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Molecular Recognition

# Supramolecular Chemistry in Water

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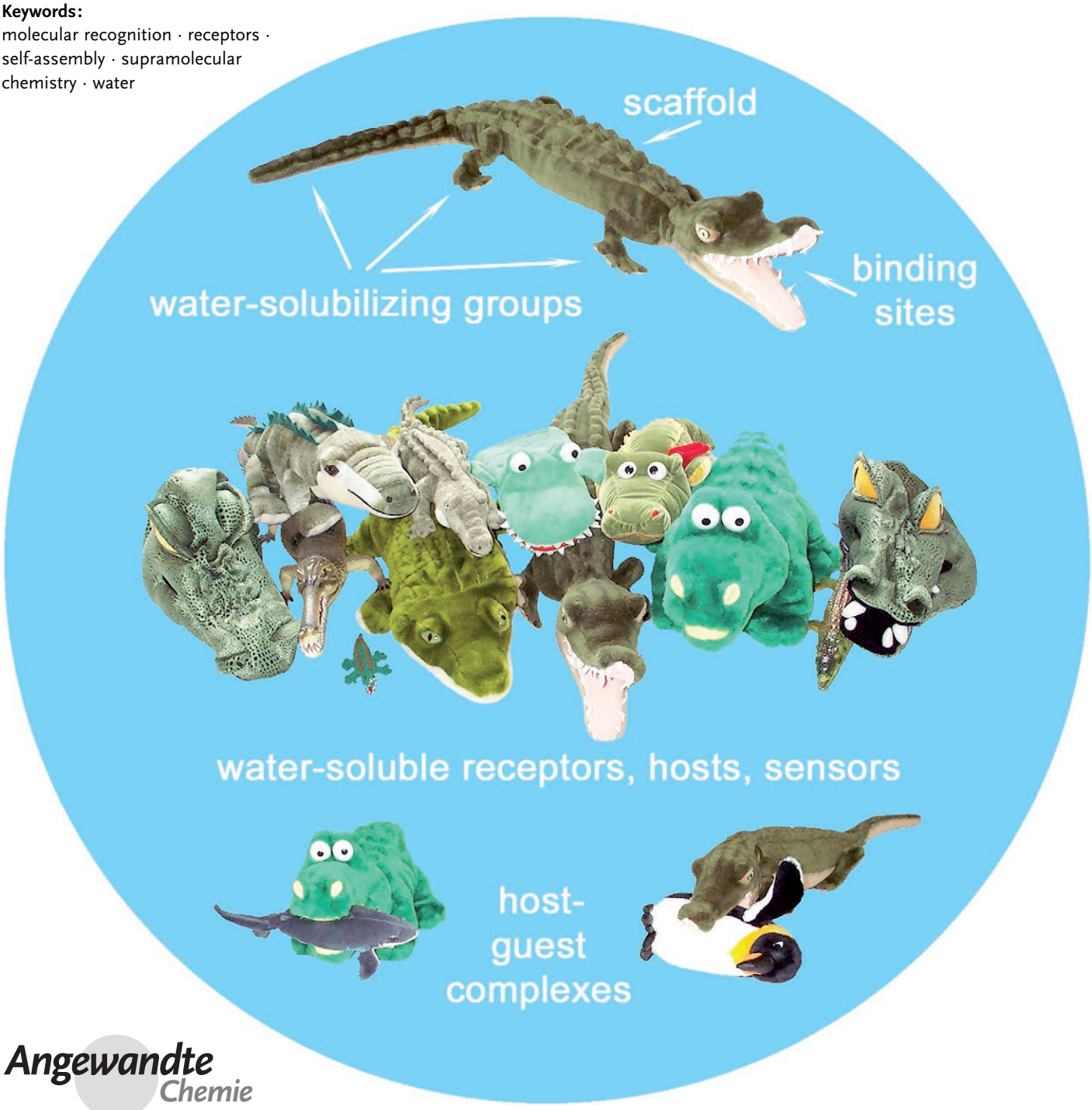
molecular recognition · receptors · self-assembly · supramolecular chemistry · water



*Supramolecular chemistry in water is a constantly growing research area because noncovalent interactions in aqueous media are important for obtaining a better understanding and control of the major processes in nature. This Review offers an overview of recent advances in the area of water-soluble synthetic receptors as well as self-assembly and molecular recognition in water, through consideration of the functionalities that are used to increase the water solubility, as well as the supramolecular interactions and approaches used for effective recognition of a guest and self-assembly in water. The special features and applications of supramolecular entities in aqueous media are also described.*

**From the Contents**



## 1. Introduction

Water is unique.[1] It provides an environment for life and mediates, regulates, and controls many processes in nature. As a consequence of its many anomalous properties, water provides both a challenge and opportunities.[2–5] Water is used more and more as a reaction medium, because it is an inexpensive "green" solvent and its usage has minimal ecological impact. Furthermore, its unique properties give rise to accelerated reaction rates and enhanced reaction selectivities.[6]

Water molecules form an infinite dynamic network of hydrogen bonds with localized and structured clustering.[4] This very favorable process is the main reason not only for the deviation of a variety of its physical properties,[4,5] but also for the hydrophobic effect: oil and water molecules attract one another; however, not nearly as strongly as water molecules attract one another.[3] On the other hand, polar molecules experience strong hydration by water and participate in the hydrogen-bonding network, which dramatically influences the properties of the solvated species. These properties of water provide two main challenges for supramolecular chemistry in aqueous media: how to gain (high) water solubility and how to avoid, minimize, or exploit the strong involvement of water in noncovalent processes.

One of the goals of supramolecular chemistry[7] is the creation of synthetic receptors that have both a high affinity and a high selectivity for the binding of guests in water.[8–11] Natural receptors such as enzymes and antibodies show strong and selective host–guest complexation through multiple weak, noncovalent interactions between the functional groups on the binding partners.[10] These natural systems provide the inspiration for the rational design of synthetic receptors that can be used to gain an understanding of the binding forces that contribute to the formation of complexes.[8,12] Most of the synthetic receptors have so far been studied in organic solvents, although all of the recognition events in nature take place in aqueous medium. The design of synthetic receptors which can be used in water represents a special challenge. First, the host needs to be soluble in water. This severely limits the type of building blocks which can be used for its construction. Second, special interactions and approaches have to be chosen to overcome the competitive influence of the water. Another important feature of large water-soluble receptors is the encapsulation of several (different) guests. This facility allows molecular interactions to be studied within a confined space and to carry out chemical reactions between them in aqueous media. A cavity catalyzes and directs synthesis, and also protects the reaction from water. The confined space strictly controls the inclusion and the subsequent chemical transformations through steric factors.[13]

This Review presents an overview of the developments in supramolecular chemistry in water since 2000. The Review is divided in three main parts: receptors, self-assembly, and self-sorting in aqueous media. It starts with relatively simple receptors containing one or more binding sites, as well as some dipodal receptors. Subsequently, tripodal receptors, tweezers, clips, appropriately functionalized cyclophanes, cucurbiturils, and (hemi)carcerands are discussed. Some classes of receptors, such as cyclodextrins,[14] crown ethers,[15,16] and azamacrocycles[17,18] are, in general, not included because of the huge number of publications dealing with these relatively simple water-soluble supramolecular platforms. The next section deals with self-assembly in water, for example, of capsules, helicates, metal–organic macrocycles, and cages. Examples of social and "narcissistic" self-sorting in aqueous media are described in the last part of this

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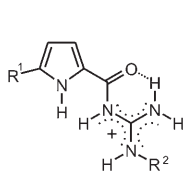
Review. The molecular recognition, reactions, properties, and applications of the supramolecular entities in aqueous media are outlined in all parts of the Review.

To the best of our knowledge, this is the first review covering different kinds of receptors, the self-assembly, and the recognition of a variety of guests in water. However, earlier developments in the field can be found in more specialized papers, such as an excellent review on anion recognition in aqueous media by Kubik et al.,[11] as well as general books[8,10,19] and reviews[12,20,21] on recognition and self-assembly, in which some features of supramolecular processes in water are presented.

## 2. Relatively Simple Receptors containing One or Several Binding Sites

### 2.1. Guanidinocarbonylpyrroles, -pyridines, and -pyrazoles

Schmuck et al. have recently reported the guanidinocarbonylpyrroles **1**.[22,23] The combination of multiple hydrogen bonds along with electrostatic interactions allows the effective binding of amino acids and peptides in aqueous solution.



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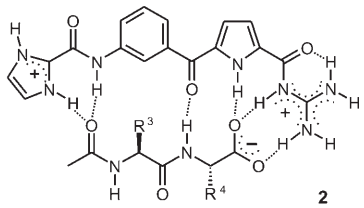

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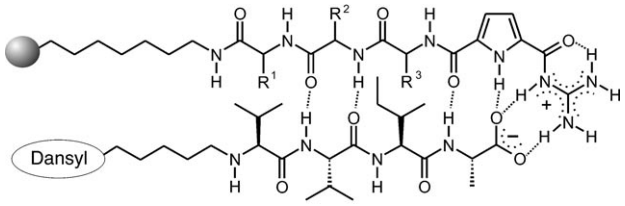
Addition of NH or charged substituents to either the pyrrole or the guanidinium moiety of **1** significantly increases the affinity toward carboxylates. Compound **1** ($R^1 = R^2 = H$) binds Ac-L-Ala-$O^-$ with $K_a = 130\,M^{-1}$ (in water/DMSO 2:3).[24] Attachment of a peptide at the guanidinium moiety leads to receptor **1** ($R^1 = H$, $R^2 = CH_2CH_2CO$-Val) which strongly binds carboxylates or amino acids with $K_a \geq 10^3\,M^{-1}$ in an aqueous buffer solution.[25] Functionalization of the pyrrole moiety gives receptor **1** ($R^1 = C(O)NHEt$, $R^2 = H$), which binds acetate with $K_a \approx 3 \times 10^3\,M^{-1}$ and N-acetylated amino acids with $K_a = 360$–$1700\,M^{-1}$ (water/DMSO 2:3).[24] Extra ionic interactions introduced by the imidazolium moiety in de novo designed receptor **2** led to the efficient binding of dipeptides in water,[26] with binding constants up to $5.43 \times 10^4\,M^{-1}$, which is almost 10 times higher than the binding affinity toward simple amino acids. A search for the best binding motif for the Ac-Val-Val-Ile-Ala-$O^-$ peptide[27] in water has been carried out by screening a combinatorial library (512 members) of structurally related tripeptide-functionalized receptors **3** bound to beads for their binding properties against a fluorophore-labeled derivative of the tetrapeptide.[28] The binding constants vary from $20\,M^{-1}$ (in $H_2O$, pH 6.1, 10 μM bis-Tris buffer; Tris = tris(hydroxymethyl)aminomethane) for the worst tripeptide linker sequence up to $4200\,M^{-1}$ for the best one.

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Receptors **4**, which are analogues of **1**, but contain a pyridine instead of a pyrrole moiety, bind dipeptides in aqueous solution much less effectively ($K_a = 30$–$460\,M^{-1}$ in water/[$D_6$]DMSO 2:3).[23]

A combination of two aminopyrazole substituents with di- or tripeptides gives water-soluble amyloid-β-peptide-specific ligands.[29,30] For example, receptor **5** binds the KLVFF peptide sequence in the central region of the amyloid-β-peptide, which is responsible for pathogenic aggregation of the Alzheimer peptide ($K_a = 1700\,M^{-1}$ in water).[29]

Kilburn and co-workers elaborated a methodology to prepare libraries of symmetrical[31] and unsymmetrical[32] N,N′-dipeptide-substituted guanidinium receptors bound to beads, and screened them toward dye-labeled peptides in aqueous media. This approach resulted in several stereoselective receptors for peptides in water. For example, receptor


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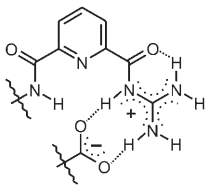
*David N. Reinhoudt studied chemistry at the Delft University of Technology (graduated in 1969 with Professor H. C. Beijerman). After working at Shell, in 1975 he was appointed first as extraordinarius and in 1978 as full professor at the University of Twente. His research focuses on nanotechnology, molecular recognition, and noncovalent combinatorial synthesis as well as applications of supramolecular chemistry. He is the scientific director of the MESA$^+$ Research Institute and since 2002 he has been the chairman of the Board of NanoNed, the Dutch Network for Nanotechnology.*



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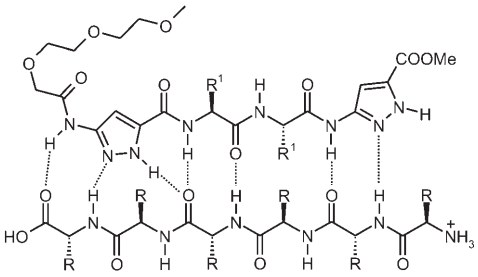
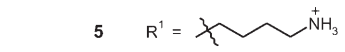
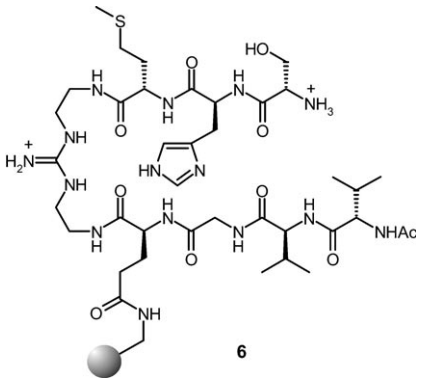


5 $R^1$ =



**6**, attached to a resin, binds *N*-Ac-Lys-D-Ala-D-Ala ($K_a \approx 1350\,M^{-1}$) preferentially to *N*-Ac-Lys-L-Ala-L-Ala ($K_a \approx 250\,M^{-1}$) in aqueous buffer solution.



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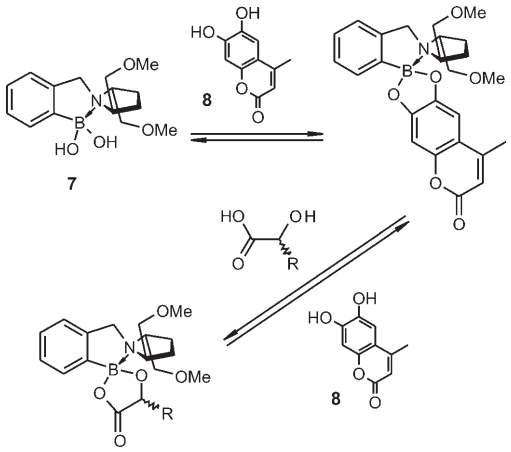
*Willem Verboom studied chemistry at Utrecht University, and received his PhD with Prof. Dr. H. J. T. Bos in 1980. He then joined the group of Prof. Dr. Ir. D. N. Reinhoudt at the University of Twente, where he is now associate professor in organic chemistry. His research focuses on the functionalization and application of molecular building blocks, in particular calixarenes and cavitands, for the development of specific receptors and larger noncovalent assemblies. Since 2001 he has been secretary of the "Design and Synthesis" group for the chemical section of the Netherlands Organization for Scientific Research.*

### 2.2. Boronic Acid Receptors

Aromatic boronic acids strongly interact in aqueous media with bifunctional substrates such as α-hydroxy acids and vicinal diols as well as with sugars.[33,34] Although the first study of the complexation of saccharides by boronic acids in water appeared more than half a century ago,[35] this functionality is still being used for the design of new sensitive and selective receptors.[36,37] The influence of the $pK_a$ value of the boronic acid, the pH value of the aqueous medium, and the influence of substituents (especially amines complexed to the boronic acids) have been studied to understand the mechanism of complexation and for implementation in sensors.[37,38] A number of fluorescent sensors for saccharides contain a boronic acid substituent.[33] In general, the high sensitivity of fluorescence enables recognition and sensing experiments to be carried out at low concentrations. It is not necessary to attach water-solubilizing groups to this type of receptor to enhance the water solubility and so enable the experiments to be performed in water or a mixture of an organic solvent and water.

