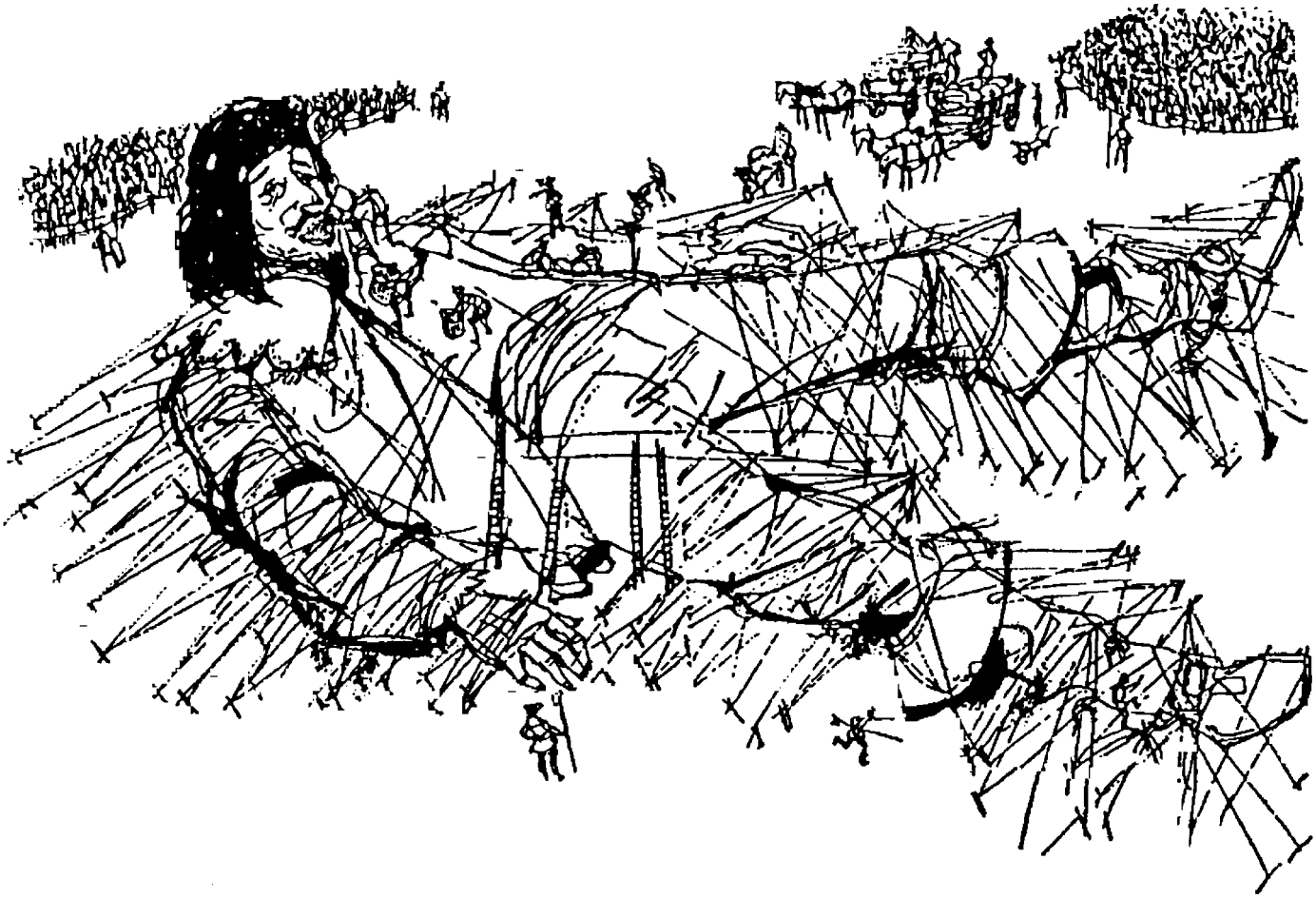
The Cooperativity Concept



Gulliver constrained by a multitude of weak "bonds". Illustration by Ulrike Schramm in Jonathan Swift's *Gullivers Reisen*; reprinted with permission from Überreuter Verlag, Vienna.

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Noncovalent Synthesis Using Hydrogen Bonding

Leonard J. Prins, David N. Reinhoudt, and Peter Timmerman*

Hydrogen bonds are like human beings in the sense that they exhibit typical grouplike behavior. As an individual they are feeble, easy to break, and sometimes hard to detect. However, when acting together they become much stronger and lean on each other. This phenomenon, which in scientific terms is called *cooperativity*, is based on the fact that "1+1 is more than 2". By using this principle, chemists have developed a wide variety of chemically stable structures that are based on the reversible formation of multiple hydrogen bonds. More than 20 years of fundamental studies on these phenomena have gradually developed into a new discipline within the field of organic synthesis, and is nowadays called "*noncovalent* synthesis". This review describes noncovalent synthesis based on the reversible formation of multiple hydrogen bonds. Starting with a thorough description of what the "hydrogen bond" really is, it guides the reader through a variety of bimolecular and higher order assemblies and exemplifies the general principles that determine their stability. Special focus is given to reversible capsules based on hydrogen-bonding interactions that exhibit interesting encapsulation phenomena. Furthermore, the role of hydrogen-bond formation in self-replicating processes is actively discussed, and finally the review briefly summarizes the development of novel materials (nanotubes, liquid crystals, polymers, etc.) and principles (dynamic libraries) that recently have emanated from this intriguing field of research.

