\text{F}^-$	133	-27	0.10
$\text{Cl}^-$	181	58	-0.76
$\text{Br}^-$	196	81	-1.00
$\text{I}^-$	220	117	-1.36
$\text{NO}_3^-$	179	66	-0.85
$\text{ClO}_4^-$	240	107	-1.26
$\text{B}_{12}\text{H}_{12}^{2-}$	400 <sup>[b]</sup>	208 <sup>[b]</sup>	-2.31 <sup>[b]</sup>
$\text{B}_{12}\text{Cl}_{12}^{2-}$	525 <sup>[b]</sup>	214 <sup>[b]</sup>	-2.37 <sup>[b]</sup>
$\text{B}_{12}\text{I}_{12}^{2-}$	590 <sup>[b]</sup>	240 <sup>[b]</sup>	-2.63 <sup>[b]</sup>

[a] From Ref. [34]; [b] from Ref. [106]; [c] from Ref. [109]; [d] values taken from Ref. [109] and multiplied by 1.25 as described in Ref. [37].

Nau and co-workers demonstrated that large anions such as dodecaborates are particularly strong structure-breakers, with  $\Delta S_{\text{struc}}$  values exceeding  $150 \text{ JK}^{-1}\text{mol}^{-1}$  (Table 3), and they used this property to rationalize the unusually strong binding of such, in their terminology, "superchaotropic" anions to  $\gamma$ -cyclodextrin (see Section 5.2).<sup>[106]</sup>

Although Table 3 suggests that larger, charged dispersed ions tend to have positive  $\Delta S_{\text{struc}}$  values it is important to note that hydrophobicity does not necessarily qualify an ion to be also a structure-breaker. The tetrabutylammonium is, for example, a structure-maker due to hydrophobic hydration,<sup>[107,108]</sup> that is, the structuring of the water molecules surrounding the hydrophobic side chains (see Section 3.1).

Thus, correlations can be found between the position of ions in the Hofmeister series and their effect on the water structure, at least in the first hydration shell. There is even evidence that the Hofmeister series of anions arises from electrostatic interactions and can be rationalized by using a relatively straightforward model based on the radial charge densities of anions.<sup>[103]</sup> This model allows the quantification of ion effects such as hydration enthalpies, diffusion coefficients, or Gibbs energies for the transfer of an anion from water to methanol. However, it is questionable whether the probably only local effects of ions on water structure are solely responsible for their influence on the solubility of large biomolecules such as proteins. There are, in fact, arguments against this view. An important one is that the same ion can cause both the salting-in and the salting-out of proteins under certain conditions.<sup>[110]</sup> Alternative concepts therefore exist that attribute Hofmeister's findings to direct interactions between

proteins and ions: ions that interact with proteins are believed to screen protein-protein interactions and thus improve protein solubility, while salting-out ions exclude water molecules from protein surfaces, leading to protein precipitation. Indeed, it was shown that weakly hydrated anions ( $\text{I}^-$ ,  $\text{ClO}_4^-$  or  $\text{SCN}^-$ ) and strongly hydrated cations ( $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ , or  $\text{Li}^+$ ) interact with protein backbones, while strongly hydrated anions ( $\text{F}^-$  or  $\text{SO}_4^{2-}$ ) and weakly hydrated cations ( $\text{Cs}^+$  or  $\text{NH}_4^+$ ) do not.<sup>[102]</sup> Further evidence for direct interactions between salting-in anions and hydrophobic solutes came from Gibb and co-workers who investigated the effect of salts on the interaction of adamantane carboxylate (AC) with the so-called octa acid **23a** (Figure 7).<sup>[111]</sup> This work revealed that salting-out anions strengthen the interactions between AC and **23a**, while salting-in anions cause a reduction of complex stability. Since complex formation is mainly driven by the release of water molecules from hydrophobic parts of the two binding partners that make contact in the complex, the effect of salting-out anions was attributed to the enhancement of the hydrophobic effect (see Section 3.1), caused by the anions' tendency to preferentially interact with water molecules rather than the receptor. Salting-in anions such as perchlorate, on the other hand, were shown to enter the hydrophobic binding pocket of **23a**. Although the underlying interaction is not very strong, the perchlorate complex has a  $\log K_a$  of 2.0, for example, the competition of AC and the anion for the binding site of the receptor provides a rationale for the observed reduction of AC affinity. The stabilizing effect of salting-out anions on the stability of the perchlorate complex is consistent with this finding.<sup>[112]</sup> Calorimetric investigations showed that the formation of the perchlorate complex is exothermic and associated with an adverse entropic term, which was attributed to the simultaneous inclusion of on average 3.1 highly organized water molecules along with the anion into the binding pocket. Accordingly, the replacement of the perchlorate anion by AC is associated with a slightly positive  $\Delta H^\circ$  but a pronounced gain in entropy.<sup>[113]</sup>

Based on these results, the authors argued that direct interactions between certain anions with the surface-exposed hydrophobic residues of proteins account for their influence on protein solubility. To test this assumption, the effects of anions on the solubility of ubiquitin was studied.<sup>[114]</sup> Several binding sites for charge-dispersed anions were detected in this small protein, with anion binding to these sites leading to an improvement of protein solubility under suitable conditions. Under conditions where the screening of positively charged solubilizing groups along the protein backbone was dominant, however, also protein precipitation occurred. Protein solubility thus depends on an interplay of different factors. Other authors also demonstrated the binding of weakly hydrated anions to hydrophobic regions of proteins,<sup>[115]</sup> while no direct anion-protein interactions were found in a related study,<sup>[116]</sup> which led the respective authors to conclude that the effects of the investigated anions were in this case mediated by solvent interactions, that is, by the way in which the protein interacts with water molecules. Hofmeister's results therefore still raise many questions, even after more than 125 years of research.

### 3. Ion-Dipole and Dipole-Dipole Interactions

#### 3.1. Some Remarks About the Hydrophobic Effect

Interactions between binding partners with extended hydrophobic surfaces are driven in water to a large degree by the hydrophobic effect.<sup>[13–15]</sup> This effect is due to the thermodynamic advantage of incorporating several hydrophobic solutes into a single cavity within the network of water molecule rather than including them separately into individual cavities. Direct interactions may become operative once the solutes are close, which then contribute to the overall binding process.

The hydrophobic effect is a specific feature of water, in which cavity formation is energetically more costly than in other solvents. The actual thermodynamic signature of this process depends on the size and shape of the solute, with the association of small hydrophobes usually being entropically favored and enthalpically nearly neutral.<sup>[12]</sup> The reason is that the creation of a small cavity does not require water molecules to give up hydrogen bonds. However, the hydrogen bond network has to reorganize around the solute, which is penalized by entropy as demonstrated by the negative structural entropy of small organic molecules.<sup>[117]</sup> Merging individual cavities allows the reincorporation of water molecules into the bulk since fewer water molecules are required to create a single, albeit slightly larger cavity than many individual ones. While this process should not produce a substantial change in enthalpy, it is entropically favored, which is why a positive entropy term is often considered an indication for a binding process driven by the hydrophobic effect.

Receptor-substrate interactions that are solely due to entropy are, however, not very common in water. The formation of cyclodextrin complexes is endothermic in a few cases, for example, but mostly displays a negative binding enthalpy.<sup>[17]</sup> High negative binding enthalpies are also characteristic for most of the receptors discussed in this review and cases also exist where binding is additionally entropically disfavored. These thermodynamic signatures are inconsistent with the “classical” view of the hydrophobic effect, prompting Diederich to coin the term “nonclassical” hydrophobic effect for binding processes that are driven by enthalpy in water.<sup>[118]</sup> While the distinction between “classical” and “nonclassical” hydrophobic effect might suggest that two fundamentally different binding mechanisms are at work, the reason for the different thermodynamic signatures is more likely that synthetic receptors are not the small and convex molecules to which the “classical” view of hydrophobic effect applies. Rather, receptors are large, have extended aromatic surfaces, contain polar and charged groups, and, most importantly, have cavities into which the substrate and also water molecules can be included, even if only fleetingly. The structural changes in the solvation shells of typical receptors combined with the potential release of the water molecules occupying their cavities prior to substrate binding can therefore produce enthalpic and entropic effects that differ profoundly from what is usually expected for the “classical” hydrophobic effect.

Unfortunately, hydration enthalpies and entropies of receptors are often unknown and the structural changes in the hydration shell of a receptor during substrate binding unclear. Only few studies specifically addressed the effects of receptor hydration on binding properties,<sup>[119–121]</sup> but independent evidence exists that the arrangement of water molecules surrounding larger hydrophobic planar or concave surfaces in water differs characteristically from that around small convex molecules.<sup>[12,16]</sup> Water molecules surrounding such hydrophobes cannot retain all the hydrogen bonds, which is enthalpically unfavorable but an entropic advantage because the loss of hydrogen bonds adds degrees of freedom. Depending on the size and shape of the solute, a transition thus exists between hydrations that are enthalpically more or less neutral and entropically unfavorable to those that are enthalpically unfavorable but entropically advantageous. In the latter case, the release of water molecules from the solvation shell during complex formation should add negative enthalpic and entropic terms to the overall thermodynamics of binding, which is indeed observed for many receptor-substrate interactions.

That the exothermicity of binding processes could indeed be due to the release of water molecules that cannot retain all their hydrogen bonds when occupying (or visiting) the hydrophobic cavities of synthetic receptors was already suggested by Bender as early as 1967.<sup>[122]</sup> Work by Nau and Biedermann lends support to this assumption.<sup>[15]</sup> This group derived the average number of water molecules included into the cavity of typical receptors by molecular dynamic calculations and then determined the average number of hydrogen bonds of each included molecule. Experimental evidence indeed exists for the hydration of receptor cavities. Sulfonatocalix[4]arene **18a**, for example, hosts one water molecule that is stabilized by OH- $\pi$  and dispersion interactions,<sup>[123,124]</sup> which is consistent with the results of Biedermann and Nau (Table 4), while sulfonatocalix[5]arene contains three water molecules in the solid state.<sup>[125]</sup> X-ray crystallography moreover demonstrated that also cucurbituril cavities are extensively hydrated.<sup>[126]</sup> Biedermann and Nau then related the number of hydrogen bonds per cavity water molecule to the average number of hydrogen bonds in the bulk, thus obtaining an estimate of the hydrogen bond deficit of the cavity water molecules. Table 4 shows that this hydrogen bond deficit differs from receptor to receptor and that it is

**Table 4.** Hydrogen bond deficit of the cavity water in different receptors.<sup>[15]</sup>

Receptor	N <sup>[a]</sup>	m <sup>[b]</sup>	Z <sup>[c]</sup>
$\alpha$ -Cyclodextrin	3.6	2.86	3.1
$\beta$ -Cyclodextrin	4.4	2.96	3.1
Calix[4]arene	0.8	2.15	1.2
Pillar[5]arene	0.5	1.24	1.2
Cucurbit[6]uril	3.3	1.71	6.3
Cucurbit[7]uril	7.9	2.52	8.7
Cucurbit[8]uril	13.1	3.06	7.3