Enantioselective association events between boronic acid receptors **7** and bifunctional substrates such as (*R*)-hydroxycarboxylates and vicinal diols have been studied by Anslyn and co-workers to develop enantioselective colorimetric and fluorescent indicator displacement assays (for example, Scheme 1).[39,40] The use of a variety of receptor–indicator



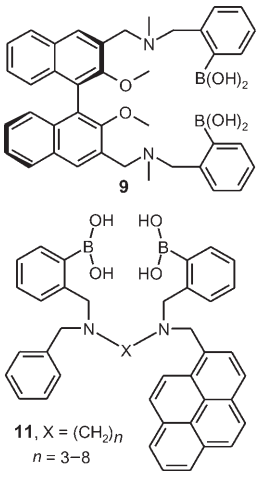
***Scheme 1.*** Enantioselective displacement assays for the fluorescent indicator 4-methylesculetin.

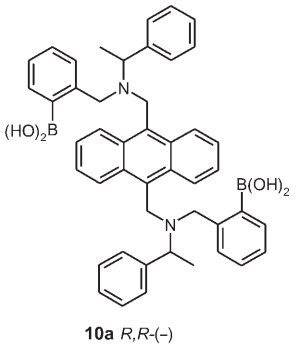
pairs (with $K_a$ values ranging from $9.4 \times 10^2\,M^{-1}$ to $5.7 \times 10^4\,M^{-1}$ (for example: $K_a \approx 3 \times 10^4\,M^{-1}$ for **7**·**8**) in 75% methanolic aqueous solution buffered with 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES) buffer at pH 7.4) provided a broad dynamic range, over which these assays are effective for analyzing chiral α-hydroxy acid and diol samples. The determined *ee* values were in good agreement with the actual numbers.[39]

James and co-workers reported dipodal diboronic fluorescent[41,42] and electrochemical[43] sensors **9**–**11** for saccharides and sugar acids in aqueous media. The chiral fluorescent sensor **10** is highly sensitive, chemoselective, and enantiose-

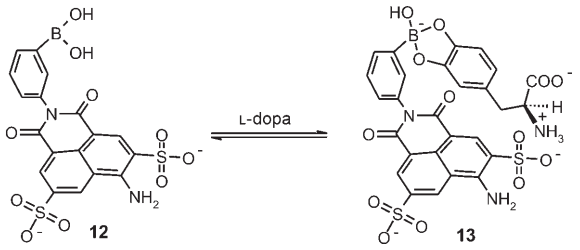
  

lective to D- or L-tartaric acid ($K_a$ value up to $8.3\times10^5\,M^{-1}$), D-glucaric acid ($K_a$ value up to $5.4\times10^5\,M^{-1}$), D-gluconic acid ($K_a$ value up to $5.4\times10^4\,M^{-1}$) in 52.1 % methanol in water (pH 5.6; 50 mM NaCl ionic buffer).[41]




The combination of a boronic acid and sulfonium groups in one receptor led to a good binding of L-dopa in aqueous solution ($K_a = 1.6\times10^3\,M^{-1}$, 0.1M 3-(*N*-morpholine)propanesulfonic acid (MOPS) buffer, pH 7.2; Scheme 2).[44]



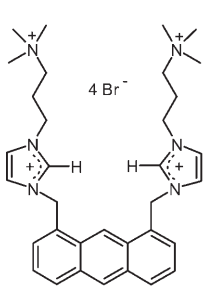

***Scheme 2.*** Binding of L-dopa.

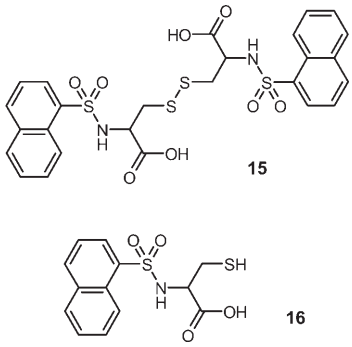
### 2.3. Simple Dipodal Receptors

Water-soluble dipodal receptors have been prepared by direct combination of two charged,[45,46] acidic,[47] or organometallic groups[48–50] or by their attachment to a (fluorescent) scaffold. The multivalent interactions[51] provided by two properly located binding sites result in them showing good recognition properties, despite the competitive influence of the water.

Receptors containing imidazolium groups are suitable for anion recognition in aqueous media.[45,46] For example, water-soluble imidazolium-substituted anthracene derivative **14** shows selective binding of GTP over ATP, ADP, AMP, pyrophosphate, $H_2PO_4^-$, $F^-$, and $Cl^-$ ions. The selectivity for GTP ($K_a = 8.7\times10^4\,M^{-1}$ in aqueous solution containing 10 mM HEPES buffer, pH 7.4) is about six times that of ATP, and over 100 times those for ADP, AMP, pyrophosphate, $H_2PO_4^-$, $F^-$, and $Cl^-$ ions.[46]

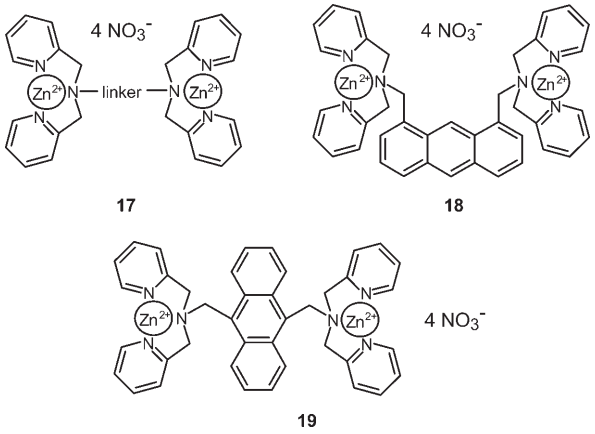
The dynamic combinatorial library approach has been successfully used to generate dipodal receptors for the




efficient multivalent binding of the protein CaM (calcium transducer calmodulin), which regulates a wide range of physiological processes by binding to numerous enzymes.[47] A library of fifteen components was generated from five symmetric disulfides at pH 7.5 in aqueous media. The largest amplification was observed for **15** upon addition of CaM. This bidentate ligand binds CaM ($K_d \approx 10\,\mu M$, CaM/**15** 1:1) more efficiently than the monofunctional thiol **16** ($K_d \approx 814\,\mu M$, CaM/**16** 1:2) in an aqueous buffer solution.[47]

The small dipodal receptors **17** bearing dipyridylamine–zinc(II) binding sites strongly complex a variety of phosphorus-containing anionic species under neutral aqueous conditions through metal–ligand interactions.[48–50] Variation of



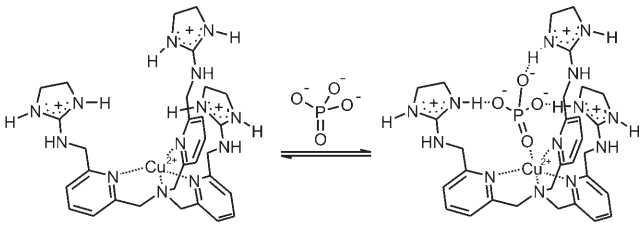

the linker, and hence, the distance between the binding sites, in **17** resulted in a very effective receptor for a bisphosphorylated peptide. It is also able to disrupt the phosphoprotein–protein interactions effectively as a consequence of its very high binding affinity to the phosphoprotein ($K_a$ values up to $8.1\times10^6\,M^{-1}$).[49] Receptor **18** displays a very high binding affinity toward phosphate-containing species: it binds adenosine triphosphate and adenosine monophosphate with $K_a > 10^7\,M^{-1}$ in aqueous buffer solution (50 mM HEPES, 50 mM NaCl, pH 7.2).[50] It also shows a very high selectivity for monoalkyl phosphates ($K_a \approx 1\text{–}3\times10^5\,M^{-1}$ in 10 mM HEPES, pH 7.2)[50] over dialkyl phosphates (too low to be detected),[48,50] because of the possibility of multivalent binding in the former case. Receptors **18** and **19** have a high affinity toward O-phosphorylated tyrosine ($K_a \approx 3.1\times10^5\,M^{-1}$ and $\approx 6.1\times10^5\,M^{-1}$, respectively) and recognize peptides

containing a phosphorylated tyrosine moiety with $K_a$ values of up to $8.9\times10^5\,M^{-1}$ (in aqueous HEPES buffer solution, pH 7.2).[50] Anthracene-based receptor **19** preferentially binds glycosyl pyrophosphate monoesters in the presence of the corresponding diesters ($K_a \approx 3.8\times10^5\,M^{-1}$ and $4.4\times10^3\,M^{-1}$ for mono- and diesters, respectively), which allows effective real-time monitoring of glycosyltransferase activity under neutral aqueous conditions.[48]

## 3. Tripodal Receptors

The tripodal water-soluble receptors **20**–**22** have been prepared by functionalization of trisubstituted amine or 1,3,5-triethylbenzene platforms with amine, pyridine, ammonium, and guanidinium groups or their metal complexes. Anslyn and co-workers designed receptors that provide excellent shape, size, and charge complementarity to phosphate (Scheme 3)

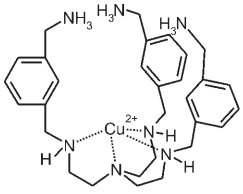


**20**

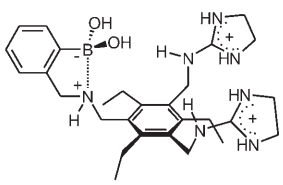
***Scheme 3.*** Phosphate binding to receptor **20**.

and arsenate which allow selective binding of these anions in water at neutral pH ($K_a$ value of **20** with $HPO_4^{2-}$: $1.5\times10^4\,M^{-1}$, of **20** with $HAsO_4^{2-}$: $1.7\times10^4\,M^{-1}$, and of **20** with other anions studied: $<100\,M^{-1}$).[52,53] Receptor **20** has been used in an indicator displacement assay to determine the phosphate concentrations in both horse serum and human saliva at biological pH values.[53]

Tritopic receptors such as **20**–**22** efficiently recognize and distinguish highly functionalized guests in water. For example,



**21**

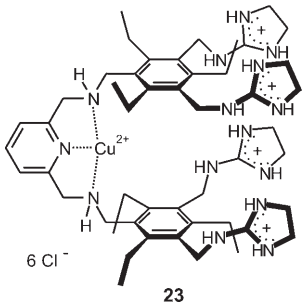


**22**

receptor **21** binds tricarballate and 1,2,3,4-butanetetracarboxylate with $K_a \approx 1.8\times10^4$–$2.2\times10^5\,M^{-1}$ in aqueous solution (HEPES buffer, pH 7.4), which is 1–3 orders of magnitude higher than the binding of glutarate and acetate ($K_a \approx 3\times10^2$–$2\times10^3\,M^{-1}$).[54] A variety of modified triethylbenzene receptors functionalized with guanidinium and/or boronic acid substituents (for example **22**, contains two 2-aminoimidazolium substituents and one boronic acid function intramolecularly complexed with a nitrogen atom) have been studied.[55–58] These receptors efficiently complex citrate, tartrate, and malate (in the case of receptor **21** with $K_a = 2.0\times10^5\,M^{-1}$, $5.5\times10^4\,M^{-1}$, and $4.8\times10^4\,M^{-1}$, respectively, in 75% methanol in water, 5–10 mM HEPES, pH 7.4), respectively.[56] If at least one boronic acid substituent is present on the scaffold, then recognition of saccharides (glucose, fructose) and aromatic polyols (gallate, 3,4-dihydroxybenzoate, catechin, etc) takes place with $K_a \approx 1.4\times10^2$–$2.0\times10^4\,M^{-1}$ (in methanol/water = 3:1, 5–10 mM HEPES, pH 7.4).[56] These receptors also allow differentiation between the structurally related tartrate and malate in aqueous methanol solution.[57] Studies in aqueous buffer solution revealed an enthropically driven aggregation of citrate with the trisimidazolium analogue of **22** upon dilution.[58]

The attachment of three pyrrologuanidinium moieties to the triethylbenzene scaffold resulted in an excellent receptor for tricarboxylates in water: benzene-1,3,5-tricarboxylate (trimesic acid tricarboxylate) is bound with $K_a = 3.4\times10^5\,M^{-1}$ (pH 6.3), citrate with $K_a$ values up to $2.3\times10^5\,M^{-1}$ in water and $8.4\times10^4\,M^{-1}$ in bis-Tris buffer solution, and Kemps triacid tricarboxylate with $K_a = \approx 5.1\times10^4\,M^{-1}$ (bis-Tris buffer solution).[59]

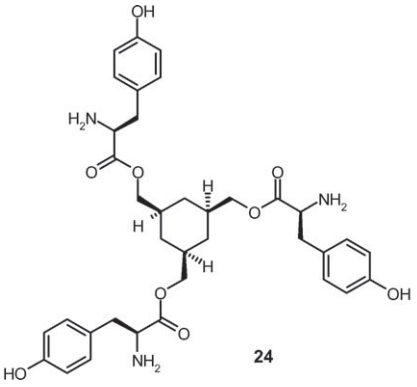
Receptor **23**, which is obtained by the combination of two triethylbenzene scaffolds functionalized with guanidinium substituents through a copper–pyridine binding center, is selective for 2,3-biphosphoglycerate ($K_a = 8\times10^8\,M^{-1}$ in water/methanol (1:1) at pH 4, 25 °C). The binding of phos-



**23**

phoenolpyruvate, 2-phosphoglycerate, and 3-phosphoglycerate, which are analogues of 2,3-biphosphoglycerate, is more than one order of magnitude weaker ($K_a = 4.7\times10^6$–$1.3\times10^7\,M^{-1}$). The complexation of other types of anions, such as β-glycerophosphate ($K_a = 6\times10^4\,M^{-1}$) and acetate ($K_a = 7\times10^3\,M^{-1}$) is even 4–5 orders of magnitude weaker.[60]

The amine–phenol binding pattern, which only exists in a small pH range in water, has been used for the construction of a pH-switchable receptor.[61] The tripodal cyclohexane-based receptor **24** prefers the cuplike structure **25** in the range of $9.2 < pH < 10.5$, but at other pH values it adopts an open conformation. Small cations and anions are bound in the cuplike structure in water ($K_a \approx 4.9\times10^2\,M^{-1}$, $6.8\times10^2\,M^{-1}$, $1.4\times10^3\,M^{-1}$, and $1.9\times10^3\,M^{-1}$ for the binding of $Cl^-$, $Br^-$, $Zn^{2+}$, and $Cd^{2+}$, respectively, at pH 9.5). The limited space of the self-assembled cavity of **25** means that larger ions, such as sulfate and nitrate, cannot be complexed at all.[61]

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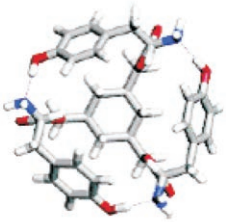

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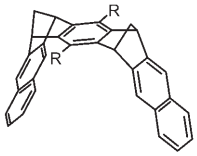

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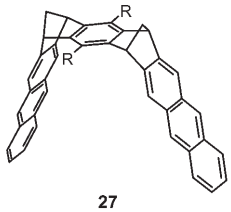

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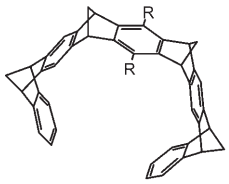

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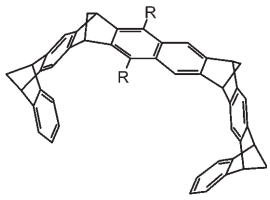

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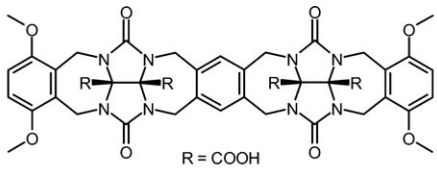
## 4. Molecular Tweezers, Clips, and Pinwheels

Tweezers and clips are two-armed acyclic receptors with flexible cavities which can wrap around guests or clip them between two rigid molecular planes, respectively. The molecular clips[62–65] **26** and **27** and the tweezers[62,66] **28** and **29** have a high solubility in water as a result of the presence of methylphosphonate ($R = OPMeO_2^-$ with $Li^+$ or $Bu_4N^+$ as counterions)[62–66] or phosphate substituents ($R = OPO_3^{2-}$, as a $Li^+$ salt)[64] in the central arene ring. Clip **26** forms complexes in water with a variety of organic cations, such as alkyl (or aryl) pyridinium,[63,65] pyrazinium,[63,65] imidazolium,[65] thiazolium,[64] sulfonium,[64] and tetrabutylammonium.[65] Important examples of guests include the enzyme cofactor model *N*-methylnicotinamide iodide[65] as well as enzyme cofactors, such as nicotinamide adenine dinucleotide ($NAD^+$)[65] and thiamine diphosphate (TPP),[64] which are strongly bound by clip **26** ($R = NBu_4^+$) in $D_2O$ with $K_a = 8.3 \times 10^4\,M^{-1}$, $9.1 \times 10^3\,M^{-1}$, and $1.4 \times 10^4\,M^{-1}$, respectively.[64,65] Formation of the complex is driven by the inclusion of a guest between the naphthalene planes through hydrophobic, cation–π,[67] CH–π, and π–π interactions between guests (typically flat, electron-poor aromatic rings) and the naphthalene sidewalls (the distance between them is 10 Å). Ion-pair interactions between the phosphonate (or phosphate) moiety of the host **26** and the part of the guest containing a hydrogen-bonding site and positively charged quaternary ammonium or sulfonium groups also contribute. The last type of interaction is usually very weak in water, but plays an important role in the case of multivalent host–guest interactions in aqueous media.