Keywords: hydrogen bonds · molecular recognition · noncovalent interactions · self-assembly · supramolecular chemistry

1. Hydrogen Bonding

"The discovery of the Hydrogen Bond could have won someone the Nobel Prize, but it didn't."
George A. Jeffrey, Wolfram Saenger, 1991

1.1. Introduction

Molecules can be simply regarded as a collection of atoms connected by high-energy covalent bonds (50–100 kcal mol^{-1}) that result from partial overlap between atomic (hybrid) orbitals. In chemical reactions, different molecules "interact" with each other by the stepwise breaking and making of covalent bonds. These are relatively slow processes that usually have high kinetic barriers. For more than a century organic chemists have been studying chemical reactions in a systematic way, which has ultimately led to the development of a wealth of synthetic methods. Virtually every chemical transformation can nowadays be achieved, which renders the total synthesis of structurally very complex molecules with molecular weights $\leq$1000 Da, such as taxol or brevetoxin, possible.[1–3] However, the synthesis of molecular structures with molecular weights $\geq$1000 Da through the stepwise formation of covalent bonds generates a formidable challenge. With the exception of the synthesis of polymeric structures (both synthetic and biological in origin), which uses repetitive reaction sequences, the field of covalent synthesis reaches the limit of what is synthetically achievable in terms of time requirements and yields.

1.2. Noncovalent Synthesis

Molecules can also "interact" with other molecules through weak interactions (0.1–5 kcal mol^{-1}), such as hydrogen bonding, van der Waals, or dispersive forces, which are collectively known as noncovalent interactions. Such interactions play a key role in fundamental biological processes, such as protein folding or the expression and transfer of genetic information. The universal importance of molecular recognition phenomena observed in biological systems seriously started to

[*] Dr. P. Timmerman, Ir. L. J. Prins, Prof. Dr. D. N. Reinhoudt
Laboratory of Supramolecular Chemistry and Technology
MESA$^+$ Research Institute
University of Twente
P.O. Box 217, 7500 AE Enschede (The Netherlands)
Fax: (+31) 53-4894645
E-mail: P.Timmerman@ct.utwente.nl

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Table 1. Characteristics of covalent and noncovalent synthesis.

	Covalent	Noncovalent
building block	atoms	molecules, ions
target	molecule	assembly
molecular weight	1 – 1000 Da	1 – 100 kDa
bond type	covalent	ionic, hydrophobic, metal coordination, hydrogen bond
bond energy	35 – 135 kcal mol^{-1}	2 – 20 kcal mol^{-1}
kinetic stability	high	low
ΔG components	$\Delta H \gg T\Delta S$	$\Delta H \approx T\Delta S$
solvent effects	secondary	primary
characteristics	–	cooperativity

fascinate synthetic chemists in the early 1970s. Inspired by the accidental discovery of the crown ethers by Charles Pedersen in 1967, the research groups of Lehn and Cram started to explore the chemistry of synthetic receptors for small charged and neutral molecules, for which they were awarded the Nobel Prize in 1987. Subsequently, these and other groups have extended this work to synthetic receptors involving hydrogen bonding and other noncovalent interactions. More than 30 years of research in this field shows that noncovalent interactions have an enormous potential for the construction of chemical structures exhibiting a high degree of structural complexity. This novel synthetic approach, also known as "noncovalent synthesis", is actively explored in a variety of chemistry subdisciplines (for the characteristics of both covalent and noncovalent syntheses see Table 1).[4] Several types of noncovalent interactions have been studied in this respect, for example, hydrophobic interactions,[5, 6] metal coordination,[7, 8] ionic interactions,[9] and hydrogen-bonding interactions. This review covers noncovalent synthetic work in which formation of hydrogen bonds is of primary importance. Since some of the work covered here has been the topic of previous reviews,[4, 10–19] we will concentrate on concepts and principles that have emerged from this area over the past decade.

1.3. The Hydrogen Bond

Weak interactions between molecules containing hydroxyl groups were already noted in 1892 by Nernst.[20] Although nameless at that time, Werner included them ten years later in his concept of "Nebenvalenz" (minor valence), which was in fact a proper description of the phenomenon of hydrogen bonding.[21] Suggestions that the hydrogen atom was the center of this weak interaction were first made in 1920 by Huggins as well as Latimer and Rodebush.[22, 23] It was not


D. N. Reinhoudt


P. Timmerman


L. Prins

David N. Reinhoudt was born in 1942 in The Netherlands. He studied Chemical Technology at the Delft University of Technology and obtained his PhD in chemistry in 1969 with H. C. Beijerman. In the period 1970 – 1975 he worked at Shell where he started the crown ether research program. In 1975 he was appointed as a part-time professor (extraordinarius) at the University of Twente, followed by the appointment as a full professor in 1978. He is the scientific director of the MESA$^+$ Research Institute. The major part of his research deals with supramolecular chemistry and (nano)technological applications, for example, in "lab-on-a-chip", electronic or optical sensor systems, catalysis, and molecular materials. He is the author of more than 650 scientific publications, patents, review articles, and books. He has been honored with the Izatt – Christensen award (1995) and the Simon Stevin Mastership (1998).

Peter Timmerman was born in Ommen, The Netherlands in 1966. He received his degree in chemistry in 1989 with G. W. Klumpp at the Free University in Amsterdam. In 1994 he obtained his PhD at the University of Twente (UT) with D. N. Reinhoudt working on the synthesis of rigid cavities by the combination of calix[4]arenes and resorcinarenes, for which he was awarded the Backer Prize. Then he moved to the Eidgenössische Technische Hochschule (ETH) in Zürich, Switzerland for a postdoctoral stay with F. N. Diederich, where he worked on the chemistry of fullerenes. In 1995 he returned to the University of Twente, where he currently holds a Docent position in the group of D. N. Reinhoudt. His current research interests center around the various aspects of self-assembly based on hydrogen bonding and ionic interactions, with a particular focus on noncovalent combinatorial synthesis.