[a] Average number of cavity bound water molecules; [b] Average number of hydrogen bonds per bound water molecule; [c] Hydrogen bond deficit calculated by using the equation  $Z = N(3.62 - m)$ , with 3.62 referring to the average number of hydrogen bonds per water molecule in bulk water.

especially large for cucurbit[7]uril (CB7), a compound whose complexation equilibria indeed feature particularly pronounced negative enthalpies and entropies of binding (see Section 3.2). The term “high-energy water” has been introduced for water molecules with a hydrogen bond deficit, but the use of this term without a proper context can be misleading and is therefore avoided here.<sup>[16,33,127]</sup>

Work of Ashbaugh and Gibb suggests that structural effects may also cause receptor cavities to be preferentially dewetted (void of water molecules) in the absence of a guest.<sup>[121]</sup> Evidence for this notion came from the comparison of the properties of the two structurally closely related receptors **23a** and **23b** (Figure 7).<sup>[120]</sup> Molecular dynamics simulations revealed that the four methyl groups encircling the cavity of **23b** have a pronounced impact on cavity hydration: whereas the probability of observing a completely empty cavity is only 5% for receptor **23a**, the same probability amounts to 73% in the case of **23b**. Accordingly, water is a much poorer guest for **23b** than for **23a** and therefore competes less strongly in complex formation. As a consequence, the interactions of **23b** with different carboxylic acids are more exothermic than those of **23a** and since the enthalpic advantage exceeds the extent to which entropy becomes less favorable, **23b** is the better receptor. Substrate binding in water can therefore strongly benefit from the ability of receptors to template cavity formation in the water matrix. For further examples, see Sections 4.2 and 7.

It must be noted that the enthalpic and entropic net contributions to complex formation never have only a single cause. In addition to the potential release of cavity water, restructuring of the solvation shell in other parts of the receptor, some of which may be polar and therefore well solvated, and dehydration of parts of the (often convex) substrate also play a role. Substrate binding can moreover involve the displacement of receptor substituents from the cavity, or the decomplexation of counterions as discussed for receptor **18a**, making it difficult to precisely attribute the thermodynamics of binding to a single cause. How unpredictable the interplay of these processes can be is reflected in the dependence of the affinity of cyclophane **24** for  $\alpha,\omega$ -alkyldiammonium ions on the length of the alkyl chain (Figure 9).<sup>[128]</sup> The combination of the hydrophobic effect and ionic interactions causes complex formation to be exothermic in this case, independent of the chain length of the guest. However, the progressive increase of the absolute binding enthalpy with increasing chain length cannot be explained by the release of

cavity water alone. While geometric considerations suggest that the diammonium ion with the C4 chain should be bound most strongly, since it allows the oppositely charged groups in the receptor and the substrate to come closest, the complexes of the guests with the C7 and C8 chains turned out to be significantly more stable ( $\log K_a$  in both cases 7.6). This unexpected trend was attributed to the more efficient hydration of the charged groups of host and guest if the ammonium groups protrude from the cavity openings. The shorter guests need to be desolvated for complex formation, which is enthalpically more costly.

Hydrophobic effects can therefore be complex. The enthalpically favorable desolvation of the binding partners and/or the solvation of the complex nevertheless represent important and often decisive elements of complex formation in water.

### 3.2. Receptors for Charged Substrates

Prototypic complexes in which ion-dipole interactions are responsible for substrate binding are those between alkali metal ions and crown ethers. Water molecules are strong competitors in these interactions because they interact with both binding partners, and since the polarity of the binding partners renders substantial contributions of the hydrophobic effect to binding unlikely, crown ether complexes are not very stable in water. With a  $\log K_a$  of 2.1, the potassium affinity of 18-crown-6 is, for example, more than two orders of magnitude lower in water than in methanol.<sup>[129]</sup> That these complexes form at all is due in part to the chelate effect, which causes the interaction of a cation with the oxygen atoms of a crown ether to be entropically more favorable than with the same number of oxygen atoms from individual water molecules. Unsurprisingly, the cation affinity of cryptands in water is substantially higher than that of crown ethers. Complex formation is also often strongly exothermic, in spite of the energetic cost of dehydrating the cation.<sup>[129]</sup>

Other receptors with converging arrangements of oxygen atoms, albeit much better preorganized ones than those of crown ethers, are cucurbiturils<sup>[23,24]</sup> and the metallacrowns developed in the Severin group.<sup>[85]</sup> The latter type of receptors can be assembled from  $[(\text{cymene})\text{RuCl}_2]_2$  and suitable 3-hydroxy-2-pyridone derivatives. The thus formed complexes are rigid and their converging arrangement of oxygen atoms allows ion-dipole interactions with metal ions. Solubilizing groups such as the piperidine residues in **25** (Figure 10) mediate water

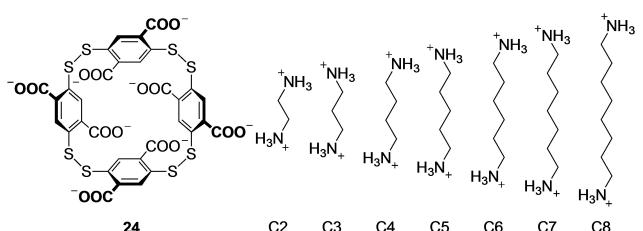


Figure 9. Structures of receptors **24** and of the  $\alpha,\omega$ -alkyldiammonium ions used as guests.

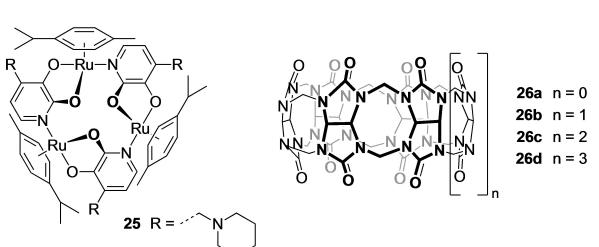


Figure 10. Structures of metallacrown **25** and the cucurbit[n]urils **26a-d**.

solubility. The size of the cavity is well suited to host a lithium ion, explaining the remarkable lithium selectivity of these hosts. Receptor **25**, for example, has a  $\text{Li}^+/\text{Na}^+$  selectivity of 10,000/1 and binds  $\text{Li}^+$  in 100 mM phosphate buffer (pH 7.0) with a  $\log K_a$  of 3.4, which is three orders of magnitude higher than the  $\text{Li}^+$  affinity of 12-crown-4.

The oxygen atoms along the rims of cucurbiturils create openings that are larger than the diameter of a crown ether with the same number of oxygen atoms, thus causing the cation selectivity of cucurbiturils to be not very pronounced. While earlier binding studies were performed in solvent mixtures such as water/formic acid mixtures, in which partial protonation of the cucurbituril carbonyl groups reduces cation affinity,<sup>[130]</sup> recent work also provided insight into metal ion binding at neutral pH. These measurements included various singly, doubly, and triply charged metal ions as well as cucurbiturils ranging from the smallest five-membered ring to cucurbit[8]uril (CB8) **26a–d** (Figure 10).<sup>[131]</sup> The results showed that the cation affinities of cucurbiturils are typically intermediate between those of crown ethers and cryptands. Only the smallest cucurbit[5]uril (CB5) exhibits a peak selectivity, binding potassium best and larger and smaller cations with a lower affinity. The cation affinity of the larger cucurbiturils generally increases with increasing ionic radius and charge of the cation and can reach the micromolar range. Hence, the preorganization of cucurbiturils is beneficial for cation affinity. However, this cation affinity also causes binding studies performed in buffer to be strongly affected by the competing effects of the cationic buffer components.

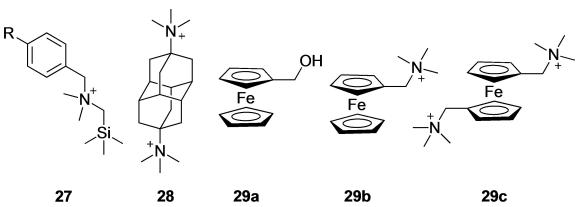
Remarkably strong complexes are formed between cucurbiturils and ammonium ions in water.<sup>[132]</sup> Especially  $\alpha,\omega$ -diammonium ions, in which the two cationic groups are properly spaced to allow simultaneous interactions with the carbonyl groups at the two cucurbituril portals, form complexes with stabilities ranking at the upper end of the stability scale of synthetic host-guest systems.<sup>[133]</sup> Although the interaction of ammonium and carbonyl groups is rather based on hydrogen bonding than ion-dipole interactions, these complexes are discussed here, in the context of cucurbituril-based receptors. Depending on the guest, hydrogen bond formation either involves the NH groups in protonated amines or the  $\alpha\text{-CH}$  groups in quaternary ammonium ions that also feature substantial positive potentials. These interactions cause a pronounced stabilization as demonstrated by the typically higher stability of CB7 complexes with cationic guests than with neutral analogs, but the exact extent of the stabilization is not easy to assess since it results from a balance of the Gibbs free energy required to desolvate the cationic head group of the guest and the intrinsic strength of the respective ammonium-carbonyl interactions. Information in this context was obtained by comparing the stabilities of the complexes of a series of cationic silyl ethers of the general structure **27**, which structurally differ only in the aromatic substituent that remains outside the CB7 cavity and whose solvation in water therefore does not affect binding.<sup>[134]</sup> The work showed that complex stability slightly increases as the electron-withdrawing effect of the substituent becomes stronger. However, this increase was

less pronounced than expected based on the effect of the substituent on the intrinsic strength of the ammonium-carbonyl interactions. The observed trend was rationalized by the stronger hydration of the ammonium group as the substituent becomes more electron-withdrawing. Accordingly, the stabilities of cucurbituril complexes reflect the balance between the efficiency with which a guest interacts with the receptor and with water molecules, which can lead to unexpected trends. The CB7 complexes of 1-adamantylamine hydrochloride and the corresponding quaternary ammonium ion have a comparable stability,<sup>[135]</sup> for example, although the primary amine is the better hydrogen bond donor, and the complex of the diamantane derivative **28** is even more stable than that of the corresponding nonmethylated analog.<sup>[133]</sup>

In general, complex stability is higher for guests that efficiently fill the cucurbituril cavity,<sup>[24]</sup> with some complexes having a remarkable stability, especially in the case of CB7. The  $\log K_a$  values of the CB7 complexes with the three ferrocene derivatives **29a–c** (Figure 11) amount to 9.5, 12.6, and 15.4, for example.<sup>[136]</sup>

These extraordinarily high binding constants are not only observed for ferrocene complexes (and therefore not due to the special nature of the ferrocene moiety), but also for certain adamantane complexes.<sup>[137]</sup> An almost attomolar stability was reported for the complex between CB7 and diamantane **28**, which is thus orders of magnitude more stable than one of the most efficient natural protein-substrate combinations, the biotin-avidin complex.<sup>[138]</sup> It should be noted that stability constants of this magnitude have to be determined by using competitive titrations, and to facilitate these measurements and make the comparison of results from different laboratories more reliable, suitable reference compounds were identified that permit the quantification of the stability of CB7 complexes in the  $\log K_a$  range from 3 to 15.<sup>[138]</sup>

The thermodynamic parameters of the reaction between **29a–c** and CB7 provide insight into the driving force of complex formation. Table 5 shows that although binding is strongly exothermic in all three cases, the actual enthalpic term



**Figure 11.** Structures of the cationic silyl ether **27**, the diamantane derivative **28**, and the ferrocenes **29a–c**.