The molecular tweezer **28** ($R = OPMeO_2Li$) is an excellent receptor for lysine and arginine which not only selectively recognizes simple protected peptides in water ($K_a$ values for AcLysOMe and TsArgOEt in $D_2O$ are $2.3 \times 10^4\,M^{-1}$ and $7.8 \times 10^3\,M^{-1}$, respectively), but is also able to bind lysine or arginine incorporated into a peptidic framework (for example, KKLVFF, the lysine-containing self-complementary central part of the Alzheimer peptide, is bound with a $K_a = 3.8 \times 10^4\,M^{-1}$ in 25 mM $NaH_2PO_4$ buffer in $D_2O/CD_3OD$ 1:1).[66]

The molecular clip **27** and tweezer **29** ($R = OPMeO_2Li$) form highly stable dimers in water ($K_a$ values in $D_2O$ at 25 °C are $2.28 \times 10^6\,M^{-1}$ ($\Delta G = -36.4\,kJ\,mol^{-1}$, $\Delta H = -87.4\,kJ\,mol^{-1}$, $T\Delta S = -51.0\,kJ\,mol^{-1}$) and $1.6 \times 10^5\,M^{-1}$ ($\Delta G = -29.7\,kJ\,mol^{-1}$, $\Delta H = -57.7\,kJ\,mol^{-1}$, $T\Delta S = -28.0\,kJ\,mol^{-1}$), respectively).[62] The dimerization of both compounds, which is strongly enthalpy-driven ($\Delta H \ll 0$) and is accompanied by an unfavorable entropy loss ($T\Delta S < 0$), represents a beautiful example of a nonclassical hydrophobic effect,[68] in which enthalpic gain originates from hydrophobic interactions.[62]

The bis(glycoluril) tweezer **30** has a high water solubility and binds dimethyl viologen ($K_a = 2.06 \times 10^3\,M^{-1}$) and a variety of mono- and disubstituted amines such as Me-$(CH_2)_n NH_2$ ($n = 2$–5) and $H_2N(CH_2)_m NH_2$ ($m = 4$–8) with $K_a$ values up to $1.52 \times 10^4\,M^{-1}$ in $D_2O$ buffered with 5 mM sodium phosphate.[69] The complexation of the alkanediamines is dependent on the chain length and arises from hydrophobic interactions between the central polymethylene part of the guest and the tweezer interior, as well as hydrogen-bonding and ion–dipole interactions between the urea oxygen atoms and the ammonium ends of the guest (for example, structure **31**).[69] The ion–dipole interaction is strongly influenced by the phosphate buffer, metal cations of which

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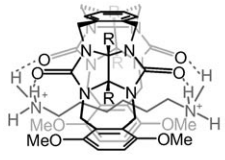

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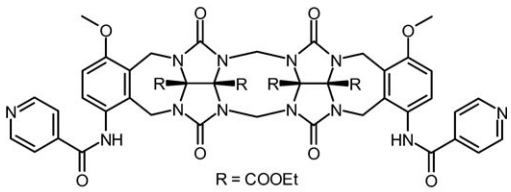


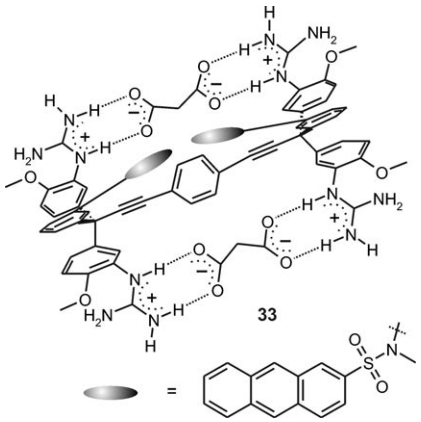

32

compete with the guests in aqueous media for complexation with the oxygen atoms.[69]

The cucurbituril tweezer **32** dimerizes isostructurally in a wide range of solvents,[70] and keeps the same association motif both in nonpolar aprotic media, such as chloroform, and in polar protic competitive solvents, such as methanol and water (dimerization of **32** in $D_2O$ $K_a = 3.6 \times 10^4\,M^{-1}$). The behavior is maintained by compensative cooperative hydrogen-bonding and π–π interactions. Hydrogen bonds provide the main self-association force in nonpolar media, while π–π interactions dominate in water.[70]

The cooperative pinwheel chemosensor **33** possesses four guanidinium recognition elements to cooperatively bind two dicarboxylates of different sizes.[71] The cooperative effect



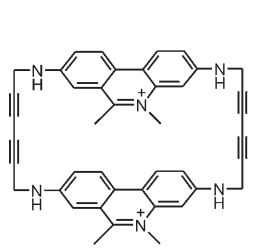

contributes to favorable binding constants for dicarboxylates in water, as well as a high degree of selectivity over monocarboxylates. This situation allows the sensing of dicarboxylates in the presence of a 1000-fold excess of monocarboxylates, such as acetate (for example, phthalate binding: Hill coefficient = 2.0, $K_a = 1.2 \times 10^9\,M^{-2}$ in a 10 mM solution of sodium acetate in water).

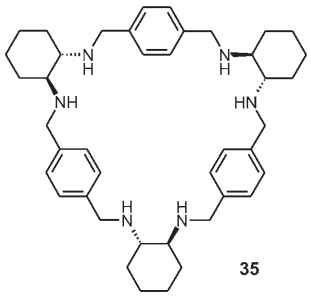
## 5. Cyclophanes

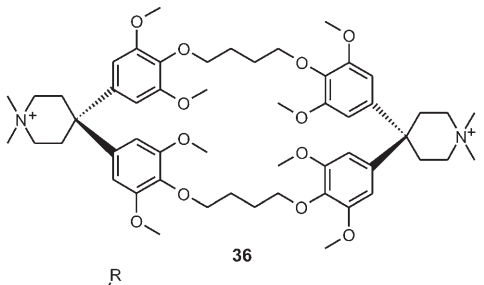
Cyclophanes are defined as molecules that have a cavity capable of binding guests.[72] The description of the host–guest behavior of cyclophanes in water will start with molecules containing several (hetero)arene moieties connected by a variety of linkers. Special examples, such as calixarenes as well as the related cavitands and carcerands, will then be described.

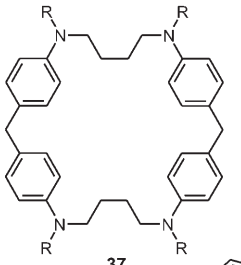
### 5.1. Cyclophanes containing Several (Hetero)Arene Moieties connected by Different Linkers

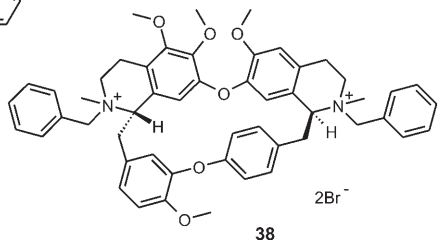
A variety of groups, such as pyridinium,[73,74] ammonium,[75,76] carboxylic,[77] phosphonic moieties, and saccharides, have been used to solubilize cyclophane scaffolds in water. The presence of adamantyl substituents and subsequent complexation with β-cyclodextrins also significantly increases the solubility of cyclophanes in water.[78] Schneider and coworkers reported pyridinium-containing cyclophane receptors that strongly bind AMP in water ($K_a = 6.3 \times 10^5\,M^{-1}$ for **34**). Complexation of AMP gives a significant fluorescent response (large increase in the emission), while complexation of GMP and UMP by **34** does not give rise to specific changes in the fluorescence spectra.[74] Receptor **35** efficiently recog-



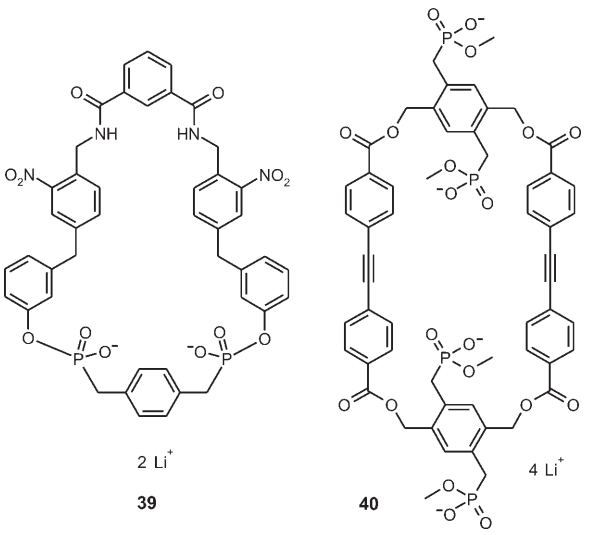

nizes benzenetricarboxylates in water: for example, the $K_a$ value for trimesate is between $1.5 \times 10^4$ and $3.9 \times 10^6\,M^{-1}$, depending on the degree of protonation of **35**.[75] Cyclophane **36** has been proposed as a substance for removing chloronaphthalenes from water: photoexcitation of complexes of cyclophane **36** and 1- or 2-chloronaphthalene in aqueous solution causes rapid dechlorination of the guest, through a reaction driven by electron transfer from the host to the excited guest, which leads to covalent attachment of the naphthyl group to the host **36**.[76] Functionalized cyclophanes **37** (with saccharide- or ammonium-containing substituents, as well as adamantane or dansyl functions solubilized by complexation with β-cyclodextrin) form strong complexes with α- and β-naphthalene sulfonate dyes ($K_a$ values up to $1.1 \times 10^4\,M^{-1}$) or pyrene ($K_a$ values up to $1.1 \times 10^5\,M^{-1}$) in neutral aqueous media.[78] The chiral dicationic N,N′-dibenzy-

lated cyclophane-type derivative of a bisisoquinoline macrocyclic alkaloid (*S*,*S*)-(+)-tetrandrine (**38**) binds amino acids (stereoselectivity $\geq 10$) and (di)carboxylates with $K_a$ values up to $135\,M^{-1}$ in water.[79]

Cyclophanes **39** and **40**, which contain exo- and endocyclic phosphinium and phosphonium groups, respectively, are good receptors for catecholamines in aqueous media.[80–82] Receptor **39** binds adrenaline, noradrenaline, and dopamine (binding constants ca. $1.5–2.5 \times 10^2\,M^{-1}$) to form 1:1 complexes in methanol/water (1:1).[81] Two guest molecules can be bound by cyclophane **40** in water. Although the binding is non-cooperative, its affinity for the guest is higher than that of receptor **39** toward catecholamines and related structures such as β-blockers with extended aromatic π surfaces ($K_a$ values up to $7 \times 10^3\,M^{-1}$ for each single complexation step or $5 \times 10^7\,M^{-2}$ for both steps).[80]

Pyrenophanes **41** substituted by various hydrophilic ammonium, hexaammonium, bis(diazoniacrown), and tetrakis[octa(oxyethylene)] functionalities show a moderate solubility in water.[83] The cationic pyrenophanes **41** are multipoint recognition hosts, which possess both a hydrophobic cavity and charged substituents, thus providing a very efficient recognition motif for guests with multiple functional groups such as nucleotides. The complexation mode (Figure 1) includes the incorporation of the (hetero)arene moiety of the guest into the cavity as a result of hydrophobic and π-stacking interactions, which are supported by electrostatic interactions between the anionic phosphate moieties and the ammonium groups of the host. The relative affinity toward nucleotides is triphosphate > diphosphate > monophosphate (for example, $K_a(ATP) = 1.0 \times 10^6\,M^{-1}$, $K_a(ADP) = 5.3 \times 10^3\,M^{-1}$, $K_a(AMP) = 1.9 \times 10^3\,M^{-1}$ in water).[83] It is spectacular that an increase in the charge of the guest has a substantial influence on the stability of the complex, despite the strong competition of the water with electrostatic interactions. This is the result of multivalent interactions[51] and excellent fitting between the host and the guest: as soon as the hydrophobic moiety of the guest is included into the pyrenophane, a high effective molarity[84] is provided for the electrostatic complexation at the periphery.



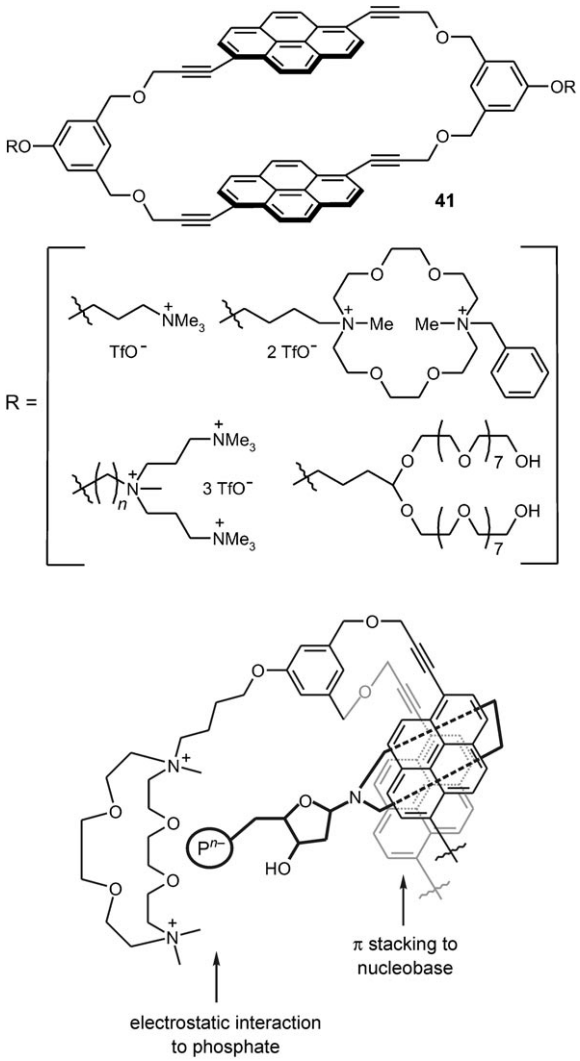
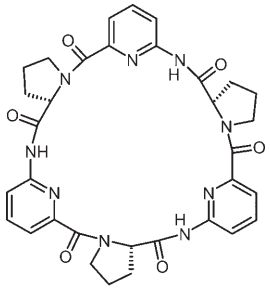




***Figure 1.*** Recognition of nucleotides by pyrenophanes **41**.

The cyclophane-like hexameric cyclopeptide receptor **42** binds small inorganic anions, such as sulfate or iodide, in aqueous media to form a 2:1 complex in which two $C_3$-symmetric receptors **42** provide six hydrogen bonds to a single desolvated anion within a sandwich-like complex.[85–88] The complexation is accompanied by a strong cooperativity: for