Leonard Prins, born in 1974, studied Chemical Technology at the University of Twente, The Netherlands. He obtained his undergraduate degree in 1996 with D. N. Reinhoudt. In 1997, after spending three months in the group of R. Ungaro in Parma, Italy, he rejoined the Reinhoudt group as a graduate student. His research deals with the noncovalent synthesis of chiral hydrogen-bonded assemblies.

until 1935–6 that Bernal and Huggins proposed the actual term "hydrogen bond" (abbreviated as H-bond),[24, 25] which has become generally adopted to describe this phenomenon. Soon after, it became apparent that associations between molecules containing polar X–H bonds and nonbonding electron pairs on atom Y are generally characterized by relatively high interaction energies.[26, 27] Since then, H-bonding interactions have continued to fascinate chemists—from theoreticians to biochemists and material scientists.[28]

H-bonds connect atoms X and Y that have electronegativities larger than that of hydrogen, namely, C, N, O, F, P, S, Cl, Se, Br, and I. The XH group is generally referred to as the "proton donor" (D) and the Y atom is called the "proton acceptor" (A) group. The strength of a H-bond increases with an increase in the dipole moment of the X–H bond and the electron lone pair on atom Y. Hence, the strongest H-bonds are formed between atoms N, O, and F acting as X and Y, although C–H can also act as a donor.[29] "π" H-bonds involve an interaction between a partially positive hydrogen atom and the electrons of unsaturated double and/or triple bonds.[30]

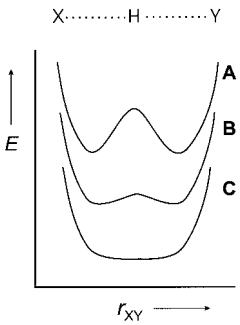
The first theoretical models suggested that H-bonding exclusively involves an electrostatic interaction between the partially positive hydrogen atom of the donor and the lone pair of the acceptor.[31] Nowadays, it is generally accepted that H-bonding can be described neither by electrostatic theory nor by weak covalent bonding alone, but involves a complicated superposition of five individual contributions[32, 33] which are of similar magnitude:

1) electrostatic or coulomb energy (ΔE_{COU})
2) exchange repulsion (ΔE_{EX})
3) polarization energy (ΔE_{POL})
4) charge-transfer energy or covalent bonding (ΔE_{CHT})
5) dispersion forces (ΔE_{DIS}).

The surprising success of the early electrostatic models in calculating H-bond energies has been attributed mainly to an accidental cancellation of the other contributions. The conclusion of valence bond (VB) and molecular orbital (MO) theories is that H-bond energy is mainly electrostatic at long distances, but at shorter distances repulsion between the electrons of the H–X bond and the lone pair on atom Y as well as delocalization of electrons from the lone pair π orbital on the acceptor to a σ* antibonding orbital on the proton donor come into play.[34] MO calculations indicate that 0.01 to 0.03 electrons are transferred upon formation of the H-bond.

Most theories of H-bonds claim an angle dependence of the H-bond energy, with a maximum value for a linear bond.[35] Kollman and Allen proposed that the ideal geometry involves a compromise between the optimal angle for ΔE_{COU} and ΔE_{CHT}, since the other three energy contributions are virtually angle insensitive.[27] The preference for linear H-bonds was demonstrated for small-ring lactams and monocarboxylic acids.[26] The situation becomes more complicated when the acceptor has more than one lone pair or when the donor has more than one hydrogen atom capable of forming H-bonds, and can lead to the formation of three-center ("bifurcated") or four-center ("trifurcated") H-bonds.[36] These and other factors are reflected in the deviations from planarity that are often observed in crystals.

The energy of a H-bond in the gas phase is typically in the range of 2–20 kcal mol^{-1}, which is much weaker than covalent bonds, but significantly larger than dipolar or London dispersion force energies (< 2 kcal mol^{-1}). If either the donor or acceptor is charged the electronic attraction will be amplified, and consequently the H-bonds become much stronger (10–45 kcal mol^{-1}).[37, 38] The thermodynamic stabilities of H-bonded complexes in solution are very dependent on the solvent. The stabilities are usually highest in apolar solvents without H-bonding properties, such as alkanes. The stabilities are lower for solvents that can act either as a H-bond donor or acceptor by themselves, because of competitive H-bonding with the solvent. Kinetic studies by Hammes and Park revealed that H-bond formation is diffusion controlled, with the rate of dissociation being a direct measure of the relative strength.[39]



Scheme 1. Potential energy wells for three different types of hydrogen bonds: A) the double-well potential, B) the low-barrier potential, and C) the single-well potential.

H-bonds have been classified into three different types: A) weak or double-well H-bonds, B) low-barrier H-bonds (LBHBs), and C) very strong or single-well H-bonds (Scheme 1). For single-well potentials the hydrogen atom is symmetrically fixed between the two donor atoms, while for double-well potentials there are two minima in which the hydrogen atom is closer to one of the donors. The single-well potential is generally observed for short, "strong" H-bonds, namely, those in which the O···O distance is less than 2.5 Å, such as in the maleate or phthalate monoanions,[40] while double-well potentials are more common for longer H-bonds (O···O distance is approximately 2.8 Å). Recently, the existence of low-barrier H-bonds with energies between 12 and 24 kcal mol^{-1} was claimed, where the balance of the pK_a values of the donor and acceptor was suggested to be an essential feature.[41] Cleland and Kreevoy, and Frey et al. proposed the formation of such LBHBs in the transition state in enzyme-catalyzed reactions to explain the observed rate enhancements.[42, 43] In the meantime, this theory was disproven by other groups, who showed that extra stabilization of a H-bond does not occur when the difference in the pK_a values of the donor and acceptor approaches zero.[44–47]

1.4. Experimental Detection of H-Bonds

Unlike the formation of covalent bonds which involves massive shifts of electron density, the rearrangements that occur as a consequence of H-bonding are more subtle. There is a small shift of electron density from the proton acceptor to the donor, which can be taken as a characteristic for the formation of a H-bond. The effectiveness of a certain technique is dependent on whether it can measure a property that *changes* upon formation of a H-bond. This section

summarizes the most important techniques that have been used for this purpose.