**Table 5.** Thermodynamic parameters of the reactions between **26c** (CB7) and the ferrocene derivatives **29a–c** at 298 K.<sup>[136]</sup>

Ferrocene	$\log K_a$	$\Delta G^{0[a]}$	$\Delta H^{0[a]}$	$T\Delta S^{0[a]}$
<b>29a</b>	9.5	−54	−90	−36
<b>29b</b>	12.6	−72	−89	−17
<b>29c</b>	15.4	−88	−90	−2

[a] Energies in  $\text{kJ mol}^{-1}$ .

is surprisingly insensitive to the structure of the guest. The increase of complex stability when moving from the neutral to the monocationic and further to the dicationic ferrocene is therefore entirely due to the decreasing entropic disadvantage of complex formation, which is probably due to the fact that the release of ordered water molecules surrounding the charged residues of **29b** and **29c** is entropically more favorable than the dehydration of the neutral **29a**. Thus, the stability of the complex does not appear to benefit from the enhancement of electrostatic interactions with the increasing number of positive charges in the guest, although the crystal structure of the CB7 complex of **28** suggests that such interactions exist.<sup>[137]</sup> Their contribution to the binding enthalpy appears to be exactly offset, however, by the greater enthalpic cost of desolvating the charged residues.

While the pronounced negative binding enthalpies certainly reflect the tight fit of the guest molecules in the CB7 cavity,<sup>[136]</sup> they are also consistent with the enthalpically favorable release of cavity water, which is especially pronounced in the case of CB7 as discussed in Section 3.1.<sup>[15]</sup> The adverse entropic terms supports this interpretation since reintegration of the cavity water molecules into the water matrix reduces their degrees of freedom. Accordingly, the exceptionally high stabilities of certain cucurbituril complexes likely originate from a combination of different factors, the most important of which are the perfect structural and electronic complementarity of the binding partners, their rigidity, which reduces the entropic disadvantage of complex formation, and solvent effects.

### 3.3. Receptors for Neutral Substrates

Classic receptors for neutral substrates in water are cyclodextrins. Guest binding involves different types of interactions, including hydrogen bond formation and dispersion interactions. In addition, dipole-dipole interactions between the dipole moment of the cyclodextrin ring and the dipole moment of the included guest contribute to complex stability. The complex of  $\beta$ -cyclodextrin with 4-nitrobenzoic acid ( $\log K_a = 2.5$ ) is, for example, less stable than that of benzoic acid ( $\log K_a = 3.1$ ) because the nitro group reduces the dipole moment of benzoic acid. Conversely, the complex of 4-nitrophenol ( $\log K_a = 2.5$ ) with its larger dipole moment is more stable than that of phenol ( $\log K_a = 1.9$ ).<sup>[17]</sup> These effects are long known and not caused by solvent effects, and will therefore not be further discussed here.

## 4. Cation- $\pi$ , Anion- $\pi$ and CH- $\pi$ Interactions

### 4.1. Some Remarks About Interactions Involving $\pi$ -Systems in Water

Aromatic systems feature characteristic electrostatic potentials along their surface, which allow them to engage in interactions with oppositely charged or polarized substrates.<sup>[139]</sup> These interactions are mainly electrostatic in nature and can be

remarkably strong. In the gas phase, the interaction between a potassium ion and the face of a benzene ring is, for example, almost as strong as the interaction between  $K^+$  and a water molecule.<sup>[140]</sup> Like salt bridges, such cation- $\pi$  interactions<sup>[140,141]</sup> become weaker as the polarity of the medium increases, but there is an important difference between ion pairing and cation- $\pi$  interactions: in the case of salt bridges, two strongly hydrated ions have to come together to form an ion pair and the interaction is therefore penalized by the partial desolvation of both binding partners. In the case of a cation- $\pi$  interaction, only the cation is strongly hydrated while the aromatic ring is not. Accordingly, solvation effects should affect cation- $\pi$  interactions to a smaller degree than ion pairing, which was confirmed computationally.<sup>[142]</sup> The corresponding study demonstrated that the interaction energy between an ammonium ion and acetate drops by a factor of more than 50 when going from the gas phase to water. By contrast, the strength of the cation- $\pi$  interaction between ammonium and benzene, although intrinsically weaker in the gas phase than ion pairing, diminishes only by a factor of 3, causing the respective complex to be more stable in water than the ammonium acetate ion pair.

For a series of different cations, the intrinsic strength of cation- $\pi$  interactions correlates with the charge density of the ion, becoming weaker in the gas phase for the alkali metal ions in the order  $Li^+ > Na^+ > K^+ > Rb^+$ , for example. In solution, ion hydration causes deviations from this trend because the more strongly bound ions are also the ones more strongly hydrated. For the above series of ions, this effect causes benzene to bind most strongly to  $K^+$  in water.<sup>[143]</sup> Complex formation of  $Li^+$  and  $Na^+$  is less favorable because of the strong hydration of the smaller cations while the lower charge density of  $Rb^+$  renders the interaction with an aromatic ring intrinsically weaker than that of  $K^+$ . Experimentally, cation- $\pi$  interactions have been shown to be worth circa  $2 \text{ kJ mol}^{-1}$  per phenyl ring, which is roughly half the interaction energy of a salt bridge (see above).<sup>[143]</sup> Cation- $\pi$  interactions between ions and receptors whose binding sites are surrounded by several, ideally electron-rich aromatic rings can nevertheless make substantial contributions to complex stability.

By contrast, anion- $\pi$  interactions, the electrostatic interaction between an anion and the face of an electron-deficient  $\pi$ -system,<sup>[144,145]</sup> are generally weaker than cation- $\pi$  interactions. The number of receptors in which anion- $\pi$  interactions contribute to substrate binding in water is therefore low. Together with dispersion interactions and the hydrophobic effect, CH- $\pi$  interactions mediate the binding of neutral substrates to receptors with aromatic residues as discussed in Section 4.3.

### 4.2. Receptors for Charged Substrates

The concept of cation- $\pi$  interactions emerged in conjunction with the work of the Dougherty group on the receptor properties of a series of cyclophanes with ethenoanthracene units.<sup>[140]</sup> In this context, it became clear that cation- $\pi$

interactions between positively charged substrates and the aromatic side chains of amino acids also mediate the cation binding of certain proteins.<sup>[139,141,146]</sup> Examples include acetylcholine receptors, in which an “aromatic box” in the active site serves to recognize the cationic head group of the substrate. Today, cation- $\pi$  interactions are considered one of the most important types of noncovalent interactions and they are typically invoked to explain the cation affinity of synthetic receptors with electron-rich aromatic moieties such as cyclophanes, cryptophanes, calixarenes, cavitands, pillararenes, the coordination cage developed by Raymond, and the molecular tweezers and clips developed by Klärner. The binding properties of these systems have been reviewed,<sup>[76,86,139–141,147,148]</sup> and only a few aspects relating to cation recognition in water will therefore be discussed here.

Evidence that cation- $\pi$  interactions contributed to the substrate affinity of the family of cyclophanes developed by Dougherty came from the comparison of the affinities of **30a** and **30b** (Figure 12) for the *N*-methylquinolinium cation **31**.<sup>[149]</sup> With a  $\log K_a$  of 5.6, the complex of **30a** with **31** is about one order of magnitude more stable than that of **30b** in borate buffer at pH 9.0, which was attributed to the larger number of possible cation- $\pi$  interactions in **30a**. If dispersion interactions would dominate binding, **30b** should be the better receptor since cyclohexane is more polarizable than benzene. The cationic **31** is also more strongly bound by **30a** by a factor of approximately 10 than the isosteric but neutral 4-methylquinoline **32**, which confirmed the stabilizing electrostatic interactions between the cationic guest and the negative electrostatic potentials along the faces of the aromatic cyclophane residues. Structural investigations showed that the ammonium group rather than the *tert*-butyl group of **33** is preferentially inserted into the cavity of **30a**,<sup>[150]</sup> and, as observed for many other receptors in water, complex formation

is exothermic and accompanied by a favorable entropic term.<sup>[151]</sup> Building on these findings, structural variations subsequently afforded analogs of **30a** with interesting selectivities, for example for the guanidinium moiety in arginine.<sup>[152]</sup>

The beneficial effects of the ethenoanthracene residues in **30a** on cation affinity inspired other groups to use a dithiol analog of this building block for the identification of cation binders by using dynamic combinatorial chemistry.<sup>[153]</sup> In this context, Sanders and Otto showed, for example, that the addition of **34** to a mixture of dithiols in water resulted in the amplification of cyclophane **35**, which was shown to have practically the same affinity for **35** under comparable conditions as Dougherty’s original cyclophane **30a**.<sup>[154]</sup> By varying the structure of the templating ammonium salt, other cyclic oligomers of the ethenoanthracene-derived dithiol were obtained. A cationic morphine derivative, for example, afforded a macrocyclic homotrimer<sup>[154]</sup> and the small tetramethylammonium ion a homotetramer.<sup>[155]</sup> The latter result was rationalized by the tight folding of the large macrocycle around the small cation. In a similar vein, the Waters group used ethenoanthracene dithiols to develop binders that recognize posttranslational modifications in proteins. They showed in this context that **35** binds to the trimethyllysine (Kme3) residue in the peptide Ac-WGGGQTARKme3STG-NH<sub>2</sub> with a  $\log K_a$  of 5.6 (10 mM borate buffer, pH 8.5).<sup>[156]</sup> Structural variations subsequently allowed improving this affinity and changing selectivity for methylated arginine derivatives. This work, which demonstrates the potential use of such cyclophanes in biomedical applications, has recently been reviewed.<sup>[27]</sup>

In contrast to the receptors discussed in Section 2.2, the solubilizing anionic groups in receptors **30a,b** and **35** diverge from the binding site and ionic interactions between these groups and the included substrate should therefore not be very pronounced. To quantify whether these interactions nevertheless occur, the binding properties of **30a** and the neutral water-soluble analog **30c** were compared. It turned out that the cation affinity of **30c** is about one order of magnitude lower than that of **30a**, demonstrating that ionic interactions in the complexes of **30a** make a nonnegligible contribution to binding.