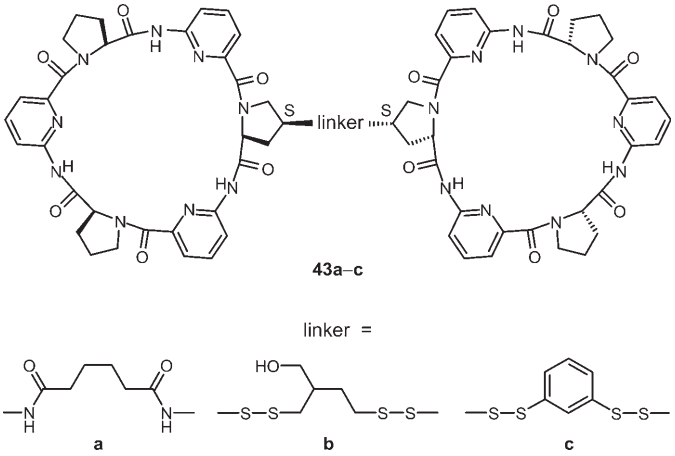


**42**

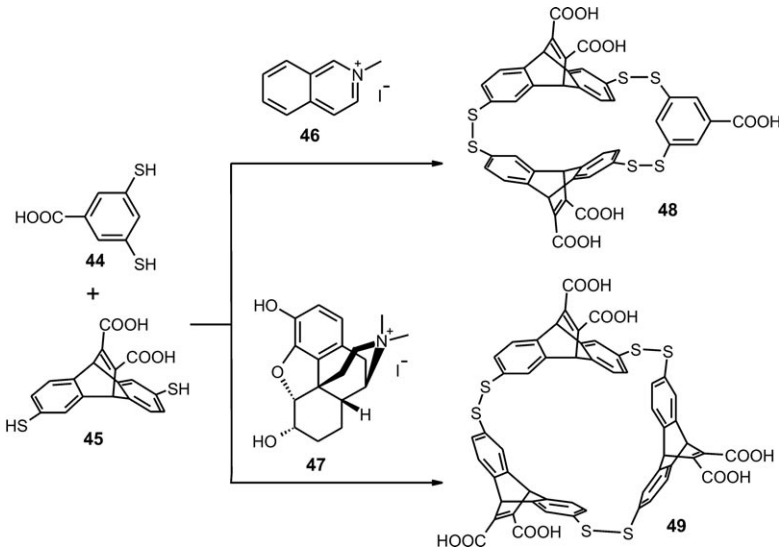
  

example, for the binding of sulfate, $K_1 \approx 3.6 \times 10^2\,\text{M}^{-1}$ and $K_2 \approx 8.8 \times 10^3\,\text{M}^{-1}$ (in $D_2O/CD_3OD$ 1:1), so that the $K_2$ value is 98 times higher than the statistical value.[88] Such an increase in the binding strength results from hydrophobic receptor–receptor interactions,[88] which become significant even in a mixture of water with an organic solvent because of the perfect positioning of the receptors around the included anion.

An excellent strategy to further increase the binding affinity of receptors such as **42** in aqueous media was realized by their transformation from trivalent **42** to the hexavalent oysterlike cyclopeptide **43a** by introduction of a linker; this arrangement significantly increases the effective molarity[84] for complexation with the second cyclopeptide.[86] Combination of this multivalent[51] strategy with dynamic combinatorial optimization of the length and size of the linker yielded cyclopeptides **43b** and **43c**, which to date are the strongest receptors for inorganic anions in aqueous media. For example, iodide and sulfate are complexed by **43c** in acetonitrile/water (2:1) with $K_a = 5.6 \times 10^4\,\text{M}^{-1}$ and $6.7 \times 10^6\,\text{M}^{-1}$, respectively.[87]



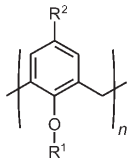

Sanders and co-workers used their approach to dynamic combinatorial disulfide libraries for a guest-amplified cyclophane synthesis in water.[89–91] The mercaptanes used form a variety of disulfides in the presence of oxygen and a small amount of base. The disulfide exchange takes place efficiently under mild conditions in the presence of catalytic amounts of thiol.[89] For example, the mixture of disulfides formed from mercaptanes **44** and **45** contains less than 10% of cyclophanes **48** and **49**, but addition of methylquinolinium iodide (**46**) or methylmorphinium iodide (**47**) leads to the formation of macrocycles **48** and **49**, respectively, in good to excellent yields (Scheme 4).[90] The hosts have a high binding affinity toward the amplifiers: for example, $K_a$(**46**@**48**) $= 2.5 \times 10^5\,\text{M}^{-1}$ ($\Delta G = -30.8\,\text{kJ mol}^{-1}$, $\Delta H = -41.6\,\text{kJ mol}^{-1}$, $T\Delta S = -10.8\,\text{kJ mol}^{-1}$) and $K_a$ (**47**@**49**) $= 7.1 \times 10^5\,\text{M}^{-1}$ ($\Delta G = -33.4\,\text{kJ mol}^{-1}$, $\Delta H = -47.8\,\text{kJ mol}^{-1}$, $T\Delta S = -14.4\,\text{kJ mol}^{-1}$) in aqueous 10 mM borate buffer (pH 9.0). The binding is enthalpy-driven and opposed by entropy, which suggests that binding is dominated by electrostatic interactions including cation–π interactions and possibly salt-bridge formation.[90]




***Scheme 4.*** Guest-amplified synthesis of cyclophanes.

### 5.2. Calixarenes

Calix[n]arenes (**50**, $n = 4$–8) are among the most versatile and useful building blocks in supramolecular chemistry.[92,93] Water-soluble calixarenes[94] have been made by attachment of sulfonates,[95] carboxylic acids, phosphonates, amines, guanidinium groups,[96] peptides,[97] and saccharides[97–100] either directly or through linkers to the upper or lower rims. More recently, calixarenes have become attractive scaffolds to make multivalent amphiphiles useful in both biological and chemical applications.[93,101]




The tetrapropoxycalix[4]arene **50** ($R^1$ = Pr, $R^2$ = H), a simple calix[4]arene bearing only propyl substituents at the oxygen atoms to maintain the cone conformation and having no substituents at the upper rim, has a very low solubility in water.[102] However, in a 7:3 mixture of water with organic solvents its solubility is at least 0.4–0.5 mmol $L^{-1}$, which is sufficient for the determination of its binding constants with a variety of substituted uracil and adenine derivatives by reverse-phase HPLC. For example, uracil, 5-nitrouracil, and adenine are bound by **50** ($R^1$ = Pr, $R^2$ = H) with $K_a \approx 8.9 \times 10^3\,\text{M}^{-1}$, $5.4 \times 10^4\,\text{M}^{-1}$, and $1.2 \times 10^4\,\text{M}^{-1}$, respectively, (in water/methanol/acetonitrile/tetrahydrofuran 70:15:10:5), respectively.[102] When hydrophobic interactions as well as NH–π interactions are responsible for the formation of the host–guest complex,[102] one can expect a very efficient recognition of (substituted) uracil and adenine in water by a properly functionalized calix[4]arene.

Calix[n]arenes with sulfonate substituents at the upper rim are highly solubile in water and form complexes with a variety of charged and neutral guests. Calix[4]arene tetrasulfonate **50** ($n = 4$, $R^2 = SO_3H$, $R^1$ = H) binds small neutral organic molecules such as acetonitrile, acetone, butanone, and 1-propanol ($K_a \approx 15$–$65\,\text{M}^{-1}$; pD 7.3),[103] benzene derivatives such as benzaldehyde and iodobenzene ($K_a \approx 8$–$191\,\text{M}^{-1}$; pD 7.3–7.4),[104,105] and heterocycles such as 2,2′-bipyridine

($K_a \approx 10260\,M^{-1}$; pH 2.0)[106] and 4,4′-bipyridine ($K_a \approx 1185\,M^{-1}$; pH 2.0)[106] to form 1:1 complexes in water. Monovalent monoatomic cations ($K^+$, $Rb^+$, $Cs^+$, $Tl^+$) form inclusion complexes in the cavity of **50** ($n=4$, $R^2=SO_3H$, $R^1=H$) as a result of the favorable enthalpies ($\Delta H<0$) of the cation–π interactions; the $K_a$ value for the binding of $Tl^+$ in aqueous solution adjusted to pH 2 is $460\,M^{-1}$.[107] Divalent cations bind to the sulfonate groups outside the cavity. The complexation of these cations ($K_a = 2\times10^3$–$1.6\times10^4\,M^{-1}$) is purely entropy driven ($T\Delta S \gg 0$) and accompanied by an unfavorable enthalpy ($\Delta H>0$), which is typical for purely ionic binding, and involves dehydration of the species upon formation of the complex.[108] These hosts also bind trimethylammonium ions ($K_a \approx 2.5\times10^3$–$8\times10^4\,M^{-1}$ in $D_2O$, pD 7.3).[109–111] The inclusion process is enthalpically favored and entropically unfavored (for example, the complexation of **50** ($n=4$, $R^2=SO_3H$, $R^1=CH_2COOH$) with tetramethylammonium chloride in water, pH 7, 25 °C: $K_a \approx 3.2\times10^3\,M^{-1}$, $\Delta G=-20.1\,kJ\,mol^{-1}$, $\Delta H=-24.3\,kJ\,mol^{-1}$, $T\Delta S=-4.2\,kJ\,mol^{-1}$). The negative entropy contribution is mainly caused by a stiffening of the system upon inclusion of the guest into the host cavity.[106,110,111] The complexation of aliphatic guest molecules takes place through inclusion of the alkyl unit into the calixarene cavity,[112] which is accompanied by an upfield shift by up to 2 ppm of the methyl protons of the guest in the $^1H$ NMR spectra.[103] In the case of benzene derivatives, either the aryl moiety or the substituents can be located in the cavity.[105,109,110] Salts of sulfonated calix[4]arenes are highly solubile in water and have thus been used for the preparation of 1:1 capsules (see Section 8.1) with the tetracationic counterparts in water; the resulting capsules precipitate, since they are ion-paired, less-polar, and hence, less water-soluble.[113] Calix[5]arene pentasulfonate **50** ($n=5$, $R^2=SO_3H$, $R^1=H$ or $CH_2COO^-$) binds trimethylammonium cations ($K_a \approx 4\times10^3$–$1.3\times10^5\,M^{-1}$ in $D_2O$, pD 7.3)[109] in water in such a way that the alkylammonium group is exclusively included in the cavity. Calix[6]arene hexasulfonate **50** ($n=6$, $R^2=SO_3H$, $R^1=H$) forms complexes with 4-nitrophenol ($K_a=192.6\,M^{-1}$, $\Delta G=-5.3\,kJ\,mol^{-1}$, $\Delta H=-68.2\,kJ\,mol^{-1}$, $\Delta S=-185\,J\,K^{-1}\,mol^{-1}$; the values were determined by differential scanning microcalorimetry).[95] Calix[6]-arene functionalized with sulfonate and carboxylate groups ($n=6$, $R^2=SO_3H$, $R^1=CH_2COOH$ binds a variety of amino acids in water; among 15 examples reported, the highest binding affinity was obtained for aspartic acid, arginine, and tryptophane ($K_a=4.1\times10^3\,M^{-1}$, $3.6\times10^3\,M^{-1}$, and $2.5\times10^3\,M^{-1}$, respectively).[114] The calix[6]arene hexasulfonate also solubilizes the fullerene $C_{60}$ in water (as a 1:1 complex; logarithm of the extraction constant from toluene to water is 5.48).[115] The sulfonated calixarenes exhibit neither toxicity nor immune responses, which has resulted in their increased use in biopharmaceutical studies, such as drug delivery.[116]

Calix[4]arenes bearing dihydroxyphosphoryl groups at the upper rim are highly active enzyme inhibitors.[117,118] For example, calix[4]arenes functionalized with two chiral α-aminophosphonic acid substituents at diametrical positions on the upper rim (**50**, $R^2=H$ and $-CH(NH_2)PO(OH)_2$) show the best inhibitory activity toward porcine kidney alkaline phosphatase, with an inhibition constant $K_i=(1.7\pm3)\,\mu M$ in aqueous solution (pH 9, 0.1 M Tris-HCl buffer).[117] Calix[4]-arenes phosphorylated at the upper or lower rim also form 1:1 complexes with uracil derivatives ($K_a$ values up to $5.43\times10^4\,M^{-1}$ in solution containing 70% water),[119] and some herbicides (2,4-dichlorophenoxyacetic acid and atrazine with $K_a$ values up to $5.1\times10^3\,M^{-1}$ and $6.8\times10^3\,M^{-1}$, respectively, in water).[120] Water-soluble calix[4]arenes bearing one, two, or four ionizable dihydroxyphosphoryl groups at the lower rim ($pK_a=2.85$–$3.10$ in water/methanol 3:7) form salts with L-(−)-α-phenylethylamine and (1*S*,2*R*)-(+)-ephedrine, which are useful for their diastereomeric separation.[121] Amphiphilic calix[4]arenes having four hydrophobic acyl chains at the upper rim as well as two hydrophilic dihydroxyphosphoryloxy groups at the lower rim self-assemble at the air–water interface as stable Langmuir monolayers.[122] Calix[4]arenes substituted at the upper rim by hydroxyethoxyphosphoryl groups self-assemble into capsules with their tetracationic counterparts in polar solvents.[123] Unfortunately, the 1:1 complexes are often insoluble in water and in some cases even precipitate from methanol. A calix[4]arene containing four phosphonate groups at the upper rim complexes the hydrochloride salts of (1*R*,2*S*)-(−)-ephedrine, (1*R*,2*S*)-(−)-norephedrine, (*R*)-(−)-noradrenaline, and 2-phenylethylamine.[124] The binding constants for the 1:1 complexes vary from $45\,M^{-1}$ to $145\,M^{-1}$ in $D_2O$ buffered with 200 mM phosphate. An analogue of calix[3]arene, homocalix[3]arene, forms 2:1 complexes with $C_{60}$ in water.[125]

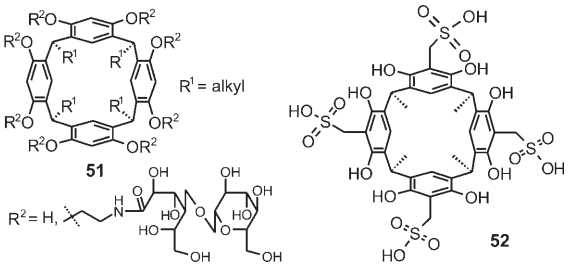
Ungaro and co-workers have studied a variety of calix[4]-arene-based glycoclusters,[97,99,100] which, because of the cluster glycoside effect,[126] bind a variety of proteins, such as cholera toxin,[99] concavalin A,[100] and peanut lectin[100] in aqueous media. Simultaneous complexation of proteins and anions takes place in the glycoclusters, in which the saccharide functions are connected to the calix[4]arene scaffold by a thiourea linker.[100]

### 5.3. Resorcin[4]arenes

Resorcin[4]arenes **51** ($R^1=$ alkyl, $R^2=H$) are macrocyclic molecules containing eight hydroxy groups at the upper rim that form intramolecular hydrogen bonds.[127] Resorcin[4]-arenes **51** ($R^1=C_5H_{11}$) containing eight saccharide moieties form small micelle-like nanoparticles ($d\approx3$ nm) covered with saccharide functionalities in water. These glycoclusters can interact with biological saccharide receptors and exhibit unprecedented hydrogen-bonding capacities; they are agglutinated with $Na_2HPO_4$ and assemble on plasmid DNA in a number-, size-, and shape-controlled manner to give artificial glycoviral particles ($d\approx50$ nm) capable of transfection.[128,129]

Water-soluble sulfonated resorcin[4]arene **52**[130–133] recognizes amino acids in aqueous solution ($K_a$ values up to $150\,M^{-1}$, pD 7.2).[130] The tetrasodium salt of **52** strongly binds organic and inorganic ions (methylpyridinium: $K_a \approx 10^5\,M^{-1}$),[131] as well as differently sized and shaped metal complexes as a result of the combination of electrostatic, hydrophobic, and CH–π host–guest interactions in neutral and basic aqueous solution ($[Co(histidine)_2]^+$, $[Co(en)_2$-