1.4.1. ^{1}H NMR Spectroscopy

The electron densities at the protons involved in H-bonds are decreased, and consequently their NMR signals are shifted to lower magnetic fields.[26, 48, 49] The magnitude of the chemical shift is indicative of the strength of the H-bond. The greatest shortcoming of ^{1}H NMR spectroscopy is that no observable is directly related to the concentration of the monomer (in the fast exchange regime). Therefore, most H-bonding studies have been conducted by monitoring ^{1}H NMR shifts as a function of concentration. Regression analysis of the raw data gives *indirect* information about the strength of the H-bond. Several other approaches to deduce the existence of H-bonds are available, such as measuring hydrogen exchange rates (EXSY), ^{2}H quadrupolar splittings, and ^{1}H/^{2}H isotope shifts. Recently, scalar couplings across H-bonds between two ^{15}N spins have been observed ($^2J = 6.5$-7.0 Hz).[50] Such couplings are comparable in size to the average vicinal coupling between protons in a H-C-C-H fragment, and for the first time enable the *direct* measurement of a H-bond. Furthermore, 2D NMR techniques, such as NOESY, COSY, and TOCSY, have greatly facilitated the characterization of H-bonded assemblies with sizes approaching that of biological assemblies.

1.4.2. Vibrational Spectroscopy

The formation of H-bonds causes a large red-shift ($\geq 100\ cm^{-1}$) of the fundamental X–H stretching vibration, and occurs as a consequence of a lengthening of the X–H bond. In addition, the intensity of the new band is significantly increased, sometimes by more than an order of magnitude, and broadened. The magnitude of the red-shift correlates linearly with the H-bond strength (Badger–Bauer relation).[37] The strength of intermolecular H-bonds is directly related to the intensity of the H-bonded X–H frequency. Raman vibrational intensities are much less affected by H-bonding.

1.4.3. X-Ray and Neutron Diffraction

X-ray and neutron diffraction "see" hydrogen atoms in a different way and with different accuracy (± 0.02 and 0.001 Å, respectively), because X-ray scattering occurs by the electronic cloud of the H atom, whereas neutron scattering occurs mainly by the H nucleus.[51] Although there are a considerable number of neutron diffraction studies on H-bonded crystals, X-ray diffraction studies remain one of the most commonly applied techniques.

1.4.4. Mass Spectrometry

The detection of H-bonded structures by mass spectrometry is severely hampered by the difficulty of ionizing these structures in a nondestructive way. Several ion-labeling techniques in combination with soft ionization methods, such as electrospray ionization (ESI) and matrix-assisted laser-desorption/ionization (MALDI), have significantly improved this, as demonstrated for multi-component H-bonded assemblies of relatively high thermodynamic stability (see Sections 3 and 4).[52, 53]

1.4.5. Quantum Mechanics

Quantum chemical calculations offer a rich source of supplementary information concerning H-bonding.[37] For example, most of the experimental data on H-bonding are obtained in various solvents, whereas simulations are often carried out in isolation from the surroundings, which increases their added value. Moreover, it has proven difficult to directly extract the H-bond energies from spectroscopic data, while calculations can address the energetics directly. Growing sophistication in computer hardware and more efficient algorithms have dramatically increased the level of accuracy that can be expected from computer calculations.

1.5. The Biological Importance of H-bonds

H-bonds have an enormous impact on our daily life. Without them wooden structures would collapse, cement would crumble, oceans would vaporize, and all living things would disintegrate into random dispersions of inert matter. Moreover, the remarkable properties of H_2O, that is, its extremely high boiling point (100 °C versus -60.7 °C for H_2S), the contraction of solid H_2O on melting, and a maximum density of liquid H_2O at 3.984 °C, all rely merely on the formation of H-bonded networks.[54]

Most natural building blocks, such as carbohydrates, amino acids, and nucleic acids, offer a rich source of H-bond donors and acceptors. This most likely arises because life has evolved in an aqueous environment where interactions with water play an important role. Therefore, the existence of H-bonds has long been regarded to play a crucial role in many biogically relevant processes, such as recognition between DNA base pairs, ligand-binding to receptor sites, enzyme catalysis, and α-helix or β-sheet formation. Although it is generally accepted that such processes additionally involve ion–ion, dipole–dipole, hydrophobic, and steric interactions, the relative contributions of each interaction is still poorly understood. However, recent findings in DNA base pairing and receptor–ligand binding studies convincingly showed that the contribution of H-bonding to the overall binding energies has long been overestimated at the expense of hydrophobic interactions.[55, 56] As a matter of fact, the average energy of a neutral H-bond in solution is up to 1.5 kcal mol^{-1}, which means that H-bond formation simply cannot be the main driving force for binding processes that occur in water. H-bonds are, in fact, very important for the specificity of the structure, but do not contribute much to the overall thermodynamic stability. For example, they can play an important role in specifying a unique conformation of a protein relative to a dynamic-averaged ensemble of folded states.