Similar long range electrostatic interactions could also exist in the complexes of the conformationally fixed calix[4]arene derivative **36** (Figure 13) with quaternary ammonium ions and could partly account for the preferential inclusion of the cationic head group of the guest into the calixarene cavity, but the extent of this stabilization beyond the also existing cation- $\pi$  interactions has not been assessed.<sup>[157]</sup> More informative are investigations in which the deepened cavitands **37a–d** were used. The parent receptor **37a** forms stable complexes with cationic guests such as acetylcholine in water.<sup>[158]</sup> According to the observed complexation-induced signal shifts in the <sup>1</sup>H NMR spectra, the ammonium group of acetylcholine resides at the bottom of the cavity in the complex, suggesting that cation- $\pi$  interactions between the cationic residue and the electron-rich moieties of the receptor control the mode of binding. Independent studies showed, however, that the ammonium group of **33** either resides at the bottom or the opening of the

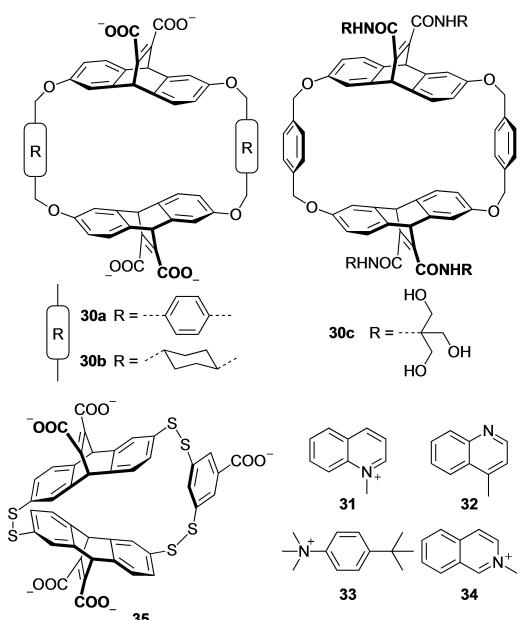


Figure 12. Structures of cyclophanes **30a–c** and **35**, and the guests **31–34**.

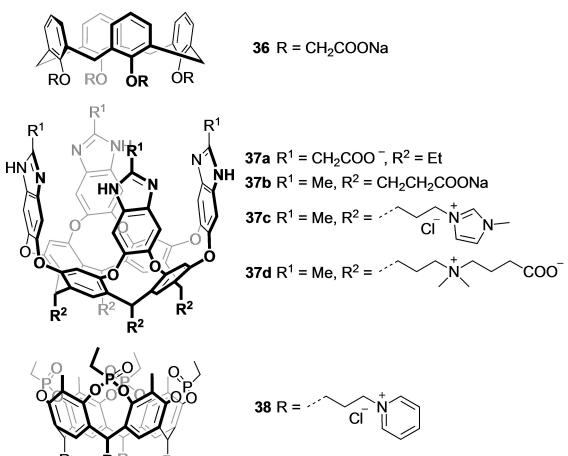


Figure 13. Structures of receptors 36, 37a-d, and 38.

cavity of 37a, depending on the conditions, and that cation-π interactions can thus be overcompensated by other effects.<sup>[159]</sup> Insight into the extent to which the different types of interactions operate in these complexes was obtained by comparing the behavior of receptors 37b-d and structurally related cavitands toward 33 and a series of other guests containing both a quaternary ammonium group and a *tert*-butyl residue.<sup>[160]</sup>

The authors showed that all investigated cavitands prefer to bind guests in which the hydrophobic *tert*-butyl group and the cationic ammonium group are positioned at a relatively large distance by incorporating the *tert*-butyl group into the cavity. The desolvation of the *tert*-butyl group and its dispersion interactions with the cavity walls are obviously more favorable than the desolvation of the ammonium group that would allow binding to benefit from cation-π interactions. Shorter guests behave similarly, but not with cavitands 37b-d. In these receptors, the imidazole methyl groups produce a hydrophobic environment along the cavity rim that is also suitable for positioning the *tert*-butyl residue at the cavity opening. The guest 33 thus inserts into the receptor cavity either with the ammonium group or the *tert*-butyl group first and since guest exchange is slow on the NMR time-scale, both arrangements can be distinguished. In the complex between 33 and 37d containing the zwitterionic solubilizing groups, the two isomeric complexes are almost equally populated, while the arrangement with the ammonium group located outside the cavity is favored by circa 4 kJ mol<sup>-1</sup> in the case of 37c. This situation is reversed for the negatively charged receptor 37b. The authors therefore concluded that long range ionic interactions can control the mode of binding, and that these interactions can tip the balance between a complex that benefits from cation-π interactions and one that does not.

In spite of the cationic nature of the solubilizing substituents, the cation affinity of the tetraphosphonate cavitand 38 (Figure 13), which was described by Dalcanale and co-workers, benefits from cation-π interactions in water.<sup>[161]</sup> Such cavitands interact with zwitterionic amino acids and *N*-methyl amino acids in methanol by hydrogen bonding between the NH group

of the guests and the converging P=O oxygen atoms along the cavity. In the case of *N*-methyl amino acids, the complexes are additionally stabilized by cation-π interactions between the aromatic receptor residues and the *N*-methyl group incorporated into the cavity. In water, only *N*-methyl amino acids are bound (with an affinity that is about 3 orders of magnitude lower than in methanol), likely because hydrogen bonding alone is not sufficient to mediate complex formation in the more competitive solvent. The complexation of *N*-methyl amino acids is strongly exothermic in water and opposed by entropy, which was attributed to the size of the receptor cavity that is too small to host water molecules. Cavitand 38 therefore templates water cavitation in a similar manner as receptor 23b. Thus, complex formation does not benefit from receptor dehydration in this case, and the thermodynamics of complex formation reflect the enthalpically favorable direct interactions of the binding partners in conjunction with their entropically unfavorable loss of degrees of freedom.

Receptors engaging in anion-π interactions have mainly been studied in organic solvents.<sup>[144,145]</sup> Since X-ray crystallography suggested that anion-π interactions cause the bromide counterions of the water-soluble tricationic compound 39 (Figure 14) to reside above the planes of the triazolium moieties in the solid state, anion binding of this and related tripodal receptors was also studied in water.<sup>[162]</sup> Binding is weak: the best receptor binds iodide with a log K<sub>a</sub> of 2.7, for example, and the contributions of ionic and anion-π interactions to complex formation could not be separated.

#### 4.3. Receptors for Neutral Substrates

CH-π interactions between the edges and the faces of aromatic rings stabilize the complexes between many cyclophanes and aromatic guests.<sup>[139]</sup> Classic examples of such cyclophanes, all of which bind neutral aromatic substrates in water, are Koga's protonated tetraamine 40, Diederich's family of dicationic diphenylmethane derivatives, of which 41 is a member, and Stoddart's blue box 42 (Figure 15). In the case of the latter two receptors, solvent-dependent binding studies demonstrated that complex stability increases when going from organic solvents to water, as expected for receptors whose binding benefits from the hydrophobic effect.<sup>[118,163]</sup> It is also worth noting that the negative binding enthalpies associated with complex formation of 41 in water led to the concept of the

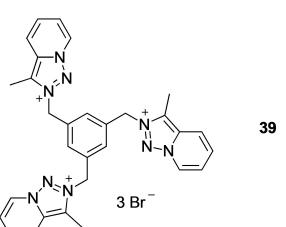


Figure 14. Structure of receptor 39.

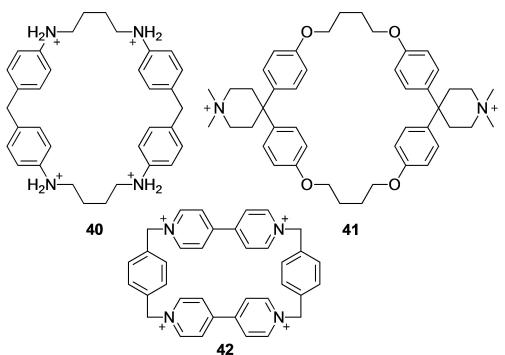


Figure 15. Structures of receptors 40–42.

“nonclassical” hydrophobic effect.<sup>[118]</sup> Since these investigations have been reviewed,<sup>[139]</sup> they are not described in detail here.

CH- $\pi$  interactions between the faces of aliphatic cycloalkanes and  $\pi$ -systems also exist,<sup>[164]</sup> contributing to the substrate recognition of the carbohydrate receptors that were developed in the groups of Davis and others. These systems are discussed in Section 5.3 and the interaction of alkanes with water-soluble cavitands in Section 7.

## 5. Hydrogen Bonding

### 5.1. Some Remarks About Hydrogen Bonding in Water

Hydrogen bonds are formed between positively polarized hydrogen atoms in one molecule and regions of negative electrostatic surface potential, usually caused by the presence of a heteroatom, in the corresponding binding partner. The polarization of the hydrogen atom in the hydrogen bond donor is often due to a directly bound heteroatom, but structural effects can also allow CH bonds to serve as donors. Since only the strongest hydrogen bonds are able to outcompete the hydration of neutral binding partners,<sup>[165]</sup> examples are hydrogen bonds between the OH groups of hexafluoroisopropanol or nonafluoro-*tert*-butanol and the oxygen atoms in sulfoxides or phosphine oxides, other hydrogen donors and acceptors can only contribute to substrate binding in water if additional factors reinforce the complex. Charge-assisted hydrogen bonds are, for example, stronger than hydrogen bonds between neutral compounds, and introducing charges into one or both binding partners can therefore be beneficial. Charged groups are, however, also more difficult to dehydrate than neutral ones so that potential effects of charge-assisted hydrogen bonds can turn out to be smaller than expected. Multivalency also plays a role, that is, the formation of multiple hydrogen bonds between host and guest. Finally, hydrogen bonds are stronger in an environment that has a lower permittivity than water, and hydrogen bonds in proteins are therefore mostly buried within the folded protein chain. For the same reason, hydrogen bond formation between synthetic receptors and their substrates generally takes place in cavities well shielded from the surrounding solvent.<sup>[28]</sup> These cavities not only feature hydrogen

bond donors and/or acceptors along their inner surfaces but often also hydrophobic residues that can mediate further types of interactions and, more importantly, prevent the efficient hydration of the converging polar groups. Dehydration is thus facilitated, which causes binding to benefit from the release of cavity water. Accordingly, the principles of molecular recognition by hydrogen bonding in water are not very different from those discussed in previous sections.