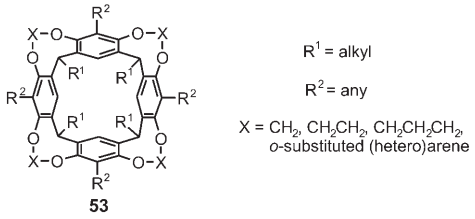
  




$(C_2O_4)]^+$ (en = ethylenediamine), and $[K([18]crown-6)]^+$: $K_a \approx 8 \times 10^5\,M^{-1}$, $1.3 \times 10^5\,M^{-1}$, and $1 \times 10^4\,M^{-1}$, respectively, in alkaline aqueous media).[132]

### 5.4. Cavitands

Cavitands are macrocyclic compounds that consist of multiple arene rings covalently linked in a highly constrictive manner to give a well-formed hydrophobic cavity.[134] The parent cavitands **53** ($X = CH_2$, $R^1$ = alkyl, $R^2$ = H, alkyl) are insoluble in water. Charged groups,[135–137] saccharide functions,[138,139] and dendritic oxo substituents[136] have been introduced to the upper and bottom rims to make them soluble in aqueous media. Water-soluble cavitand **53** ($R^1 = O(CH_2)_3OPO_3HNH_4$, $R^2$ = Me) binds acetone, acetonitrile, toluene, benzene, chloroform, ethyl acetate, methyl acetate, and methyl propionate to form 1:1 complexes ($K_a \approx 19$–$270\,M^{-1}$) in $D_2O$ (50 mM $(NH_4)_2CO_3$, pD 9.4).[135]

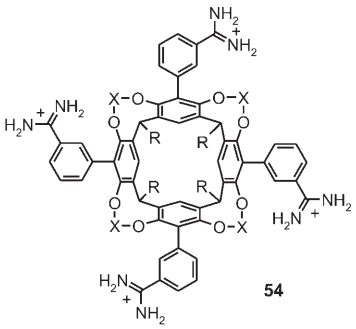



We have reported thiourea-based cavitand anion receptors **53** (R = Me, $R^1 = CH_2NHCSNH\text{-}R^2$, $R^2$ = glucose, galactose, or cellobiose; R = Me, $R^1 = CH_2S$-glucose), the water solubility of which is 0.5–0.8 mM in the case of the monosaccharide derivatives, or > 300 mM in the case of the cellobiose one.[138,139] These receptors bind inorganic ions ($Br^-$, $I^-$, $HSO_4^-$, $NO_3^-$) in MeCN/$H_2O$ (1:1) with $K_a \approx 78$–$186\,M^{-1}$, as determined by a newly developed ESI-MS method.[138] A microcalorimetric study of acetate binding by **53** (R = Me, $R^1 = CH_2NHCSNH\text{-}R^2$, $R^2$ = glucose, galactose) showed that the complexation has an unfavorable enthalpy and is entropically driven ($K_a = (2.15 \pm 0.4) \times 10^3\,M^{-1}$, $\Delta G = -19.0\,kJ\,mol^{-1}$, $\Delta H = 2.9\,kJ\,mol^{-1}$, $\Delta S = 73.4\,J\,K^{-1}\,mol^{-1}$) in $H_2O$/MeCN (1:1). However, in dry acetonitrile, the acetate complexation is enthalpy driven.[139]

Our research group has carried out a systematic investigation of the solubilities and binding properties in water of cavitands functionalized at the upper rim with dendrimers, amines, amino alcohols, pyridiniums, and pyraziniums.[136] These cavitands show a high affinity for phenol, *p*-cresol ($K_a$ values up to $1.7 \times 10^4\,M^{-1}$), and benzene ($K_a$ values up to $6.9 \times 10^3\,M^{-1}$) in $D_2O$.[136]

The cavity of the classical cavitand **53** is much smaller than that of cucurbituril and the metal–organic cages described by Fujita and co-workers (see Section 8.3). It can accommodate only one molecule of water at −50 °C in water-saturated $CD_2Cl_2$ ($K_a \approx 70\,M^{-1}$).[140]

Cavitands **53** that have a X = -$CH_2CH_2$- or -CHR=CHR- (usually *ortho*-substituted (hetero)aromatic compounds) between the resorcinarene oxygen atoms rather than a $CH_2$ group have a larger cavity and, hence, show a different complexation behavior. Diederich and co-workers have shown that tetraamidinium-functionalized cavitand **54** is a very good receptor for benzene dicarboxylates and nucleotides in water.[141] 5-Nitro- and 5-methoxy-1,3-benzenedicarboxylates form 1:2 complexes with $K_{a1} = 14.8 \times 10^3\,M^{-1}$, $K_{a2} = 3.8 \times 10^3\,M^{-1}$ and $K_{a1} = 8.6 \times 10^4\,M^{-1}$, $K_{a2} = 7.7 \times 10^3\,M^{-1}$, respectively. In the case of the 1:2 complexes with isophthalate, one of the guest molecules is included with the less-polar segment of its phenyl ring in the receptor cavity, while the second guest molecule forms an ion-paired complex outside. The complexation of the second isophthalate is completely suppressed in aqueous buffer solution, thus resulting in formation of a 1:1 complex ($K_a$ values for **54** with 5-nitro- and 5-methoxy-1,3-benzenedicarboxylates are $12.2 \times 10^3\,M^{-1}$ and $\approx 1.2 \times 10^5\,M^{-1}$, respectively, in $D_2O$ containing Tris/HCl, pH 8.3). 5-Methoxyisophthalate is bound about 5–10-times stronger than 5-nitroisophthalate in both water and in aqueous buffer solution. Among 11 nucleotides studied, AMP, ADP, and ATP form the strongest complexes with **54**. The complexation strength increases with increasing guest charge: the $K_a$ values increase in the series AMP < ADP < ATP ($K_a = 1 \times 10^4\,M^{-1}$, $4.87 \times 10^4\,M^{-1}$, and $6.6 \times 10^5\,M^{-1}$, respectively, in $D_2O$ containing Tris/HCl, pH 8.3; a 1:1 complex was observed in all cases).

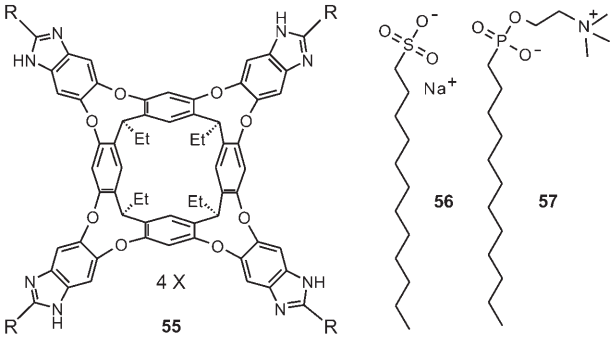



X = -$CH_2CH_2$-, R = $(CH_2)_3(OCH_2CH_2)_3OMe$

Rebek and co-workers have studied the molecular recognition in aqueous media of a variety of broad deep-cavity cavitands, such as **55**, which were made water-soluble by the attachment of carboxylate,[142–145] ammonium,[146,147] or amino[148] groups. For example, cavitand **55** ($R = CH_2COO^-$), which has a solubility of 5 mM in water, forms complexes with a variety of guests such as *S*-nicotinium, quinuclidinium ($K_a > 10^4\,M^{-1}$), tetraalkylammonium bromides ($3.8 \times 10^3$–$1.2 \times$

$10^4\,M^{-1}$), L-carnitine ($1.5\times10^2\,M^{-1}$), choline chloride ($2.6\times10^4\,M^{-1}$), acetylcholine chloride ($1.5\times10^4\,M^{-1}$).[142–144] Adamantane dissolves in an aqueous solution of **55** ($R=CH_2COO^-$) upon sonication; amantadine hydrochloride and rimantadine hydrochloride also form stable 1:1 complexes with **55** ($R=CH_2COO^-$) in water with binding constants of $1.1\times10^3\,M^{-1}$ and greater than $10^4\,M^{-1}$, respectively.[143] In these complexes the hydrophobic adamantane moiety is bound deeply within the cavity, while the primary amines are directed toward the tetracarboxylate rim and the solvent.[143] Cavitand **55** ($R=CH_2COO^-$) is an efficient phase-transfer catalyst. It transfers a hydrophobic reactant such as *N*-adamantylmethylenesuccinimide from dichloromethane to water. After reaction, when the guest becomes water-soluble, the host **55** readily releases it.[149]



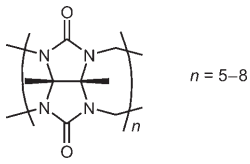

$R=-CH_2COO^-$, $-p\text{-}CH_2C_6H_4COO^-$; $X=Na^+$;
$R=-CH_2NH_3^+$; $X=Br^-$;

Cavitand **55** ($R=\text{-}CH_2COO^-$) forms complexes with the surfactants[145] **56** and **57** so that the long alkyl chains of the guests spontaneously form a helix upon encapsulation.[142] Alkanes, from pentane to dodecane, are solubilized in water by brief sonication in an aqueous solution of cavitand **55** ($R=\text{-}CH_2COO^-$). They are bound in a helical manner, but in contrast with surfacatants **56** and **57**, they tumble rapidly on the NMR timescale inside the binding pocket.[150]

Cavitand **55** ($R=p\text{-}CH_2C_6H_4COO^-$) exists mainly in the folded-"vase" conformation in aqueous solution at concentrations of less than 1 mM and forms complexes with cyclopentane, cyclohexane, and cycloheptane with $K_a>10^4\,M^{-1}$.[151] Its *para*-$C_6H_4$ substituents function as rotating doors, which increase the selectivity for small guests (for example, cyclopentane/cycloheptane 16:1) and reduce the exchange rate of small guests in and out of the cavitand in water.[151] Cavitand **55** ($R=CH_2NH_3^+$) functionalized with four ammonium groups is soluble in water at pH < 4.0 up to concentrations of 4 mM, and its 1 mM solution has a pH value of 2.6.[147] In the presence of cosolvents such as DMSO, THF, or methanol, the receptor has a vase conformation and can efficiently differentiate between functionalized adamantanes bearing carboxylate and ammonium groups. For example, 1-adamantanecarboxylic acid and 1-adamantaneacetic acid are bound very well by this receptor with $K_a=3.5\times10^3\,M^{-1}$ and $2.4\times10^3\,M^{-1}$, respectively ($D_2O$/[$D_6$]DMSO (3:1), pH 2.7), but no complexation of rimantadine or amantadine, which are protonated at pH 2.7, was detectable because of a charge repulsion between the ammonium functionality of the adamantane guest and the four positively charged groups at the upper rim of cavitand **55** ($R=CH_2NH_3^+$).[147]

## 6. Cucurbit[n]urils and Their Analogues

Cucurbiturils **58** are macrocyclic compounds made by an acid-catalyzed condensation reaction of glycoluril and formaldehyde. Characteristic structural features of cucurbiturils **58** are the hydrophobic cavity and the polar carbonyl groups surrounding the portals.[152,153] Cucurbit[5]uril and cucurbit-




[7]uril are quite soluble in water ($2–3\times10^{-2}$ M), while cucurbit[6]uril and cucurbit[8]uril are poorly solubile in water. However, all the cucurbiturils are soluble in acidic water, as well as in an aqueous solutions of alkali metals, presumably because of protonation or coordination of the metal ions to the carbonyl oxygen atoms. The solubility of cucurbiturils in common organic solvents is less than $10^{-5}$ M, and therefore the host–guest chemistry of cucurbiturils has mainly been studied in aqueous media. Several intermolecular interactions promote the binding of guests by cucurbiturils. First, similar to cyclodextrins, a hydrophobic effect applies: this composite effect is derived from the interplay between the release of "high-entropy water" upon inclusion of nonpolar organic residues and concomitant differential dispersion interactions inside the cavity and in the bulk water. Second, ion–dipole interactions of metal cations or organic ammonium ions with any of the two ureido carbonyl rims may come into play, while hydrogen-bonding interactions prevail less frequently. As a peculiarity, the complexation of metal cations at the ureido rims (which is often required to enhance solubility) can lead to ternary supramolecular complexes composed of host, included guest, and associated metal ion. In fact, it has been suggested that the cations function as "lids" to seal the portal and promote binding.[153]

Variation of the sizes of the cavity and the portal leads to a variety of cucurbiturils with different molecular recognition properties. Encapsulation of several (different) guests is even possible in the larger cucurbiturils, which leads to the possibility of chemical reactions of the guests within the cavity. Electrochemically induced reversible substitution of the guests from the cavity has been used for the "construction" of molecular machines.[153–156]

The smallest homologue, cucurbit[5]uril, can encapsulate small species such as $N_2$, $O_2$, or Ar in its cavity and binds $Pb^{2+}$ in water/formic acid (1:1) or in water ($K_{a1}>10^9\,M^{-1}$, $K_{a1}\times K_{a2}>10^{17}\,M^{-2}$) with a very high selectivity ($>10^{5.5}$) over

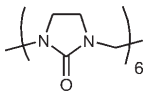
alkali, alkaline-earth, $NH_4^+$, and $Cd^{2+}$ cations.[157] Two $NH_4^+$ ions can completely seal both the openings of cucurbit[5]uril.

Cucurbit[6]uril forms very stable complexes with protonated diaminoalkanes ($^+NH_3(CH_2)_nNH_3^+$, $n = 4$-7, $K_a > 10^5\,M^{-1}$), so that the hydrophobic methylene chain of the guest is accommodated within the host cavity. The ammonium groups are positioned at the entrances and are involved in hydrogen-bonding and ion-dipole interactions with the cucurbit[6]uril oxygen atoms.[152] Cucurbit[6]uril also forms moderately stable complexes with protonated aromatic amines such as *para*-methylbenzylamine ($K_a \approx 3 \times 10^2\,M^{-1}$; the *ortho* and *meta* isomers are not included) and protonated cyclohexylamine.[158] It also encapsulates neutral molecules such as tetrahydrofuran ($K_a = 1700\,M^{-1}$) or Xe ($K_a \approx 200\,M^{-1}$) in an aqueous $Na_2SO_4$ solution.[159]

The larger cavity of cucurbit[7]uril means that it forms 1:1 complexes with ammonium-functionalized adamantane or ferrocene,[160] as well as viologen dications[161–163] and 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)naphthalene. Rimantadine is bound remarkably strongly by cucurbit[7]uril with $K_a \approx 4.23 \times 10^{12}\,M^{-1}$ (in aqueous buffer, pD 4.74).[160] This incredibly high binding constant results from a perfect fit of the adamantyl moiety of the guest in the cavity of cucurbit[7]uril and through interaction of the carbonyl groups of the host with the ammonium group perfectly positioned at the entrance. Cucurbit[7]uril can form complexes with viologen dications ($K_a \approx 10^5\,M^{-1}$ in water) in two different ways: methyl and ethyl viologen dications form inclusion complexes in which the viologen is located within the cavity, while butyl (and other viologens with longer aliphatic substituents on the nitrogen atom) form external complexes in which the viologen nucleus is not engulfed by the host.[162] Salts strongly influence the apparent association constant of cucurbit[7]uril with the methylviologen dication, with a more pronounced effect for solutions containing divalent $Ca^{2+}$ ions than for solutions containing monovalent $Na^+$ ions.[163] Neutral molecules such as ferrocene, cobaltocene, and carborane are readily encapsulated by cucurbit[7]uril in aqueous solution.[164] Cucurbit[7]uril also encapsulates two relatively small aromatic molecules, such as 2-aminopyridinium cations, and mediates the highly stereoselective [4+4] photodimerization of the guests in aqueous solution (Scheme 5), which leads exclusively to the anti-*trans* photodimer **59** ($K_a$ value for the encapsulation of the dimerization product by cucurbit[7]uril is ca. $8 \times 10^5\,M^{-1}$ in $D_2O$).[165]