The relative weakness of the H-bond is essential to processes that involve the transfer of biological information,

because in this way it can be switched on and off by energies that are within the range of thermal fluctuations at ambient temperatures.[57] On the other hand, the energy content of a single H-bond is certainly not sufficient to control the structure of biological macromolecules. Likewise, H-bonds are considered as important contributors to the selectivity in binding processes (primarily as a result of their strong directionality) which act cooperatively with other interactions to provide the necessary amount of energy for these binding processes.

2. Self-Assembly by H-Bond-Directed Dimerization

"It will be many years before our understanding of molecular structure becomes great enough to encompass in detail such substances as the proteins […]; but the attack on these substances by the methods of modern structural chemistry can be begun now, and it is my belief that this attack will ultimately be successful."

Linus Pauling, 1939

2.1. Introduction

This section describes noncovalent structures that are formed by the H-bond-directed self-assembly of two complementary components. As a consequence of their relative structural simplicity, most of these assemblies have been thoroughly characterized by using a variety of different techniques (Section 1.4). Moreover, systematic binding studies and structural modifications on these complexes have provided basic knowledge and fundamental insight into the physical parameters that govern the self-assembly process, as exemplified by the "Jorgensen model" and "Schneider's rule" (see Section 2.2). The assemblies described in this section have been classified according to synthetic motifs and motifs known from bio-recognition, such as the DNA nucleobases. The synthetic motifs have been further subdivided according to the number of H-bonds involved.

2.2. The Jorgensen Model

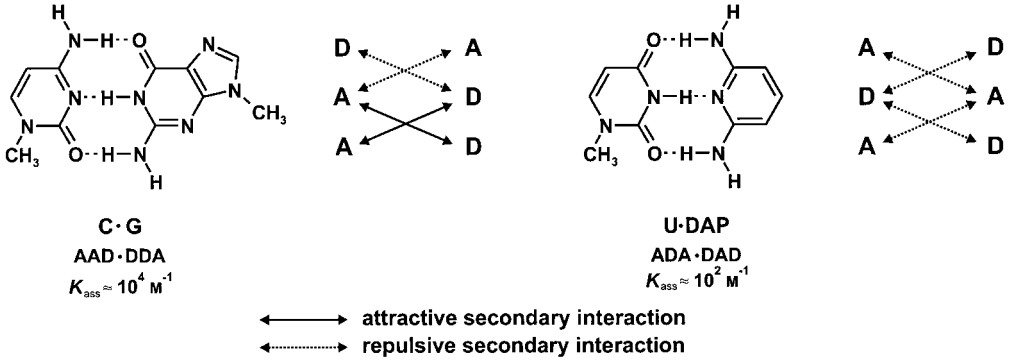
In 1967, Rich and co-workers systematically compared the experimental binding data available for triply H-bonded dimeric complexes in $CHCl_3$.[58] Surprisingly, they found very different stabilities for these assemblies, with values ranging from $\sim 10^2$ to $10^4 - 10^5\,\text{M}^{-1}$, which clearly proved that the number of H-bonds involved is certainly not the only important parameter.[59, 60] More than 20 years later, Jorgensen and co-workers showed that these differences in stability can be largely attributed to attractive and repulsive *secondary* interactions. Stabilization arises from electrostatic attraction between positively and negatively polarized atoms in adjacent H-bonds, whereas destabilization is likewise the result of electrostatic repulsion between two positively or negatively polarized atoms (Scheme 2). Monte Carlo and molecular dynamics simulations showed that the 1-methylcytosine · 9-methylguanine (C · G) dimer (AAD · DDA) is 10.7 kcal mol^{-1} lower in energy than the 1-methyluracil · 2,6-diaminopyridine (U · DAP) dimer (ADA · DAD array). This result is in close agreement with experimental binding data for these complexes.[61, 62] Formation of the C · G dimer involves two attractive and two repulsive secondary interactions, whereas in the U · DAP dimer all the secondary interactions are repulsive. The net difference of four repulsive interactions fully accounts for the lower stability of the U · DAP dimer when each interaction involves 2 – 3 kcal mol^{-1}. This model predicts the highest association constant for an AAA · DDD complex with exclusively four attractive secondary interactions. This was proven experimentally one year later by Murray and Zimmerman.[63]

Based on a comparison of experimental binding data for 58 different synthetic hydrogen-bonded complexes, Sartorius and Schneider derived a simple empirical rule that can be used to predict the binding strength of a given complex. They postulated that the free energy for dimerization consists only of two increments: a contribution of 1.88 kcal mol^{-1} for each H-bond and ± 0.7 kcal mol^{-1} for each attractive or repulsive secondary interaction.[64]

2.3. Synthetic Motifs

2.3.1. 1-H-Bond Modules and the Concept of Cooperativity

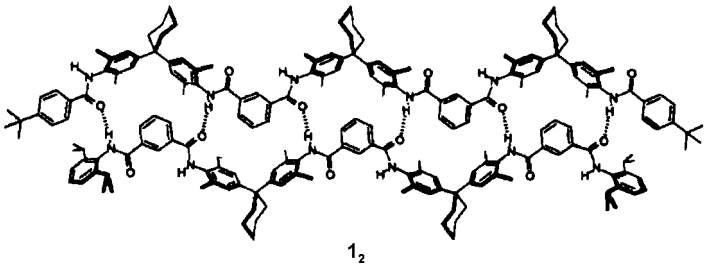
A large variety of organic functionalities exist that can dimerize through the formation of a single H-bond (1-H). For example, functional groups such as phenols, amines, *trans*-amides, sulfonamides, and phospoamides form homodimers, while heterodimeric assemblies are formed, for example, between pyridines and carboxylates. However, the relatively low stability of assemblies based on a single H-bond severely



Scheme 2. Attractive and repulsive secondary interactions account for the 10.7 kcal mol^{-1} difference in thermodynamic stability for the 1-methylcytosine · 9-methylguanine (C · G) dimer and the 1-methyluracil · 2,6-diaminopyridine (U · DAP) dimer.