### 5.2. Receptors for Charged Substrates

Anion receptors that rely on hydrogen bonds for substrate binding typically contain multiple hydrogen bond donors arranged around a cleft or cavity, often in the form of NH groups. Examples include GCP derivatives and polyammonium receptors that form charge-assisted hydrogen bonds to their respective substrates (Section 2.2). Neutral NH donors form weaker hydrogen bonds but can under certain circumstances also mediate anion binding in water as demonstrated by the cyclopeptides developed in the Kubik group. These cyclic hexapeptides contain three well-preorganized NH groups at the bottom of a concave cavity lined by hydrophobic proline rings.<sup>[166]</sup> In the crystal structure of the parent cyclopeptide 43a (Figure 16), three water molecules reside within this cavity, the arrangement of which suggests that hydrating water molecules are unlikely to form the maximum number of hydrogen bonds in solution.<sup>[167]</sup>

The respective water-soluble derivative 43b binds halides and sulfate in the form of 1:1 complexes in water, but with a low affinity: the  $\log K_a$  of the most stable sulfate complex only amounts to 1.7, for example.<sup>[168]</sup> This stability may not seem remarkable, but it still indicates that direct interactions between the anion and the three NH groups of 43b, in conjunction with solvent effects arising from the arrangement of the NH donors

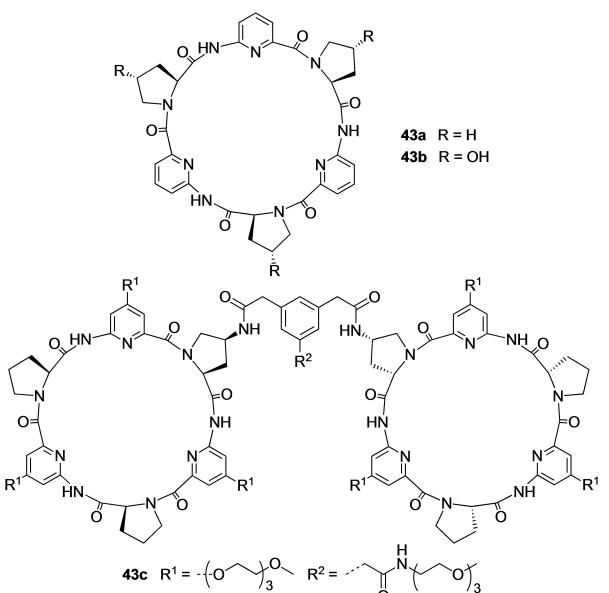


Figure 16. Structures of cyclopeptide 43a–c.

at the bottom of a hydrophobic binding site, can result in a sufficiently large thermodynamic driving force to at least partially overcome the efficient hydration of sulfate anions in water.

In contrast to **43b**, **43a** binds halides and sulfate in the form of 2:1 complexes, in which an anion is sandwiched between two cyclopeptide rings.<sup>[167]</sup> This binding mode is more efficient than that of **43b**, partly because of the larger number of water molecules that are released from the hydrophobic regions of the cyclopeptides when two rings come together.<sup>[169]</sup> Accordingly, the formation of the 1:1 complex is associated with a significantly smaller stability constant than the binding of this complex to the second cyclopeptide ring, which is associated with a more extensive desolvation of the binding partners. A further improvement of anion binding, this time as a consequence of the chelate effect, results from covalently connecting two cyclopeptide rings through suitable linkers.<sup>[170]</sup> The respective bis(cyclopeptides) are mostly less soluble than their monotopic analogs, but **43c**, which contains additional solubilizing groups attached to the aromatic cyclopeptide and linker moieties, allowed binding studies in water.<sup>[171]</sup> These investigations showed that with a  $\log K_a$  of 3.3, the sulfate affinity of **43c** is almost 2 orders of magnitude larger than that of **43b**. The iodide complex of **43c** is even more stable ( $\log K_a = 3.6$ ), while the smaller halides are bound less strongly. Sulfate versus iodide selectivity thus reversed when going from **43b** to **43c**, likely because the anion has to be completely desolvated before it can be bound between the two subunits of the bis(cyclopeptide), which is energetically more costly for sulfate than for iodide. The observed enthalpies of complex formation are consistent with this interpretation (Table 6). These enthalpies are positive in the case of sulfate and the smaller halides, showing that the binding enthalpy cannot overcompensate the enthalpic term associated with anion dehydration. Only in the case of the weakly hydrated iodide anion, a negative binding enthalpy was observed. For all anions, the main driving force of complex formation thus derives from the substantial gain in entropy, reflecting the entropically favorable release of water molecules from the solvation shells of the anions and the cavities of the cyclopeptides. An endothermic complexation of strongly hydrated pyrophosphate anions was also observed for a tetracationic resocinarene-derived receptor.<sup>[89]</sup>

Another potent class of receptors whose anion affinity in water benefits from hydrogen bonds, in this case hydrogen bonds involving CH donors, are the bambusurils developed by Sindelar.<sup>[172]</sup> The two water-soluble bambus[6]urils **44a,b** (Figure 17) recognize anions of widely varying sizes, ranging from

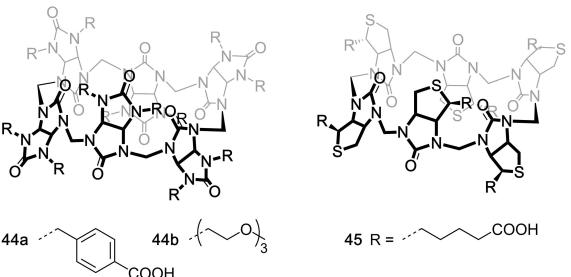


Figure 17. Structures of bambus[6]urils **44a, b** and biotin[6]uril **45**.

small fluoride to large hexafluoroantimonate anions, for example.<sup>[172]</sup> The most stable complexes are formed with iodide and perchlorate, that is, anions with ionic radii between 2.2 and 2.4 Å that are only weakly solvated in water. The respective complexes are remarkably stable: the iodide and perchlorate complexes of **44a**, for example, have  $\log K_a$  values in 20 mM aqueous phosphate buffer (pD 7.1) of 7.0 and 7.7, respectively.<sup>[173]</sup> For comparison, the fluoride complex has a  $\log K_a$  of only 2.0 under the same conditions, showing that the anion complexes of **44a** span a stability range of more than 5 orders of magnitude. Selectivity not only reflects the size complementarity of the anion and the cavity diameter but also correlates with the ease with which the anions are desolvated.

Repulsive electrostatic interactions between the bound anions and the solubilizing groups of **44a**, which are fully deprotonated under the conditions of the binding studies, destabilize the complexes, and this effect becomes stronger with decreasing distance between the carboxylate groups and the glycoluril subunits.<sup>[174]</sup> The neutral receptor **44b** does not suffer from this effect and therefore has an even larger anion affinity in water than **44a**. The  $\log K_a$  of the iodide complex amounts to 7.5, for example.<sup>[175]</sup> Complex formation of **44a** and **44b** is strongly exothermic in water and opposed by entropy, which was attributed to the release of cavity water during complex formation.

Pittelkow's biotin[6]uril **45** (Figure 17) mainly differs from bambus[6]urils in that it contains D-biotin instead of glycoluril subunits.<sup>[176–178]</sup> These units also arrange a seam of CH groups along the inner cavity, but the selectivity of **45** differs from that of **44a** because of the presence of the tetrahydrothiophene moieties. Complex formation of **45** in 100 mM aqueous phosphate buffer (pH 7.5) is, however, also exothermic and entropically unfavorable.

Six CH groups converge into the cavity of the cage-type tricationic receptor **46** (Figure 18), which furthermore has the perfect size to host a chloride anion.<sup>[179]</sup> The strong solvation of this anion causes the respective complex to only have a relatively small  $\log K_a$  of 1.4 in water, however, slightly smaller than the chloride complex of the neutral bis(cyclopeptide) **43c**.

The small but noticeable positive potentials of CH groups inside the cavities of the octa acid **23a** and cyclodextrins could also contribute to the affinity of these receptors for weakly solvated anions such as perchlorate in the case of **23a** or dodecaborates in the case of cyclodextrins. The favorable

Table 6. Thermodynamic parameters of the reactions between **43c** and different anions at 298 K.<sup>[171]</sup>

Anion	$\log K_a$	$\Delta G^{\circ[a]}$	$\Delta H^{\circ[a]}$	$T\Delta S^{\circ[a]}$
Sulfate	3.3	-18.9	5.9	24.8
Iodide	3.6	-20.6	-3.2	17.4
Bromide	3.2	-18.4	3.6	22.0
Chloride	2.2	-12.3	10.1	22.4

[a] Energies in  $\text{kJ mol}^{-1}$ .

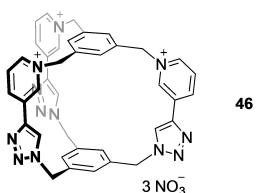


Figure 18. Structure of the chloride-binding cage 46.

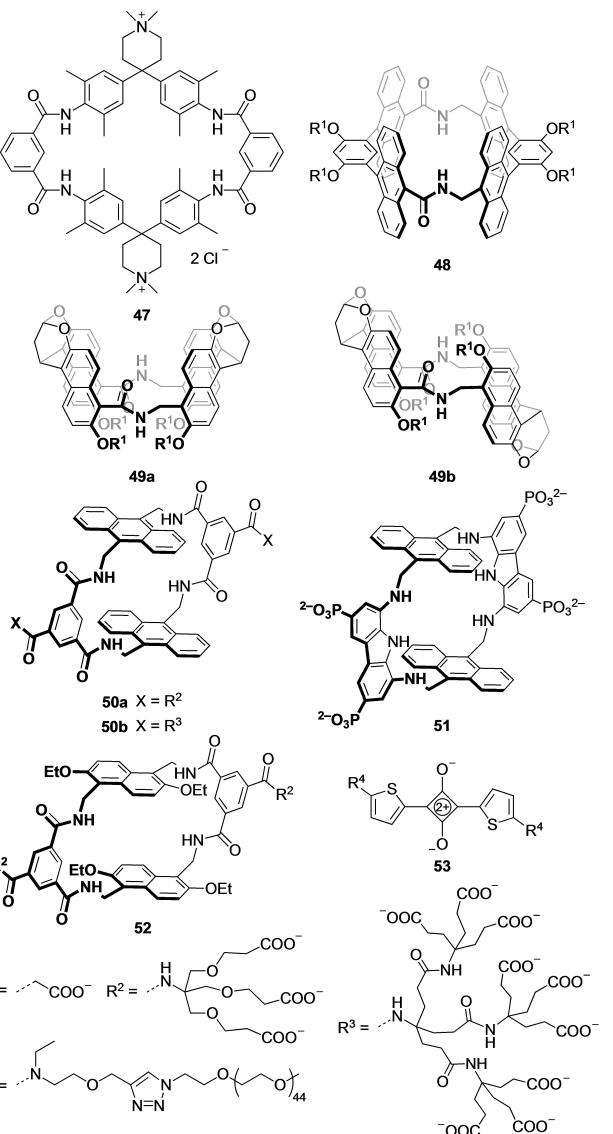
binding enthalpies and unfavorable entropies of the latter complexes are, however, mainly due to the dehydration of the dodecaborate anions (Section 2.3).<sup>[106,180]</sup>

### 5.3. Receptors for Neutral Substrates

Hunter and co-workers demonstrated some time ago that the water-soluble analog of a previously developed benzoquinone receptor, dication **47** (Figure 19), binds the same substrate also in water.<sup>[181]</sup> With a  $\log K_a$  of circa 0.7, binding is very weak, however, although some cyclic dipeptides are bound with about one order of magnitude greater affinity.