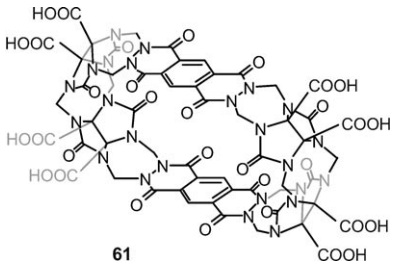
Cucurbit[8]uril encapsulates other macrocycles, such as cyclen, cyclam, and even their transition-metal complexes, in water.[166] It can also accommodate one or two methylviologen molecules; the stoichiometry of the complex is controlled by the redox chemistry of the guest.[167] The cavity of cucurbit[8]uril, which is similar to that of γ-cyclodextrin, is large enough to include two 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)naphthalene or quinolinium[168] molecules to form a 1:2 complex, or two different guest molecules such as the methylviologen dication, 2,6-dihydroxynaphthalene, or even two tetrathiafulvalene cation radicals (as a stabilized π dimer)[169] to give a 1:1:1 complex.[152] The formation of this 1:1:1 complex is driven by the markedly enhanced charge-transfer interaction between the electron-deficient and electron-rich guest molecules inside the hydrophobic cavity of cucurbit[8]uril. The ability of cucurbit[8]uril to encapsulate two molecules has resulted in it being exploited as a nanosized reaction vessel[170] and as a component of molecular machines in water.[154,156] For example, a molecular loop lock, a redox-driven molecular machine based on this phenomenon, has recently been reported.[154]

Hemicucurbit[6]uril (**60**), an analogue of cucurbit[6]uril, has a very low solubility in water; however, the solubility increases dramatically in the presence of metal or ammonium thiocyanates[171] or iodides.[172] In contrast with cucurbiturils, hemicucurbit[6]uril (**60**) is a flexible molecule which prefers an alternate conformation, in which the C=O groups of the neighboring uril moieties point in opposite directions.[171] This preferred conformation results in distinct host–guest properties: it does not form complexes with alkali, alkaline-earth, and ammonium cations at all.[173] However, it forms inclusion complexes with anions: counterion-independent binding constants for iodide ($200\,M^{-1}$) and thiocyanate ($220\,M^{-1}$) have been obtained from solubility measurements.[172] The complexation is probably due to cooperative multiple weak interactions (such as CH–anion and dipole–anion) which promote the movement of the guests from the water phase into the macrocycle, at least upon crystallization, as has been confirmed by X-ray data.[171]

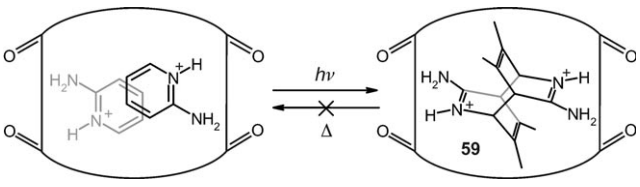


**60**

The combination of cucurbituril and cyclophane entities gives rise to receptors that possess the advantages of both types of parent molecules: solubility in water, ease of synthesis, strong binding in water, and more possibilities for monitoring binding events.[174,175] For example, receptor **61** is highly solubile in water and can tightly bind a number of organic compounds, such as α,ω-alkanediamines, substituted aromatic compounds, heterocyclic compounds, amino acids, and nucleobases in its elongated hydrophobic cavity ($5.90 \times 11.15 \times 6.92\,Å^3$) with $K_a$ values up to $8 \times 10^6\,M^{-1}$ (in 50 mM aqueous NaOAc buffer solution, pH 4.74).[174]



**61**

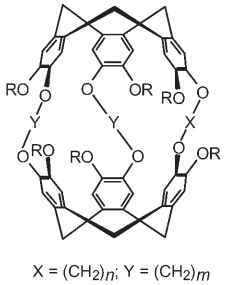


***Scheme 5.*** Photodimerization within cucurbit[7]uril.

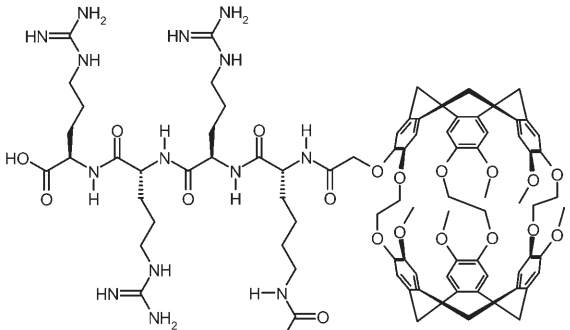
## 7. (Hemi)Carcerands

### 7.1. Cryptophane Receptors

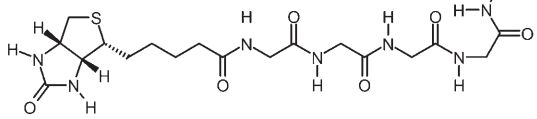
Cryptophanes **62** ($n$, $m = 2,3$) functionalized with six carboxylate groups are soluble in water at pH > 5 and bind Xe with $K_a$ values up to $6.8 \times 10^3\,M^{-1}$ (for cryptophane A: **62**; $n$, $m = 2$).[176] Cryptophane A was also solubilized in water by




**62**



**63**

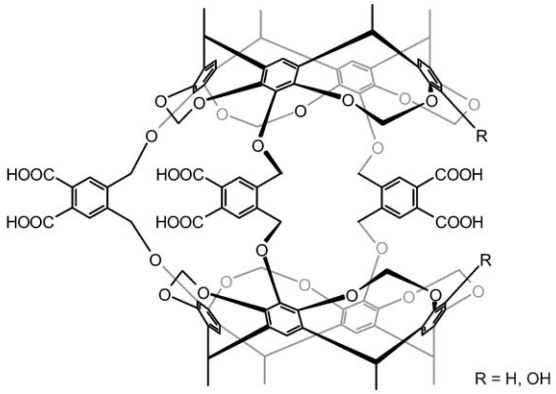


functionalization with polyguanidinium and/or polypeptide substituents (for example, as in **63**),[177] or by encapsulation in water-soluble dendrimers.[178,179] Cryptophanes can be used as xenon biosensors for magnetic resonance imaging,[177,178] in which a large difference in the $^{129}$Xe NMR shifts of free and encapsulated xenon as well as the sensitivity gain obtained with hyperpolarized xenon are used to enable the detection of a specific low-concentration target compound by NMR spectroscopy. The water-soluble cryptophane binds to a biological target through an anchor such as biotin (in **63**), which binds to the avidin part of the target molecule with $K_a \approx 10^{15}\,M^{-1}$ in water.[177]

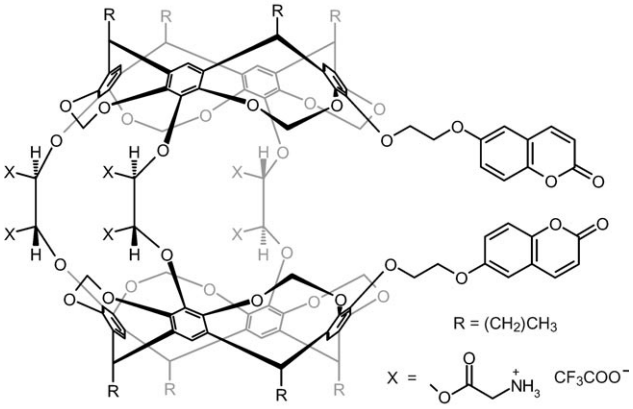
### 7.2. Cavitand-Based Hemicarcerands

Water-soluble cavitand-based hemicarcerands such as **64** with a spherical cavity of 11-Å diameter demonstrate excellent binding affinities towards a variety of guests such as xylenes, di- and trimethoxybenzenes, ferrocene, naphthalenes, norborneol, camphor, and nopinone (binding constants of $10^3$–$10^7\,M^{-1}$ in aqueous borate buffer at pH 9).[180] The complexation is driven by a significant enthalpy change and is accompanied by an unfavorable entropy change (for example, in the case of the binding of *para*-xylene by **64** (R = OH): $\Delta G = -40.5\,kJ\,mol^{-1}$, $\Delta H = -51.4\,kJ\,mol^{-1}$, $T\Delta S = -10.9\,kJ\,mol^{-1}$, $K_a = 1.3 \times 10^7\,M^{-1}$), and represents another nice example of the nonclassical hydrophobic effect.[68]

Simple molecules, such as methanol and acetone, are also encapsulated within the cavitand-based hemicarcerands **64** with $K_a$ values of $10^2$–$10^3\,M^{-1}$.[180] This finding indicates that a host–guest complexation by these receptors in water/methanol or water/acetone mixtures will be strongly decreased not only because of the smaller influence of hydrophobic interactions, but also because of a substantial competitive influence of the solvent. A study of the chiral threefold-bridged hemicarcerand **65** with six attached glycine units in protic media confirms this assumption.[181] The host is only soluble in a mixture of water and organic solvents (water/methanol/acetic acid 10:5:1) in millimolar concentrations. It encapsulates toluene, which was clearly confirmed by the appearance of the $^1$H NMR signal of the Me group from the complexed toluene at $\delta = -1.65$ ppm. Nevertheless, the $K_a$ value for the complexation of toluene by **65** is only approximately $3.7 \times 10^2\,M^{-1}$ (in water/methanol/acetic acid 10:5:1),[181] which is five orders of magnitude lower than the complexation of substituted aromatic compounds by hemicarcerand **64** in water,[180] as a result of the double "negative" influence of methanol.




**64**




**65**

## 8. Self-Assembly and Self-Sorting in Water

Self-assembly is the spontaneous, noncovalent association of two or more molecules under equilibrium conditions into stable, well-defined aggregates.[182] Water-soluble aggregates such as capsules, cyclic metal–organic arrays, and cages have

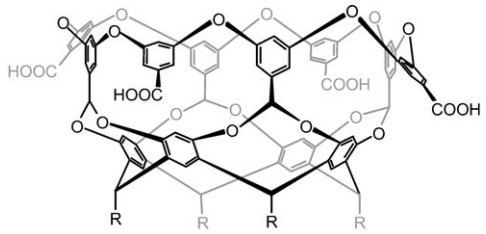
  

been realized with the help of multivalent electrostatic, hydrophobic, metal–ligand, and triple-ion interactions.

### 8.1. Capsules

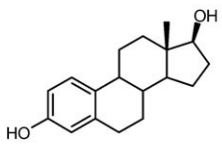
Capsules are receptors with enclosed cavities that are formed through reversible noncovalent interactions between two or more components bearing complementary functional groups.[20,183] Suitable guests template the formation of capsules and stabilize them.[20]

Two cavitand hemispheres **66**, which possess an external hydrophilic coat of eight carboxylic acid groups and a wide hydrophobic rim around the entrance to the cavity, readily self-assemble by a process driven by hydrophobic interactions.[184,185] These two hemispheres form a 1:1 capsule that encapsulates tetracene[184] or steroids, such as estradiol **67** and progesterone **68**; the apparent $K_a$ value for estradiol encapsulation in water is approximately $1\times10^8\,\text{M}^{-1}$.[185] The interaction is strongly hydrophobic, because addition of only about 20% methanol to an aqueous solution of the capsule **68@66**$_2$ leads to its dissociation.[185] The cavity of the capsule is about 1 nm wide and 2 nm high,[186] which allows the encapsulation of two molecules, such as naphthalene or anthracene.[184] In this way the effective concentration of the hydrocarbons in water is increased from $10^{-5}$–$10^{-4}$ M up to at least 3 M, and allows the observation of excimer formation in aqueous solution upon photoirradiation.[184]

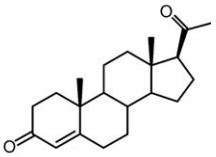



R = $CH_2CH_2COOH$

**66**




**67**




**68**

Water-soluble capsules assembled through electrostatic interactions have been prepared from other supramolecular scaffolds, such as calix[*n*]arenes,[123,187–190] trisubstituted benzene derivatives,[191] and porphyrins[192] functionalized with charged substituents. The hemispherical scaffolds are brought together by ion-pair interactions between sulfonate and pyridinium units,[192] monoalkyl esters of phosphonic acids and ammonium, pyrazolium, or imidazolium moieties,[123,193,194] and sulfonate or carboxylate groups with amidinium moieties.[187–190] Figure 2 shows a schematic representation of a capsule composed of two building blocks, each with

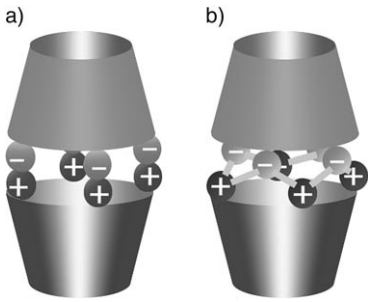



***Figure 2.*** Two types of interaction between the capsule components: ion-pair formation (a), formation of a gearlike structure (b).

four charged groups. Two modes of interaction between the capsule components are proposed: the formation of separate contact-ion pairs (Figure 2a)[188–190] and of a cyclic array of anion–cation bonds (Figure 2b).[194] The water solubility of the capsules is usually lower than that of the individual components because of the neutralization of charges and the less effective solvation of the ion pairs compared with that of the separate ions.[194] Polyethylenoxy chains have therefore been introduced to increase the water solubility of capsules.[187–190]

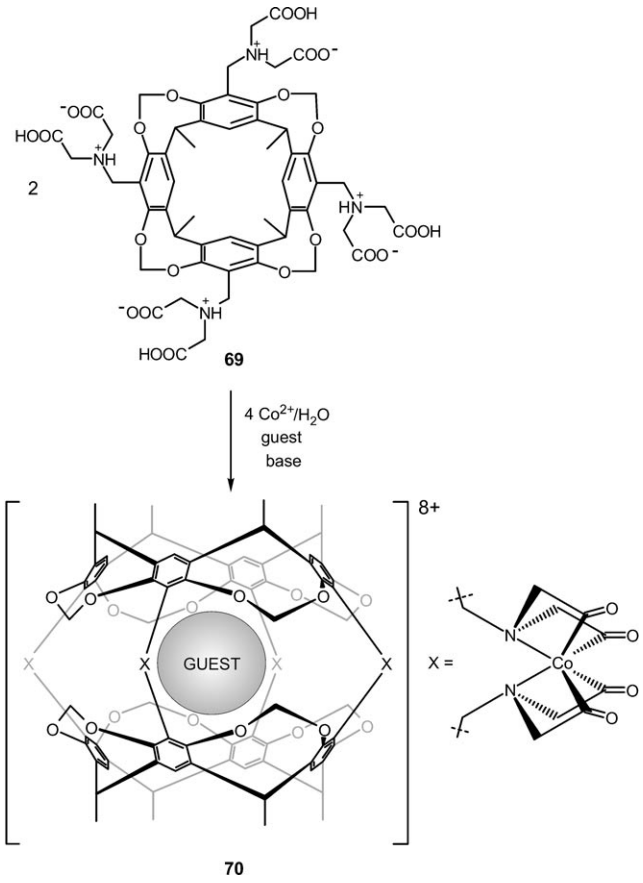
In the case of three electrostatic interactions, the binding constants in water are $1\text{–}4\times10^3\,\text{M}^{-1}$.[191,195] Capsules generated by the formation of four salt bridges are about 1–3 orders of magnitude more stable. Salts usually decrease the apparent stability constant for the formation of the capsule.[190]

In addition to the formation of complexes inside [1+1] capsules, charged guests can also be complexed in polar protic media on the exterior,[194] probably as a result of triple-ion interactions.[196] In general, the encapsulation of charged guests (ammonium ions such as methylquinuclidinium) in capsules is very weak, mainly because of the competitive influence of water.[187,188] Some guests prefer to form complexes with capsule components rather than with the capsule itself and, therefore, may cause significant dissociation of the capsule.[194] This behavior significantly differs from that of capsules studied in apolar solvents.[197] One explanation for the low host–guest affinity is the decrease in the inner volume of the capsule as a consequence of the solvation shell of the electrostatic walls of the capsule.[191,194]

Capsule complexes **70** are formed from cavitand **69** and cobalt(II) salts in water at pH > 5 through aminodiacetate–cobalt(II) interactions (Scheme 6).[198,199] Organic guests, such as aromatic compounds, alkanes, alkenes, alcohols, and haloalkanes, are entrapped within the elliptical ($10\times11$ Å$^2$) hydrophobic cavity upon formation of the capsule, as is evident from a shift in the protons of the guest molecules by up to 40 ppm in the $^1$H NMR spectrum.[198,199] A decrease in the pH value gives rise to the release of the guests, as this breaks the metal–ligand coordination to yield the initial capsule components.[199]