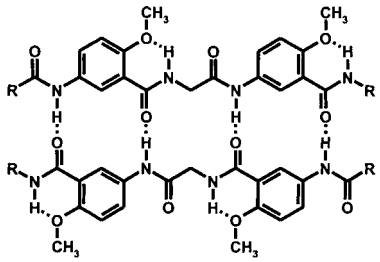
limits their direct utility in the noncovalent synthesis of well-defined assemblies.

Two different strategies have been applied to increase the stability of H-bonded assemblies in which *cooperativity* between individual binding sites plays a key role. In the first, individual 1-H bond recognition motifs are covalently connected to give multidentate modules that can associate through the formation of multiple H-bonds.[65] Hunter and co-workers employed this approach to create a series of so-called zipper complexes which are held together by a combination of multiple H-bonding interactions between different amide units and additional edge-to-face $\pi-\pi$ interactions in the spacer ($\mathbf{1}_2$, Scheme 3).[66, 67] The system



$\mathbf{1}_2$

$K_{ass} = 1.1\times10^{3}\ M^{-1}$



$\mathbf{2}_2$

$K_{ass} > 4.4\times10^{4}\ M^{-1}$

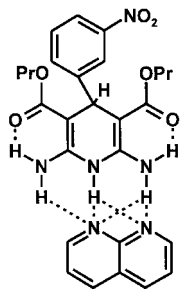
Scheme 3. Multidentate zipper complexes as reported by Hunter and co-workers ($\mathbf{1}_2$) and Gong and co-workers ($\mathbf{2}_2$).

clearly displays positive cooperativity ($\Delta G_{n\text{-mer}} > n\Delta G_{\text{monomer}}$) since the overall thermodynamic stability of the multidentate complexes increases exponentially with the number of connected binding sites. Similarly, Gong et al. recently described the dimerization of self-complementary oligoamides prepared from readily available starting materials such as isophthalic acid and 1,3-phenylenediamine ($\mathbf{2}_2$, Scheme 3).[68] More elaborate synthetic pathways were used to assemble a dimer held together by six H-bonds. This dimer has an association constant of about $10^9\ M^{-1}$.[69]

The second strategy involves the covalent synthesis of modules of rigid linear arrays of multiple H-bonding sites. This approach has received by far the most attention, and has recently resulted in the synthesis of self-complementary modules that dimerize through the formation of up to six H-bonds (see Section 2.3.4).

2.3.2. 2-H-Bond Modules

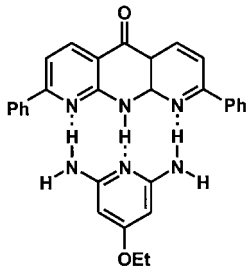
A variety of polar functionalities have a strong tendency to dimerize through the formation of two H-bonds. Many solid-state dimeric assemblies have been reported, for example, homodimers based on carboxylic acids,[51, 70] *cis*- and *trans*-amides,[71–75] imides,[76, 77] ureas,[70, 78] oxalamides,[79] and 10-hydroxy-10,9-borazarophenanthrenes,[80] or heterodimers based on carboxylic acids and amides,[81] 2-amido- or amino-pyridines,[82, 83] 2-amino-4-pyrimidones,[84] or dipyrrinone.[85] The relatively low enthalpic gain for the common AD · DA complexes (two repulsive secondary interactions) is not sufficient to fully compensate for the concomitant loss in entropy, which means that these complexes are usually only stable at relatively high ($>10^{-2}$ M) concentration. Sartorius and Schneider indeed predicted a K_{ass} value of about $60\ M^{-1}$ in $CHCl_3$, which is far too low to render the individual motif useful for noncovalent synthesis. A significantly higher value was obtained for the AA · DD complex formed from 2-methyl-1,8-naphthyridine and *N*,*N*′-dimethylurea ($K_{ass} \approx 6400\ M^{-1}$ in $CHCl_3$), which is virtually identical to the value calculated by Sartorius and Schneider.[64] However, Zimmerman and Murray observed much lower stabilities ($K_{ass} \approx 260\ M^{-1}$ in $CHCl_3$) for a closely related AA · DD complex.[86] Moreover, they showed that the stability of these complexes was significantly increased (about $3000\ M^{-1}$) by additional secondary interactions, which resulted in the formation of bifurcated H-bonds (AA · DDD H-bonded dimer **3**, Scheme 4).[87]



3

DDD · AA

$K_{ass} = 3\times10^{3}\ M^{-1}$



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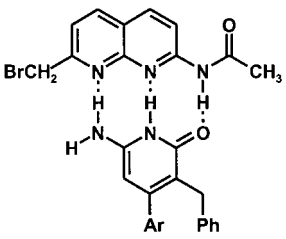
ADA · DAD

$K_{ass} = 78\ M^{-1}$



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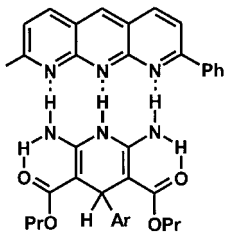
AAD · DDA

$K_{ass} = 1.7\times10^{4}\ M^{-1}$



8

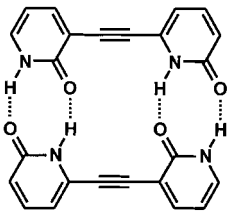
AAA · DDD

$K_{ass} > 10^{5}\ M^{-1}$

Scheme 4. Examples of a DDD · AA dimer stabilized by a bifurcated H-bond, and various 3-H-bonded dimers (ADA · DAD, AAD · DDA, and AAA · DDD arrays) with their corresponding stability constants.