Work of the Jiang group showed more recently that benzoquinone affinity can be much improved by positioning the guest in a more hydrophobic environment.<sup>[182]</sup> The corresponding receptor **48** contains only two converging NH donors as opposed to four in Hunter's receptor. The anthracene side walls of **48** create a deep hydrophobic cavity, however, into which benzoquinone and structurally related guests fit very well. The direct host-guest interactions not only involve hydrogen bonds between the NH groups of **48** and the CO groups of the substrate but also CH-π interactions between appropriately arranged aromatic residues of host and guest. In addition, solvent effects contribute to complex stability as demonstrated by favorable binding enthalpies but unfavorable or weakly favorable entropies. Remarkable complex stabilities were thus achieved: the benzoquinone complex of **48** has a  $\log K_a$  of 4.5, for example, while the  $\log K_a$  of a water-soluble anthraquinone derivative, which perfectly fills the cavity of **48**, amounts to 9.2.

Receptor **48** is part of a larger research program of the Jiang group targeting water-soluble receptors with hydrophobic cavities into which hydrogen bond donors project to mediate direct interactions with potential guest molecules. Substantial work in this context was performed using so-called naphthotubes as receptors. These macrocyclic bislactams contain two bis(naphthalene) clefts covalently linked through amide groups. They are obtained as a mixture of a *syn* and an *anti* diastereomer (**49a** and **49b**) whose binding properties are usually assessed independently after separation. These bislactams were originally introduced by Glass as receptors for long chain alkyl amines, alcohols, or carboxylic acids, which are bound in water with binding constants  $\log K_a$  up to 4.4 (for the complex between **49a** and dodecanoic acid).<sup>[183]</sup> Complex stability increases with the chain length of the guests, indicating that dispersion interactions and solvent effects contribute to complex stability. Jiang later showed that these naphthotubes

Figure 19. Structures of receptors **47–52** and the squaraine **53**.

also recognize small organic substrates in water, which are normally difficult to bind.<sup>[184]</sup> The 1,4-dioxane complex of **49a** has a  $\log K_a$  of 4.0, for example. Complex formation involves the formation of hydrogen bonds between the NH groups of the receptor and the oxygen atoms of the guest. Guests containing only one oxygen atom (tetrahydrofuran in **49a**:  $\log K_a = 2.4$ ), or two oxygen atoms not well positioned for hydrogen bond formation (1,3-dioxane in **49a**:  $\log K_a = 2.3$ ) form significantly less stable complexes. The Jiang group subsequently demonstrated that naphthotubes bind a variety of polar guests in water,<sup>[185]</sup> including surrogates of nerve agents.<sup>[186]</sup> In addition, naphthotubes can be used for the chiroptical sensing of epoxides, alcohols,<sup>[187]</sup> and carboxylic acids,<sup>[92]</sup> and for the removal of micropollutants from water, rendering them potentially useful for practical applications.<sup>[188]</sup>

Other macrocyclic tetralactams in which converging hydrogen bond donors and two hydrophobic anthracene units mediate guest binding in water are receptor **50a**, described by

Davis and co-workers,<sup>[189]</sup> and **51**, which was developed in the Roelens group (Figure 19).<sup>[190]</sup> Both receptors bind monosaccharides through a combination of hydrogen bonding and CH- $\pi$  interactions. The  $\log K_a$  of the glucose complex of **50a** amounts to 1.7, for example. Interestingly, the preorganized macrocyclic cavity of **51** does not seem to be required for carbohydrate binding in water since analogous acyclic, cleft-type receptors with only one carbazole moiety and two anthracene units also possess appreciable affinity, albeit mainly for disaccharides.<sup>[191,192]</sup>

Receptor **50b** has a high affinity also for heterocyclic substrates such as purine or pyrimidine bases.<sup>[193]</sup> The complex of **50b** with hypoxanthine has a  $\log K_a$  of 7.0 in water, for example, while an analog of **50b** with two disubstituted naphthalene residues, receptor **52**, has been shown to recognize riboflavin with a  $\log K_a$  of 7.1.<sup>[194]</sup> An extraordinarily high  $\log K_a$  of 9.0 was observed for the complex between **50a** and the squaraine derivative **53**.<sup>[195]</sup>

The latter complexes benefit from aromatic interactions between the electron-poor  $\pi$ -systems of the aromatic guests and the electron-rich aromatic units in the receptors. The lower stability of the earlier mentioned carbohydrate complexes can be attributed to the weaker nature of CH- $\pi$  interactions involving aliphatic rings and to the more difficult desolvation of the polar substrates. However, these drawbacks can be overcome as shown by Davis and co-workers by using polycyclic receptors with cavities structurally better defined than those of monocyclic analogs and a greater number of hydrogen bond donors and acceptors.<sup>[196]</sup> The first water-soluble example of such so-called "temple" receptors, compound **54** (Figure 20), has a low glucose affinity, although at the time of publication, **54** was the first receptor known to noncovalently interact with carbohydrates in water.<sup>[197]</sup> Selectivity is good as demonstrated by the difference in the  $\log K_a$  values of the complexes of **54**

with methyl  $\beta$ -D-glucoside ( $\log K_a = 1.5$ ) and the corresponding  $\alpha$ -glucoside ( $\log K_a = 0.8$ ), and disaccharides<sup>[198]</sup> and  $\beta$ -N-acetylglucosamine<sup>[199]</sup> are also bound efficiently.

Solvent-dependent binding studies showed that glucose and cellobiose affinity of **54** is higher in water than in aqueous solvent mixtures containing methanol, DMSO, or acetonitrile as co-solvents, demonstrating the importance of the hydrophobic effect for carbohydrate recognition in water.<sup>[198]</sup> Subsequent work in the Davis group, which involved varying the aromatic units comprising the "roof" and "floor" of the temple receptors and the structure and number of the linkers making up the "columns," not only revealed many principles of carbohydrate recognition<sup>[196]</sup> but eventually also afforded receptor **55**,<sup>[200]</sup> which has an outstanding glucose affinity and selectivity. With a  $\log K_a$  of 4.3, glucose is bound by **55** stronger by a factor of circa 100 than galactose and stronger by a factor of about 1000 than a range of other carbohydrates, rendering **55** useful for carbohydrate sensing<sup>[201]</sup> and other applications.<sup>[202]</sup>

Interestingly, NH donors may not be required in such "temple" receptors to achieve carbohydrate recognition in water according to results obtained by Stoddart and co-workers.<sup>[203]</sup> They introduced receptor **56** (Figure 20), consisting of two parallel pyrene units as "roof" and "floor" that can engage in CH- $\pi$  interactions with the axially oriented protons of carbohydrate rings. Polarized pyridinium CH bonds are available for hydrogen bonding interactions, while the xylylene moieties ensure the proper distance between the pyrene units. This water-soluble receptor binds  $\beta$ -D-glucoside with a  $\log K_a$  of 3.1 in water. While  $\beta$ -N-acetylglucosamine is bound more strongly than glucose, as also observed for **54**,<sup>[199]</sup> cellobiose forms a less stable complex, which does not mirror the behavior of **54**.<sup>[198]</sup> Accordingly, **56** seems to be too rigid to host guests larger than monosaccharides. The calorimetric characterization of complex formation revealed that binding is enthalpically favorable and associated with a small favorable or unfavorable entropic term, depending on the guest.

The Ballester group explored the use of aryl-extended calix[4]pyrroles for molecular recognition in water.<sup>[25]</sup> These compounds contain a calix[4]pyrrole core with pyrrole NH groups as hydrogen donors. In the cone conformation of the respective  $\alpha,\alpha,\alpha,\alpha$ -isomer, four aryl groups at the methine groups point into the same direction, creating a deep hydrophobic cavity that is open at one end and contains four converging NH groups at the bottom. Although such calix[4]pyrroles are conformationally mobile in solution, guest binding locks them into the cone conformation, often leading to remarkably stable complexes, also in water, whose binding equilibria are slow on the NMR time scale. Suitable guests are N-oxides or lactams whose NO or CO oxygen atoms form hydrogen bonds to the pyrrole NH groups. Binding studies showed that complex stability of the aryl-extended calix[4]pyrroles **57a–c** (Figure 21) is relatively independent of whether the solubilizing charged groups are cationic (**57a**) or anionic (**57b**), or are located along the upper (**57a,b**) or the lower (**57c**) rim of the cavity (Table 7). Binding is therefore not strongly affected by potential electrostatic effects of the substituents, as expected for neutral guests.<sup>[204,205]</sup>

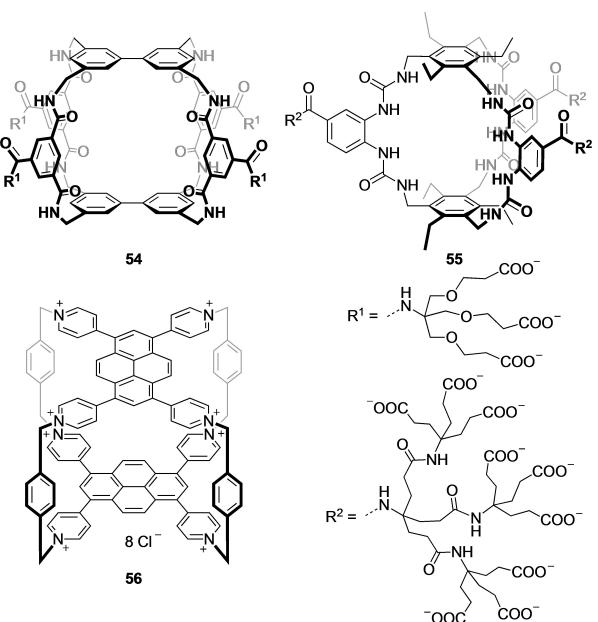


Figure 20. Structures of temple receptors **54**, **55**, and **56**.

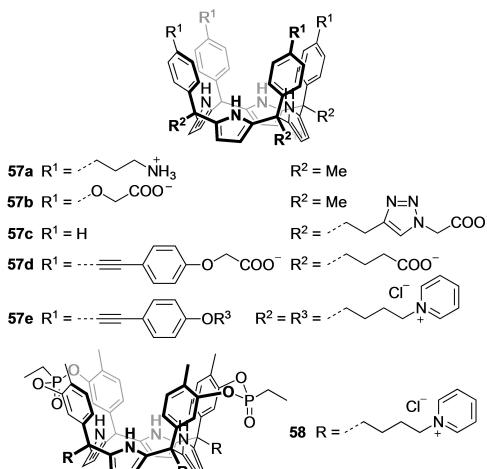


Figure 21. Structures of the aryl-extended calix[4]pyrroles 57a–e and 58.