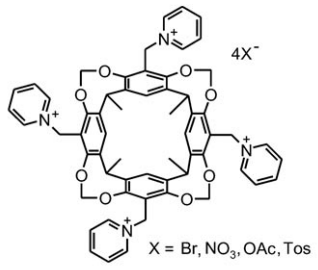
We have recently reported [2+4] capsules **72**, which are formed through multiple triple-ion interactions of tetrakispyridinium cavitand **71**, whereby a singly charged anion (bromide, nitrate, acetate, or tosylate) brings together two

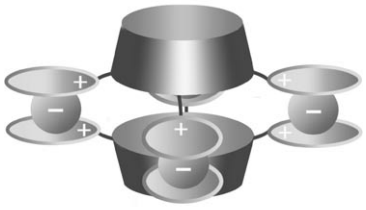



***Scheme 6.*** Formation of the self-assembled capsule-like cavitand **70**.

singly charged cations (pyridinium moieties).[196] The signal for capsule **72** in an aqueous solution has a lower intensity in the ESI mass spectrum than that in methanol because of a lower degree of triple-ion association in the highly competitive water than in methanol. The capsules encapsulate one




**71**

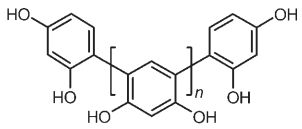


**72**

(tosylate) or two (bromide, nitrate, and acetate) anions, depending on their size.[196]

### 8.2. Helical Self-Assembled Aggregates

Oligoresorcinols **73** ($n = 4, 7$) fold into double helices in water as a result of multivalent CH–π and π–π interactions supported by hydrophobic interactions.[200] The degree of association depends on the length of **73**: for $n = 1, 4, 7$ it is equal to 1, 1.5, and 1.9, respectively, thus suggesting that the longest oligomer ($n = 7$) almost quantitatively self-assembles to form double helices. The medium-length oligomer ($n = 4$)



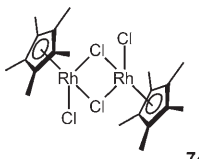

**73**

exists as an approximately 1:1 mixture of the single strand and the double helix in equilibrium, while the shortest isomer ($n = 1$) exists only as a single strand in water. The formation of the helical self-assembled aggregates is strongly medium-dependent: for example, the oligoresorcinol **73** ($n = 7$) exists exclusively as a random coil in methanol, but already self-assembles in 72 vol% water (in methanol). The double helices exist as equimolar mixtures of the right- and left-handed forms. However, the introduction of chiral groups in the oligoresorcinols amplifies the formation of one of the isomers.[200]

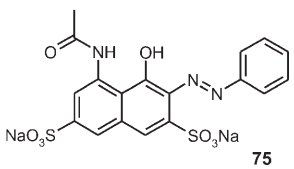
### 8.3. Metal–Organic Macrocyclic Assemblies, Cages, and Helicates

Metal–organic receptors are macrocyclic aggregates or cages formed by metal–ligand interactions.[201,202] The metal–organic receptor complexes of Ru, Rh, Pt, Pd, and Ir with pyridine and cyclopentadienyl ligands, or their analogues, are in general soluble in aqueous media, and not sensitive to air. The metal–ligand interactions generate sufficiently high association constants, even in polar competitive solvents such as water.[202]

Complexes of metal–organic half-sandwich complexes **74** with a variety of dyes, for example, azophloxine (**75**), are used as indicator displacement assays for the detection of peptides[203] and amino acids[204] in aqueous buffer solution. The **74**·**75** assay ($K_a \approx 3.2 \times 10^7\ \text{M}^{-1}$ in 100 mM aqueous phosphate buffer solution, pH 7.0) allows differentiation of peptides that contain either His or Met residues at positions one or two




**74**

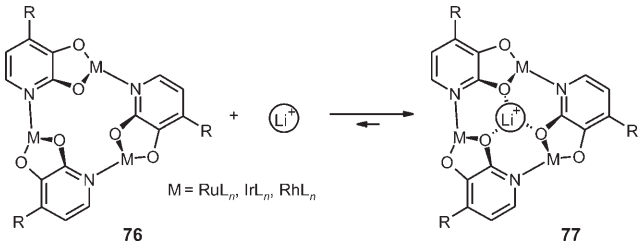



**75**

from the N terminus from other types of peptides. For example, the association constant of His-Ala, His-Gly-Gly, Leu-His-Leu, or Gly-Met-Gly with rhodium complex **74** is more than three orders of magnitude larger than that of the **74** × **75** complex. On the other hand, Val-Phe and Lys-Tyr are weak competitors: they form complexes with **74** that are $10^4$ times weaker than dye **75**. This property allows the detection of micromolar concentrations of, for example, His-Ala in the presence of a 100-fold excess of Val-Phe in aqueous solution.[203] The pH sensitivity of the binding affinity of amino acids with complex **74** has been used to develop a chemosensor for the colorimetric identification of 20 natural amino acids in water.[204]

Macrocyclic complexes of type **76** (M = Ru, Rh, and Ir, L = benzyl or cyclopentadienyl ligands, R = substituted aminomethyl groups) can be regarded as metal–organic analogues of [12]crown-3. They are able to bind lithium ions (Scheme 7), although with a much higher affinity ($K_a$ values

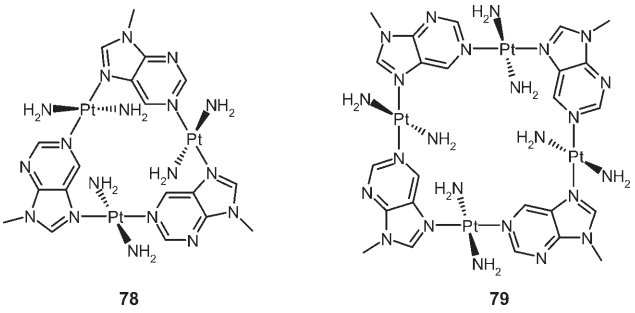



***Scheme 7.*** Formation of a host–guest complex between the self-assembled metal–organic receptor **76** and a $Li^+$ ion.

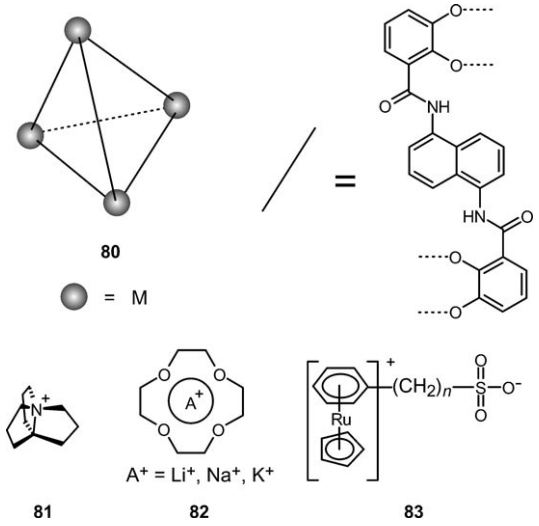
up to $5.8 \times 10^4\,\text{M}^{-1}$ in aqueous 100 mM phosphate buffer solution, pH 7.0) and selectivity over sodium (ca. $10^4$ times; $K^+$ or $Cs^+$ were not complexed).[201,202,205,206] Upon addition of iron(III) salts, receptor **76** immediately decomposes to give a dark-brown solution from which a brown powder slowly precipitates. In the presence of lithium ions, when the more stable complex **77** is formed, this reaction is kinetically inhibited, and the addition of $FeCl_3$ does not lead to an immediate color change. This difference in reactivity allows "naked-eye" detection of $Li^+$ ions in water in the pharmacologically relevant concentration range of 0.5–1.5 mM.[205] Complexes **76** also selectively extract $Li^+$ ions from an aqueous solution to the organic phase.[207]

Other types of water-soluble metallacrown compounds are formed from 9-methylpurine and *trans*-$\{Pt^{II}(NH_3)_2\}$[208] (**78** and **79**) or 1-methylcytosine and palladium–(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) linkers.[209] They are positively charged and, therefore—in contrast to classical crown compounds[15] and the metallacrowns of Severin and co-workers[205]—tend to form complexes with anionic species. For example, the metal–organic purine triangle **78** and purine square **79** trap sulfate by means of electrostatic and multiple hydrogen-bonding interactions in $D_2O$ with $K_a = 7.2 \times 10^4\,\text{M}^{-1}$ and $9.9 \times 10^3\,\text{M}^{-1}$, respectively.[208]

The water-soluble supramolecular $M_4L_6$ coordination structures **80**[210] consist of four metal atoms ($M = Ga^{3+}$, $Al^{3+}$, $In^{3+}$, or $Fe^{3+}$) situated at the corners of a tetrahedron and bridged by six naphthalene-based bis-bidentate catechol




ligands L. They possess a cavity of 300–350 $Å^3$[210] which can encapsulate a variety of lipophilic cationic molecules,



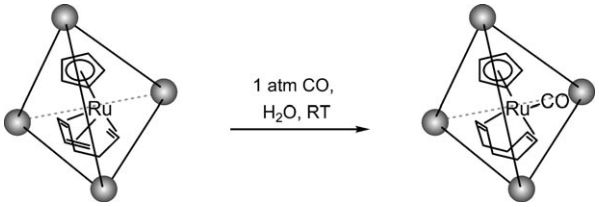

such as tetraalkylammonium,[211–215] tetraalkylphosphonium,[211,212,216,217] tropylium,[218] aromatic diazonium,[218] pyridinium,[215] cationic organometallic species,[211–213,219–222] and alkali-metal crown complexes[223] in water. For example, $[Ga_4L_6]^{12-}$ binds tetraethylphosphonium, tetraethylammonium, azoniapropellane (**81**), sodium [12]crown-4 (**82** $A^+ = Na^+$), and cobaltocenium in aqueous solution with binding constants of $1 \times 10^6$, $3.6 \times 10^4$, $1.7 \times 10^4$, $3.4 \times 10^4$, and $1.7 \times 10^4\,\text{M}^{-1}$, respectively.[211,223] The cages can selectively encapsulate the lipophilic part of complex molecules; for example, in the case of zwitterions **83**, the cationic head is encapsulated in $[Ga_4L_6]^{12-}$, while the linker to the anionic sulfonate tail passes through one of the small openings at the center of the triangular faces, thereby leaving the sulfonate substituent in water.[220]

The $M_4L_6$ tetrahedron has also demonstrated its ability to stabilize reactive intermediates in aqueous media.[210,216,217,219] For example, water-sensitive cationic α-oxyphosphonium salts[217] or metastable organometallic complexes[219]—previously synthesized only under anhydrous conditions—were stabilized in aqueous solution for several weeks. The α-oxyphosphonium salts are hydrolyzed when they dissociate from the cage, and therefore guests with larger substituents, which prevent dissociation, have a higher stability.[217]

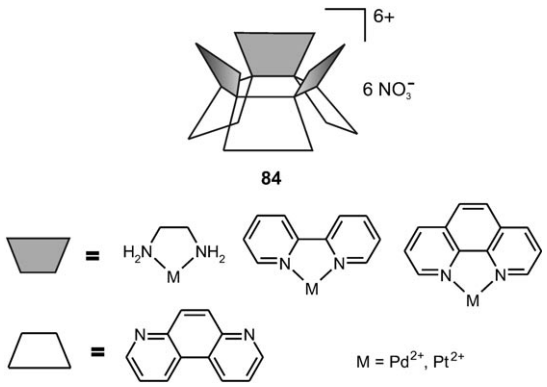
Exchange of smaller guests in the $M_4L_6$ cage[213] occurs without rupture of the metal–ligand bonds (which are stable in aqueous media) but occurs by deformation of the host structure, which facilitates the passage of guests through the $C_3$-symmetric apertures.[211,212] It is well known that—despite the competitive influence of water—the tetraalkylammonium anions are also associated substantially with the outside of the $M_4L_6$ cage, which slows down the exchange of the encapsulated guests.[211]

While encapsulated in the $M_4L_6$ cage, guests can undergo reactions—both stoichiometric and catalytic—with significant rate enhancement and improved product selectivity in some cases.[210] For example, the cage accelerates an aza-Cope rearrangement in water by a factor of 854.[214] Despite the stabilization, complexes with organometallic guest molecules are still able to react stoichiometrically with CO (Scheme 8)[219] or aldehydes[210,221] in water.

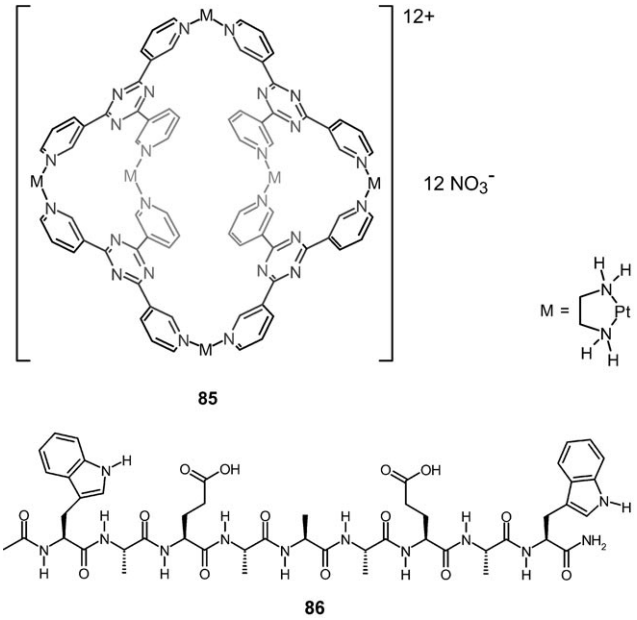



***Scheme 8.*** Reaction of the encapsulated guest species with CO.

Anion recognition in water by bowl-shaped molecules has been reported by the research groups of Fujita,[224–226] Lippert,[227,228] and Navarro.[229,230] The metallacalix[*n*]arenes ($n = 3, 4, 6$)—structural analogues of calixarenes—for example, palladium– or platinum–calix[3]arene **84**, are highly soluble in water and bind sulfate to form a 1:1 complex (apparent $K_a$(sulfate/nitrate) value ca. 250 $M^{-1}$);[224,227] a 1:3 complex was observed in the case of acetate.[224] Metallacalixarenes also preferentially complex adenosine 5′-monophosphate ($K_a$ value up to 85 $M^{-1}$)[230] compared with cytidine and thymidine 5′-monophosphates in aqueous (pH 7.1) solution.[229,230]



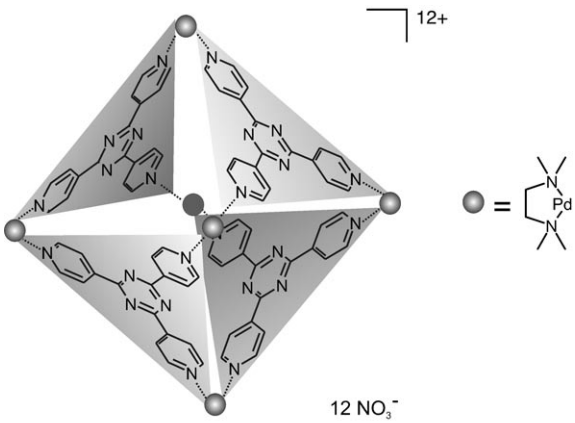

The bowl-shaped host **85**, which has a general structure similar to calix[4]arene, possesses a large hydrophobic pocket.[225,226] It forms 1:1 and 2:1 complexes, depending on the medium, with the de novo designed oligopeptide **86**.[225,226] For example, the addition of 1 v/v % chloroform to a solution of host **85** and guest **86** in 100 mM aqueous phosphate buffer



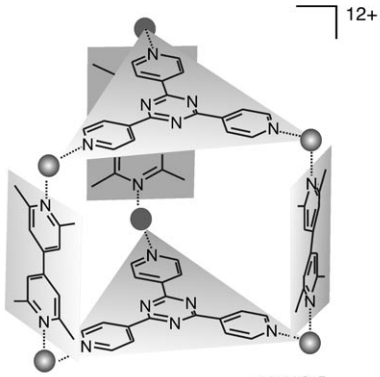

results in the formation of a 1:1 complex ($K_a \approx 1 \times 10^3\ M^{-1}$; chloroform is presumed to be encapsulated into the host cavity together with the guest).[226] Upon formation of the 1:1 complex, oligopeptide **86** adopts an α-helical conformation and the Trp1, Ala5, and Trp9 residues are on the same face of the helix and accommodated deep within the cavity.[226] The addition of $NaNO_3$ results in the formation of a 2:1 complex, in which two molecules of **85** are wrapped around the whole of **86**, becoming dominant because the enhanced ion strength increased the hydrophobic interaction between the Trp residues and the walls of the cavity of **85**.[225]