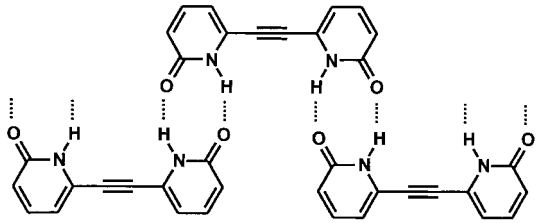
Association constants up to 4260 M^{-1} in $CD_3CN/CDCl_3$ (5/95) were found for benzamidium guests bound to naphthyridine embedded in dendrimers of various sizes.[88]

The thermodynamic stability of noncovalent assemblies based on 2-H modules can be significantly improved by connecting multiple modules in a covalent manner, similar to that discussed for 1-H-bonded modules (Section 2.3.1). The research group of Wuest, one of the pioneers in the field of noncovalent synthesis, was among the first to exemplify this principle by utilizing the self-complementarity of the 2-pyridone recognition motif.[89, 90] The bidentate modules **4** (C_s) and **5** (C_{2v}), in which two 2-pyridone units are covalently linked by a rigid acetylene spacer, exhibit very different assembly behavior as a result of the different orientation of the pyridone moieties (Scheme 5).[75] The self-complementary



4_2

$K_{ass} > 6x10^4\ M^{-1}$



5_n

Scheme 5. Self-assembly behavior of the self-complementary (C_{2v}) and non-self-complementary (C_s) dipyridone modules **4** and **5**.

C_s isomer **4** forms very stable dimers in $CHCl_3$ ($K_{ass} >$ 60 000 M^{-1} at 25 °C), whereas the C_{2v} isomer **5** forms undefined polymeric aggregates. A more flexible analogue of **4** gave very similar results, with the difference that small amounts of (cyclo)oligomeric aggregates were observed at higher concentrations. Presumably, intramolecular H-bonding within these fexible modules preorganizes the pyridone binding sites for preferential dimerization.[91]

2.3.3. 3-H-Bond Modules

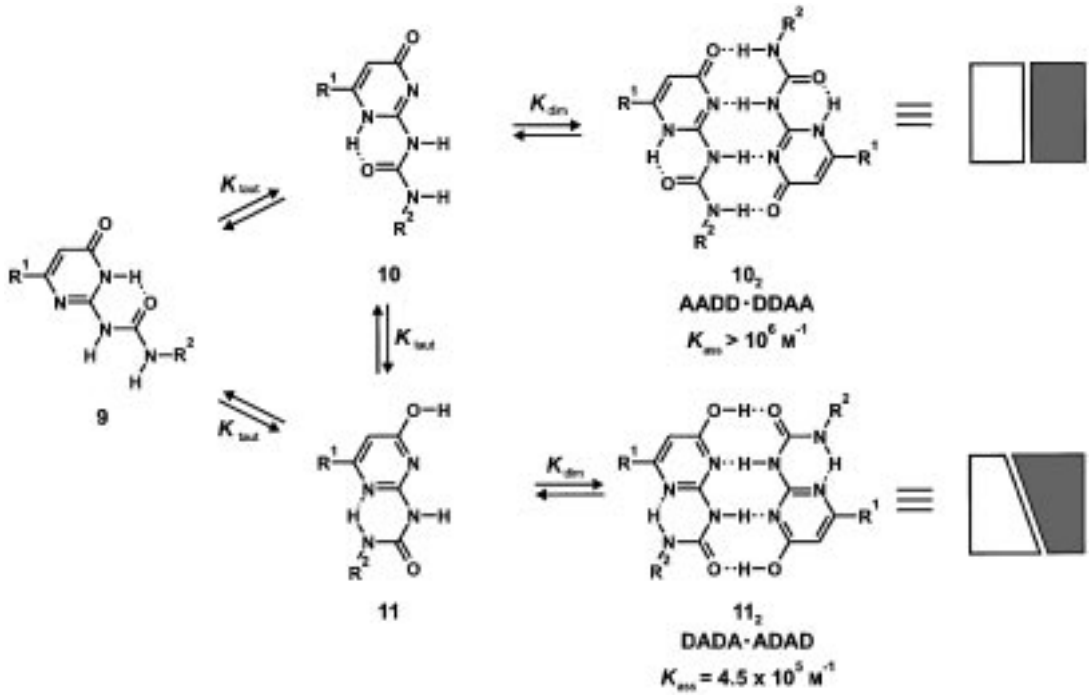
In general, 3-H-bond assembly motifs exhibit a significantly higher stability than the corresponding motifs based on two H-bonds. This feature raises their potential as a structural module for noncovalent synthesis.[92] Numerous structural variations of readily available heteroaromatics, such as pyridine[93–96] and triazine,[95, 97] have been studied in great detail. Since homodimerization is intrinsically not possible for 3-H-bond motifs, these complexes have often been designed as receptors.[98, 99] Some representative examples (**6**–**8**) with corresponding stability constants are depicted in Scheme 4. The additional H-bond in 3-H-bonded complexes contributes favorably to the overall negative enthalpy of association. However, as Jorgenson demonstrated, this stabilizing effect may be partly counterbalanced by repulsive secondary interactions that depend on the arrangement of the donor and acceptor sites in the H-bond array. Zimmerman and coworkers studied the difference in thermodynamic stability of a series of dimeric complexes with ADA · DAD, DAA · AAD, and AAA · DDD arrays with 0, 2, and 4 favorable secondary interactions, respectively, in order to test Jorgenson's hypothesis on secondary interactions.[63, 100] The stability constants were found to be of the order of 10^2, 10^3–10^4, and $> 10^5\ M^{-1}$, respectively, in $CHCl_3$, which are fully in line with Jorgenson's model.