**Table 7.** Thermodynamic parameters of the pyridine N-oxide and 4-phenylpyridine N-oxide complexes of receptors 57a–e at 298 K.

Receptor	$\log K_a$	$\Delta H^{0[a]}$	$T\Delta S^{0[a]}$	$\log K_a$	$\Delta H^{0[a]}$	$T\Delta S^{0[a]}$
pyridine N-oxide		4-phenylpyridine N-oxide				
57a <sup>[c]</sup>	4.3	n.a. <sup>[b]</sup>	n.a.	3.2	n.a.	n.a.
57b <sup>[c]</sup>	4.2	n.a.	n.a.	3.4	n.a.	n.a.
57c <sup>[d]</sup>	4.6	-18.8	7.2	5.3	-31.0	-0.8
57d <sup>[e]</sup>	5.9	-35.2	-1.3	9.1	-52.3	-0.4
57e <sup>[e]</sup>	6.3	-38.1	-2.1	9.4	-63.2	-9.6

[a] Energies in  $\text{kJ mol}^{-1}$ ; [b] n.a. – not available; [c] from Ref. [204]; [d] from Ref. [205]; [e] from Ref. [207].

The complexes of 57a,b with 4-phenylpyridine N-oxide are about one order of magnitude less stable than those with pyridine N-oxide because the extended guest cannot be fully incorporated into the cavity. This selectivity is reversed when deepening the cavity as in the super aryl-extended calix[4]pyrroles 57d,e.<sup>[206,207]</sup> Receptors 57d,e bind to 4-phenylpyridine N-oxide with nanomolar affinities, clearly demonstrating the beneficial effects of confining the guest within a deep hydrophobic cavity in water. The comparison of the Gibbs free energies associated with the binding of 57d,e to different 4-substituted pyridine N-oxides showed that complex stability increases by  $0.14\text{--}0.16 \text{ kJ mol}^{-1} \text{Å}^{-2}$  with the increasing surface area of the guest, thus providing an estimate of the extent to which the hydrophobic effect contributes to complex stability. The affinity increase observed for the conformationally rigidified calix[4]pyrrole derivative 58 (Figure 21) with increasing hydrogen bond acceptor strength of the guest's CO group in the order ketone < lactone < lactam < urea showed that the hydrogen bonding interactions with the pyrrole NH groups have a larger control over complex stability in this case than the hydrophobic effect because the trend would be opposite if complex stability would be governed by the hydrophobicity of the guest.<sup>[208]</sup> Calorimetric studies showed that complex formation is in all cases exothermic and accompanied by small favorable or unfavorable entropic contributions (Table 7).

The examples presented in this section thus show that receptors with sufficiently large cavities whose inner surfaces are lined with both hydrophobic and polar residues can efficiently bind neutral substrates in water, even strongly hydrated ones such as carbohydrates. While hydrogen bonding clearly contributes to binding, important and likely decisive contributions also come from CH-π interactions between aromatic residues of the host and the hydrophobic regions of the guests. Such interactions are even more important when they involve the edges of aromatic rings or the faces of electron-poor aromatic residues. Finally, cavity water or partially dewetted parts of the receptor cavity additionally favor complex formation.

## 6. Halogen and Chalcogen Bonding

Halogen bonds are noncovalent interactions between Lewis bases and organic halides.<sup>[209]</sup> To a first approximation, they can be understood as electrostatic interactions between the negative potential surface of a neutral or negatively charged heteroatom in the Lewis base and the region of positive electrostatic potential in the organic halide. This region is localized in the extension of the C-Hal bond and associated with the term σ-hole. Accordingly, halogen bonds are somewhat related to hydrogen bonds, with the difference that the proton in the hydrogen bond donor is replaced by a halogen atom in the respective halogen bond donor.

In contrast to hydrogen bonds, in which only protons serve as binding partners, the halogen atom in the halogen bond donor can vary, allowing the host structure to be adapted to some degree to the requirements of the guest. Organic iodides are, however, generally better halogen bond donors than respective derivatives of the smaller halides because of the greater polarizability of the iodine atom. Another difference between hydrogen and halogen bonds is the pronounced directionality of the latter, which is due to the size and location of the σ-hole in the donor. With respect to molecular recognition in water, halogen bonding benefits from the weak solvation of the relatively large halogen atoms.

Similar rules apply to chalcogen bonds, in which organic sulfur, selenium, or tellurium derivatives serve as donors.<sup>[210]</sup> The different electron distributions along halogen and chalcogen atoms cause differences in the preferred binding geometry of halogen and chalcogen bonds, however.

Important contributions to the use of halogen bonds for molecular recognition came from the Beer group.<sup>[211]</sup> Receptors developed in this context that work in water include the α-cyclodextrin derivative 59 (Figure 22) with two 5-iodotriazole moieties that binds perrhenate with a  $\log K_a$  of 2.8.<sup>[212]</sup> The same anion also binds to unsubstituted α-cyclodextrin under the same conditions, but with an about one order of magnitude lower affinity. This comparison thus provides evidence for the contribution of halogen bonding to complex stability, although electrostatic interactions between the anion and the pyridinium moieties of 59 cannot be fully ruled out. The same is true for the anion-binding rotaxane 60a whose axle features a 3,5-

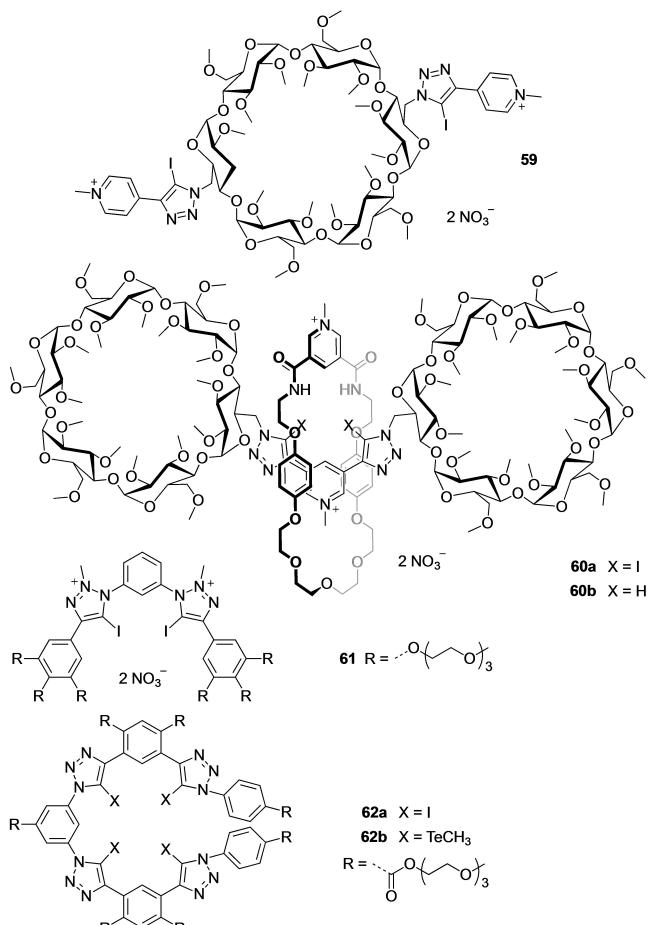


Figure 22. Structures of receptors 59–62a, b.

disubstituted pyridinium ring with two 5-iodo-1,2,3-triazole units as one part of the binding site.<sup>[213]</sup> Further contributions to anion binding come from the two amide groups in the ring, while the methylated  $\alpha$ -cyclodextrin units serve as stoppers and ensure water solubility. Among the anions tested, **60a** binds iodide most efficiently ( $\log K_a = 3.3$ ), but also has a weak sulfate affinity ( $\log K_a = 1.5$ ). Iodide binding is strongly exothermic and opposed by entropy. Interestingly, the prototriazole analog **60b** not only has a lower iodide affinity ( $\log K_a = 1.3$ ), but also binds iodide in an endothermic process that is favored by entropy. The authors attributed these opposite trends to the stronger interaction of iodide with the iodotriazole-containing receptor, which results in a more negative binding enthalpy and an unfavorable binding entropy. The observed thermodynamic parameters would, however, also be consistent with a more difficult desolvation of the prototriazole-containing receptor. The generally lower anion affinity of the prototriazole analogs of the investigated 5-iodo-1,2,3-triazole-containing receptors, which was also observed in other cases,<sup>[211]</sup> demonstrates the advantage of halogen bonding for molecular recognition in water.

The interlocked architecture does not seem to be necessary to achieve anion binding since the much simpler bis(5-iodo-1,2,3-triazole) derivative **61** (Figure 22) also binds iodide and, in

this case, also perrhenate.<sup>[214]</sup> Both anions are only weakly bound and with similar affinities ( $\log K_a$  ca. 1.7), but much stronger anion binding can be achieved by using longer oligomeric analogs of this receptor in which more than two iodotriazole units can fold around the anion. An example is the tetrakis(5-iodo-1,2,3-triazole) derivative **62a** of which further structurally related analogs were also studied.<sup>[215]</sup> This receptor prefers to bind weakly hydrated anions such as iodide, perchlorate, perrhenate, or thiocyanate. The cavity of the folded oligomer is too small, however, to bind these anions in a 1:1 fashion. The 1:1 complex thus contains the anion in a perched arrangement on top of the folded chain, leaving sufficient space on the opposite side to allow for the binding of a second receptor molecule. Complex formation thus involves the stepwise formation of sandwich-type complexes, whereby the formation of the 1:1 complexes is generally associated with smaller binding constants than the subsequent formation of the 2:1 complexes. The binding equilibria of **62b** are thus reminiscent of those of cyclopeptide **43a**. The cumulative association constants of the anion complexes of the investigated oligomeric 5-iodotriazoles reach  $\log K_a$  values of 11 and complex formation is favored by both enthalpy and entropy. Interestingly, in cases where the overall enthalpic and entropic contributions could be broken down to those associated with the individual binding steps it turned out that only the first step is exothermic and that this step is opposed by entropy. The second step is slightly endothermic but has a high positive entropy. The authors attributed the favorable binding enthalpy of the first step to the formation of the four halogen bonds that does not require the full dehydration of the anion. The endothermicity of the second step indicates that the newly formed halogen bonds do not lead to a pronounced further enthalpic stabilization, but that the anion and parts of the receptor molecules have to be extensively dehydrated for binding to occur, which is entropically favorable.

This work also involved the evaluation of receptor **62b** that can interact with anions through chalcogen bonds.<sup>[215]</sup> Receptor **62b** behaves similarly as the other receptors, but anion binding is slightly weaker, which was attributed to detrimental effects of the methyl groups at the tellurium centers on complex formation. The comparison of the behavior of the iodotriazole-containing receptors with that of the corresponding prototriazole analogs is difficult because the prototriazole derivatives form 1:1 complexes due to the larger size of their cavities.