The research group of Fujita has prepared many water-soluble nanometer-sized cages (for example, the $M_6L_4$-type coordination cage **87** and the prismatic coordination cage **88**) by self-assembly.[231,232] The cages have the ability to encapsulate large molecules or molecular aggregates,[233] as well as to regulate or catalyze specific reactions in aqueous media. Three encapsulation modes[234] have been observed in the case of the cage **87**, depending on the size and the shape of the guests: 1) formation of 1:4 host–guest complexes with small guests (ca. 6–8 Å) such as ferrocene,[235] *ortho*-carborane,[234] and adamantane;[236] 2) formation of 1:2 complexes with medium-sized, twisted or bent guests such as acenaphthylene,[237,238] diphenylmethane or 1,2-bis(4′-methoxyphenyl)-1,2-ethanedione;[234,239] 3) large guests (tri-*tert*-butylbenzene, tetrabenzylsilane, substituted phenylsilanol trimers[239–241]) with diameters of around 8 Å give 1:1 complexes.[234] Two 1,4-naphthoquinone or two azulene molecules can also be encapsulated in **87**, but inclusion of the 1,4-naphthoquinone–azulene pair is preferential (OR molecular recognition).[242] Perylene and *cis*-decaline can only be accommodated together within the cavity, and no complex formation was




**87**



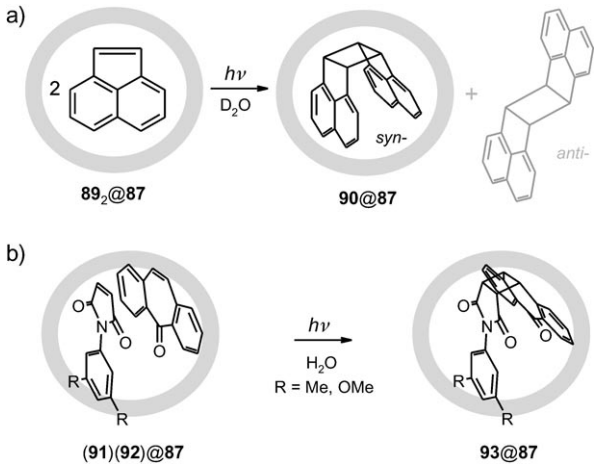

**88**

observed with either of these molecules alone (AND molecular recognition).[242] Cage **87** selectively recognizes tripeptides in water,[243] for example, the $K_a$ value with Ac-Trp-Trp-Ala-$NH_2$ is greater than $10^6\,M^{-1}$, but no binding was observed with Ac-Trp-His-Ala-$NH_2$. Guests also template the formation of metal–organic nanostructures, such as prisms,[232,244] coordination nanotubes,[245] dimeric capsules,[246] boxes,[247] clipped arene sandwiches,[248] homoleptic or heteroleptic cages,[249] as well as tetragonal pyramidal or closed tetrahedron structures[250] in water or aqueous acetonitrile/DMF solution.

Within the hydrophobic cavity of cage **87**, an adamantanoid $(H_2O)_{10}$ cluster is formed,[251] which is termed "molecular ice" because its structure is the smallest unit of naturally occurring cubic $I_c$ ice.[4] The molecular recognition by **87** is assumed to be entropy-driven, with the binding of the guests compensated by the "melting" of the encapsulated molecular ice into free water molecules.[251]

The interior of cage **88** is approximately 7.5 Å high, which allows encapsulation of two planar organic molecules, such as coronene,[232,252] pyrene,[252] thiafulvalene,[253] or organometallic complexes $[M^{II}(acac)_2]$ (M = Pt, Pd, or Cu; acac = acetylacetonato).[254] The formation of the complex is promoted by hydrophobic interactions and the formation of charge-transfer complexes between the electron-deficient 1,3,5-triazene floor and roof of the cage and the encapsulated π-electron-rich molecules. Guests strongly template the formation of organic coordination cage **88** in water.[232,252] For example, the exclusive formation of **88** was observed upon mixing its components in the presence of coronene. The alternative scenario would have been that the aqueous solution would have contained a mixture of cages **87** and **88** along with oligomers.[232,252] Cage **88** promotes the interaction between the encapsulated guests, for example, the formation of a $M^{II}$–$M^{II}$ bond between $Pt^{II}$, $Pd^{II}$, or $Cu^{II}$ from the encapsulated acetylacetonato complexes, as well as moderately protecting the metal–metal bond from being destroyed by water.[254]

The self-assembled cages act as molecular flasks to promote the intermolecular [2+2] photodimerization of large olefins in water in a very efficient fashion.[255] The remarkably accelerated, highly stereoselective [2+2] photodimerization of acenaphthylene (**89**) within the coordination cage **87** gives exclusively *syn* isomer **90** (Scheme 9a) in

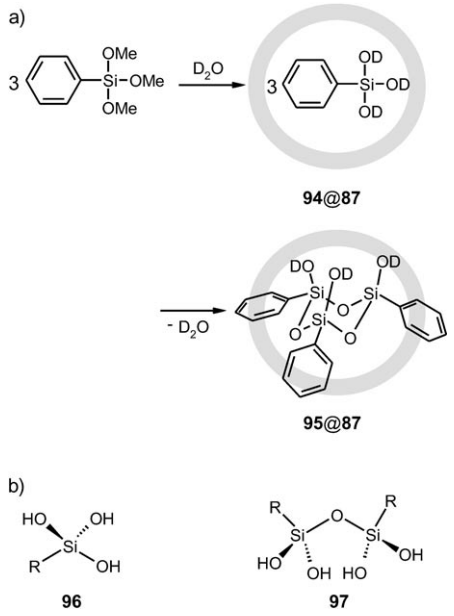



***Scheme 9.*** [2+2] Photodimerization of olefins within the self-assembled cage **87** (schematically depicted as a gray circle).

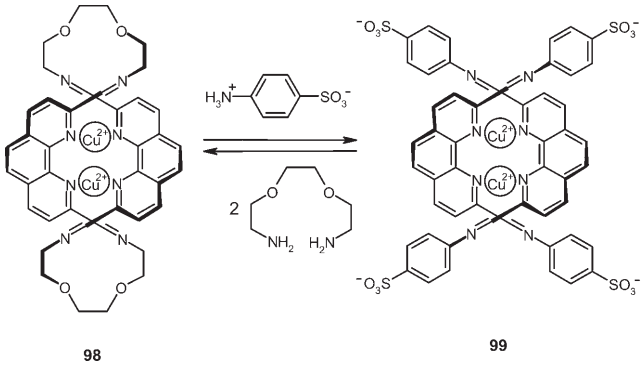
aqueous medium.[237] The accommodation of two different olefin molecules in a pairwise selective fashion makes selective [2+2] cross-photodimerization[256] possible or accelerates Diels–Alder reactions.[257] For example, substituted maleimide derivative **91** and dibenzosuberenone (**92**) undergo [2+2] cross-photodimerization to give **93** with a *syn* configuration in quantitative yield (Scheme 9b).[256] The reactions are extremely efficient in terms of reaction rate, stereoselectivity, and—most importantly—pairwise selectivity. The key step in the exclusive formation of the mixed dimer in water begins with the selective formation of a ternary complex before irradiation; this step is governed by the compatibility of the size of the guests with the restricted space of the cavity.[256] Cage **87** also efficiently promotes the photochemical oxidation of inert guests (such as adamantane) in aqueous solution.[236]

Oligomerization of silanetriols **94** within the cavity resulted in the stereoselective preparation of the all-*cis* cyclic trimer **95** (Scheme 10a).[239–241] The enclosed trimer is stable in water (at room temperature for about one month)

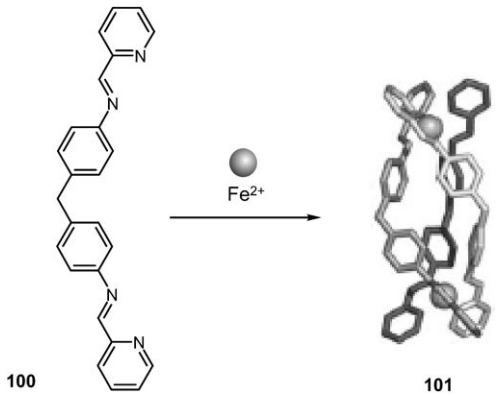
  




***Scheme 10.*** a) Formation of silanol within cage **87** (schematically depicted as a gray circle); b) Silanols prepared within other coordination cages.




***Scheme 11.*** pH-controlled switch between a macrocycle and a helicate.




***Scheme 12.*** Formation of metallosupramolecular triple helicate **101**.

and survives low pH values ($< 1.0$). In the absence of the cage, the cyclic trimer **95** is a kinetic, short-lived compound that is rapidly converted into a thermodynamically favored cyclic tetramer and further condensed products.[240] Variation of the volume of the cavity of the self-assembled coordination cage allowed the isolation of stable inclusion complexes of silanetriol **96** or silanol dimer **97**, which are otherwise very labile and cannot be isolated as a stable form in aqueous solution unless a stabilizing group or a sterically demanding group is attached.[241]

Dynamic switching of the pH value has been used for topological control of the self-assembly in water.[258] The self-assembled copper–phenanthroline core of complex **98** is stable in water, and a change in the periphery of the complex offers the possibility to switch between a macrocycle and a helical structure. For example, the addition of sulfanilic acid to an aqueous solution of **98** leads to helicate **99**, and basification of the resulting solution with $NaHCO_3$ results in the regeneration of macrocycle **98**, thereby closing the cycle (Scheme 11).[258]

Hannon and co-workers studied the DNA binding of water-soluble and stable metallosupramolecular double and triple helicates (such as **101**), in which two or three ligand strands **100** are wrapped around two metal ($Cu^+$, $Fe^{2+}$) centers (Scheme 12).[259–262] Tetracationic iron triple helicates $[Fe_2\mathbf{100}_3]^{4+}$ target the DNA major groove, by spanning five or more base pairs, and induce dramatic intramolecular coiling of the DNA; this effect is unprecedented for synthetic agents and is reminiscent of DNA coiling induced by histones in the cell nucleus.[261] Dicationic copper double helicate $[Cu_2\mathbf{100}_2]^{2+}$ binds more weakly to DNA than does $[Fe_2\mathbf{100}_3]^{4+}$ because of its lower charge resulting in a decreased role of electrostatic interactions in the binding.[260] However, $[Cu_2\mathbf{100}_2]^{2+}$ does not disturb the B-DNA configuration, and exhibits DNA-cleavage activity in the presence of peroxide, which opens up its possible application as an artificial nuclease.[260]

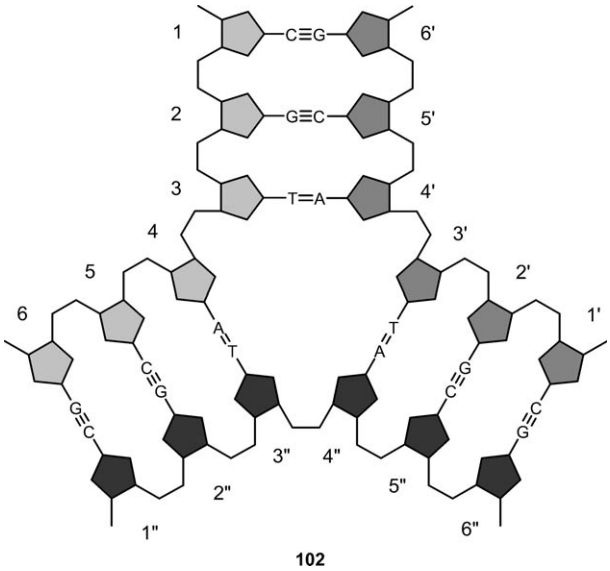
Tetracationic metallosupramolecular helicate $[Fe_2\mathbf{100}_3]^{4+}$ (**101**) fits perfectly with the size and shape of the central trigonal hydrophobic cavity of triple DNA-junction **102** (Figure 3), as revealed by an X-ray study of crystals obtained from aqueous solution.[259] This new mode of DNA recognition involves four kinds of synergistic contacts: electrostatic interactions with the highly charged $[Fe_2\mathbf{100}_3]^{4+}$, face-to-face π-stacking intercalation-type interactions, CH···X type interactions, and inclusion in the minor groove with formation of a sandwich structure.[259] Such a cyclophane-like host–guest behavior of DNA opens up promising possibilities for the development of novel kinds of anti-DNA therapeutic agents.[259]

### *8.4. Self-Sorting in Water*

In nature, the ability to efficiently distinguish between self-assembly and non-self-assembly on a molecular level takes place in aqueous media. Supramolecular chemistry is currently taking its first steps in this direction.

An efficient thermodynamic social self-sorting of 12 different host–guest components in aqueous media has been reported.[160,263] The hosts in the mixture efficiently recognize their counterparts in water using hydrophobic, electrostatic,



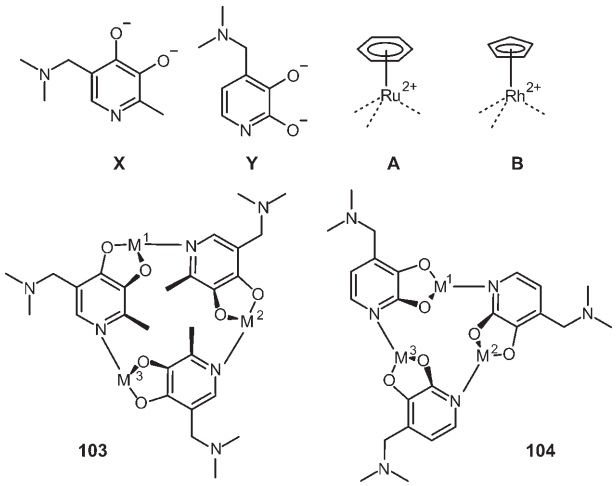

102

***Figure 3.*** DNA-junction showing the DNA sequence 5′-d(CGTACG)-3′ and the base-pair arrangement.

metal–ligand, ion–dipole, and charge-transfer interactions. Similar to complex biological systems, the mixture experiences irreversible changes on increasing the temperature to 65 °C. A less complex mixture of nine components exhibited a completely reversible behavior between 7 and 65 °C.

An exceptional example of "narcissistic" self-sorting has recently been reported.[264] Mixing the two different metal-containing fragments **A** and **B** with the ligands **X** and **Y** (the complex-forming tautomers are shown) in a $D_2O$ phosphate buffer solution (pD 8.0) results in a dynamic combinatorial library of eight macrocycles, represented by structures **103** and **104**. Each of these complexes exclusively contains one type of bridging ligand. The 16 hypothetical macrocycles with the mixed bridging ligands are not formed, since the self-assembly process is strictly self-sorting.

Biological self-sorting systems respond to stimuli from their aqueous environment and exhibit an adaptive and evolutionary behavior. The development of adaptive complex supramolecular systems can be expected in the future, which, like their biological counterparts, will make use of the numerous unique properties of water for selective interactions and self-assembly in aqueous solution.




$\{M^1,M^2,M^3\}$ = {A,A,A}, {A,A,B}, {A,B,B}, {B,B,B}

## 9. Summary

A variety of approaches have been used to design artificial receptors capable of selectively binding a number of guests in aqueous media. This has resulted in a wide range of water-soluble receptors based on different supramolecular scaffolds. Different interactions have been employed to stabilize the host–guest complexes in aqueous media, and varying degrees of preorganization have been used to overcome the competitive influence of water. The encapsulation of several guests has allowed the study of their interaction in the interior of a cage in aqueous solution. However, the role of the unique properties of water[1–4] in molecular recognition and self-assembly is not completely understood, and good receptors for many organic guests have not yet been found. Therefore, a substantial growth of research in the area of supramolecular chemistry in water is expected.

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