Although not within the focus of this review, it should be noted that chalcogen-bonding was used to mediate the self-assembly of cavitands in water, affording the corresponding capsules.<sup>[216]</sup>

## 7. Dispersion Interactions

Dispersion interactions contribute to the stability of every host-guest complex.<sup>[217]</sup> They may not be decisive for bringing the binding partners together but they always become effective once the complex is formed. The strength of dispersion interactions scales with the polarizability of the binding

partners and the size of the surface areas that come into contact, which is why complexes in which large hydrophobic residues are arranged in close proximity especially benefit from this type of interactions. Dispersion interactions thus add to the stability of complexes in water in which hydrophobic parts of the binding partners are pushed together by the hydrophobic effect. Examples are the complexes of deep cavitands such as **23a**<sup>[69]</sup> (Figure 7) or **37a**<sup>[218]</sup> (Figure 13) with substrates that have bulky aliphatic residues or long alkyl chains.

Cavitand **37a** was shown by Rebek and co-workers to form complexes with adamantane derivatives such as amantadine hydrochloride or rimantadine hydrochloride, for example, in which the bulky adamantyl group of the guests makes contact with the faces of the aromatic residues that line the inner walls of the cavitand.<sup>[158]</sup> In a similar manner, **37a** also binds to surfactants such as dodecyl sulfate or dodecyl phosphocholine in water.<sup>[219]</sup> In these cases, the alkyl groups are inserted into the cavitand cavity with the terminal methyl groups residing at the bottom and the polar head groups protruding from the opening. The alkyl chains adopt coiled conformations to minimize the areas of the chains that are exposed to the solvent and maximize the contact regions of host and guest. In contrast to anionic surfactants, alkyltrimethylammonium salts with a long alkyl chain can bind to cavitands by either including the ammonium group into the cavity to allow for cation- $\pi$  interactions or the hydrophobic alkyl chain. The complexation of dodecytrimethylammonium bromide by **37a** only involved the latter binding mode, causing the ammonium group to remain outside the cavity where it interacts with the carboxylate groups along the rim.<sup>[158]</sup> These results are in line with those obtained for a series of other cavitands in which the preferential incorporation of the *tert*-butyl groups of the anilinium derivative **33** (Figure 12) was observed,<sup>[160]</sup> showing that the hydrophobic effect in water often outcompetes complex stabilization by cation- $\pi$  interactions. Unsubstituted long chain alkanes also bind to **37a** in water, but since these substrates lack functional groups that induce a preferential inclusion geometry, they freely tumble around inside the cavity.<sup>[220]</sup> Cavitand **63** (Figure 23), by contrast, causes included alkyl chains to adopt U-shaped conformations. The chain ends of the guest are thus pushed together by complex formation, allowing the use of **63** to mediate cyclization reactions of suitable  $\alpha,\omega$ -difunctionalized substrates.<sup>[221]</sup> It should be noted

that also CH- $\pi$  interactions could be made responsible for the stabilization of an aliphatic guest inside the cavity of these cavitands. The significantly smaller positive electrostatic potential of aliphatic protons in comparison to protons along the edges of aromatic rings renders attractive electrostatic interactions in the complexes of alkanes much weaker, however, and dispersion interactions are therefore probably more important than CH- $\pi$  interactions.

The Rebek group also showed that cavitand **64** with an even deeper cavity than **37a** binds small acyclic aliphatic alcohols and ketones in water whose apolar residues preferentially reside at the cavity bottom.<sup>[222]</sup> Tetrahydrofuran and 1,4-dioxane are, for example bound with  $\log K_a$  values of 4.8 and 4.0, respectively. The 1,4-dioxane complex of **64** is thus comparably stable as that of the naphthotube **49a** (Figure 19) although direct hydrogen bonds between host and guest are missing. The authors attribute the high stability of these complexes to the incorporation of water clusters in the upper part of the cavity with which the guest molecules can interact.

Gibb's octa acid **23a** also binds *n*-alkanes in water.<sup>[69,223]</sup> In this case, the filling of the cavity produces a large hydrophobic surface at the cavity opening so that the respective complexes are prone to self-assemble to afford guest-filled capsules. Depending on the chain length of the alkane, different complex stoichiometries have been observed, with short alkanes forming 2:2 receptor/substrate complexes and longer alkanes from *n*-octane onward 2:1 complexes. Since the cavity size does not allow the incorporation of alkanes longer than *n*-nonane in their extended conformations, these guests adopt coiled conformations inside the cavity like in the related complexes of the cavitand **37a**. The octa acid **23a** has also been used as a reaction vessel to control the reactivity of certain hydrophobic guests.<sup>[121,224]</sup>

Other examples of host-guest complexes in which dispersion interactions are partly responsible for complex formation are the xenon and radon complexes of cryptophanes. Xenon is bound by the water-soluble cryptophane **65** (Figure 24) with a  $\log K_a$  of 4.6 in 20 mM phosphate buffer (pH 7.5) at 293 K, for example, in a binding process that is almost equally favored by enthalpy and entropy.<sup>[225]</sup> This stability is substantially higher than the stability of related xenon complexes in organic media, indicating that complex stability in water is reinforced by the hydrophobic effect. The stability of the radon complex is comparably high, suggesting that these complexes could be suitable for bioimaging or medicinal applications.

The extent to which dispersion interactions contribute to the complexation of noble gases by cucurbiturils was assessed

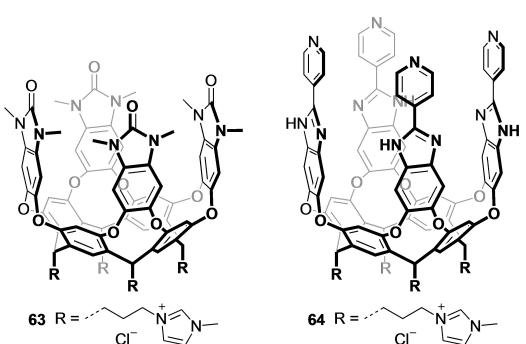


Figure 23. Structures of cavitands **63** and **64**.

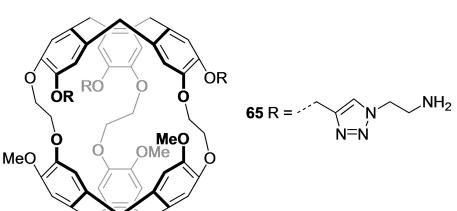


Figure 24. Structure of cryptophane **65**.

by Nau and co-workers.<sup>[226]</sup> They determined the stability of the noble gas complexes of cucurbit[5]uril **26a** (Figure 10) whose cavity is small and fully dewetted in water according to experimental and computational results. Complex stability increases with the size of the noble gas from He ( $\log K_a = 1.9$ ) to Xe ( $\log K_a = 3.9$ ). This order does not correlate with the ease with which the noble gases are desolvated since Xe has the highest water solubility in this series. Contributions of dispersion interactions to complex stability could alternatively explain this trend, which should be strongest for Xe due to its polarizability. The size of a Xe atom moreover allows it to approach the inner wall of the cucurbituril cavity at smaller distances than possible for the other noble gases. Computations showed, however, that dispersion interactions are not very efficient in the case of the weakly polarizable cucurbiturils. The dispersion interactions between noble gases and water molecules are, in fact, stronger than those with **26a**, causing water to oppose rather than favor complex formation. The actual driving force of complex formation turned out to be the gain in the Gibbs free energy when transferring the noble gas atoms from cavities in the water matrix, whose formation is energetically costly, to the already dewetted cavities of **26a**. The associated gain in  $\Delta G^0$  outweighs the loss of the dispersion interactions between the solutes and water. This work again demonstrates that the reorganization of the water structure can be more important for complex formation than the direct interactions between the binding partners, although water reorganization, in this case, does not involve the release of cavity water, but the collapse of the water cavity in which the substrate was incorporated prior to complex formation.

## 8. Summary and Outlook

Supramolecular chemistry in water started with the work on cyclodextrin complexes, long before the term supramolecular chemistry even existed. A few other receptors were investigated in water at the early stages of the research field, but substantial progress came only recently with the development of a wide variety of receptors with broad substrate spectra. As shown above, some of these receptors exhibit outstanding substrate affinities, matching or even surpassing those of analogous natural systems. Today, water-soluble receptors exist for even the most difficult substrates, for example, carbohydrates,<sup>[196]</sup> with affinities and selectivities sufficiently good to use them in practical applications. With these developments, the understanding of the principles that govern molecular recognition processes in water also improved. It has become clear, for example, that the concept of the “classical” hydrophobic effect is not or maybe only in rare cases applicable to host-guest systems. Rather than entropically favored, binding processes in water are, in fact, often strongly exothermic and can even have unfavorable entropic terms. Diederich’s concept of the “non-classical” hydrophobic effect therefore appears to be applicable not only to the cyclophanes for which it was first introduced,<sup>[118]</sup> but to the majority of receptors active in water. The existence of this technical term does not imply, however that the

underlying principles are also fully understood. Moreover, there is likely no strict separation between the “classical” and the “nonclassical” hydrophobic effect but rather a continuous transition, depending on the structures of the interacting molecules and their hydration.

Concepts have emerged in recent years that give insights into the hydration of receptors, especially their cavities, potentially providing explanations for the pronounced exothermicities of binding processes in water. These concepts take into account the shape of the binding partners, the size and shape of the (hydrophobic) surfaces that make contact in the complex, the release of water molecules from the receptor cavity during complex formation, substrate dehydration, and the degree to which the receptor cavity is dehydrated prior to substrate binding. While each of these concepts provides a plausible explanation for the behavior of the system for which it was developed, a global understanding of binding processes in water or even an overarching theory is still missing. These processes are governed to a large extent by the structural changes in the water matrix that accompany complex formation, not only in the first solvation shells of the binding partners, but possibly beyond. The respective dynamic response of the water molecules is, however, influenced by many aspects and therefore exceedingly complex. Supramolecular chemists can contribute to future studies in this field by providing suitable model systems with which certain aspects can be clarified, individually or in combination. However, as others have pointed out already,<sup>[127]</sup> a fundamental understanding of molecular recognition processes in water is unlikely to be achieved without close and mutually beneficial collaborations among scientists from different disciplines. This understanding will subsequently help transition from a currently somewhat empirical search for suitable receptors to a more guided design.

## Acknowledgements

*My own contributions to the topic of this review would not have been possible without the help and commitment of many former co-workers. I am deeply grateful to all of them. Some of their names are mentioned in the cited references.*

## Conflict of Interest

The author declares no conflict of interest.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Keywords:** hydrophobic effect • molecular recognition • supramolecular chemistry • synthetic receptors • water

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Manuscript received: February 7, 2022

Revised manuscript received: March 17, 2022