2.3.4. Modules with Four and More H-Bonds

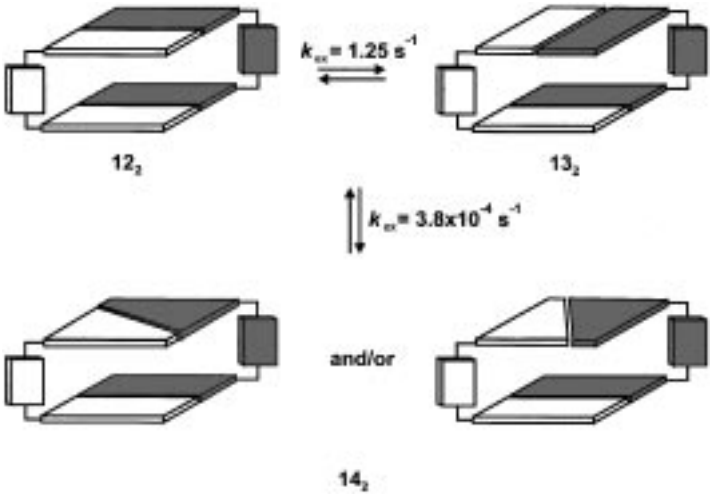
Recently the first synthetic modules that can dimerize through the formation of four H-bonds were described. Apart from the expected increase in stability, the even number of H-bond donors and acceptors allows self-complementarity to be introduced in these motifs. Self-complementarity provides an attractive property for applications in polymeric materials (see Section 6) or molecular capsules (see Section 4).

Meijer and co-workers were the first to describe a series of 2-ureido-4(1*H*)-pyrimidone derivatives that can dimerize through the formation of four H-bonds.[101, 102] The fact that certain types of ureidopyrimidones exist in three different tautomeric forms significantly complicates the assembly process. For example, the 6(1*H*)-pyrimidinone module **9** exists in a tautomeric equilibrium with the 4(1*H*)-pyrimidinone monomer **10** (AADD) and the pyrimidin-4-ol monomer **11** (DADA; Scheme 6). Both species are self-complementary with apparent dimerization constants of $> 10^6$ and $4.5 \times 10^5\ M^{-1}$ in $CHCl_3$, respectively. Predicted values using Schneider's rule were in very good agreement with the experimental value for the AADD dimer ($3.6 \times 10^6\ M^{-1}$ versus $> 10^6\ M^{-1}$), while a large difference was observed for the DADA dimer ($3.1 \times 10^2\ M^{-1}$ versus $> 4.5 \times 10^5\ M^{-1}$). This large discrepancy was attributed to preorganization of the H-bond array by formation of intramolecular H-bonds and the presence of a strong O–H ··· O=C H-bond in **11** instead of the weaker N–H ··· O=C H-bond as used in the calculation of Schneider. Indeed it was found that dimerization constants of structural analogues that cannot form the intramolecular H-bond show a much better agreement with Schneider's predictions.[101]

In subsequent work, two 2-ureido-4(1*H*)-pyrimidinones were covalently coupled through a *m*-xylylene spacer, which resulted in self-complementary molecules that can dimerize through the formation of eight H-bonds.[103] ^1H NMR spectroscopic and X-ray crystallographic analysis revealed the presence of three different isomers (**12_2**–**14_2**; Scheme 7). The individual dimers in isomer **12_2** (C_{2h}) and **13_2** (D_2) are both in the 2-ureido-4(1*H*)-pyrimidinone form and adopt either a *syn* or an *anti* orientation, which causes **13_2** to be chiral. In isomer



Scheme 6. Three different tautomeric forms of Meijer and co-workers' 6(1*H*)-pyrimidinones, with their corresponding dimerization equilibria.



Scheme 7. Tautomerization and dimerization equilibria for dimeric duplexes based on the 4(1*H*)-pyrimidinone H-bond module.

14$_2$ (C_s) one of the dimers has tautomerized to the pyrimidin-4-ol tautomer. Interconversion of isomers **12**$_2$ and **13**$_2$ is fast ($k_{ex} = 1.25\ s^{-1}$) and occurs by dissociation of one single dimer (that is, four H-bonds). Both isomers interconvert slowly ($k_{ex} = 3.8 \times 10^{-4}\ s^{-1}$) with isomer **14**$_2$, a process that involves the tautomerization of one single dimer. The very high stability of these dimeric systems combined with their easy accessibility makes them ideal modules for the noncovalent synthesis of supramolecular polymers (see Section 6.4) Recently, de Mendoza and co-workers reported the dimerization of calix[4]arenes functionalized with two 2-ureidopyrimidin-4(1*H*)-one units.[104] Similar to the assemblies of Meijer and co-workers, different tautomeric structures were observed in the ^{1}H NMR spectrum. The complex exhibits a very high thermodynamic stability, since dissociation involves the simultaneous cleavage of eight cooperative H-bonds. For this reason, dissociation of the dimeric complex in a DMSO/$CHCl_3$ mixture only starts when the DMSO content is above 50%.

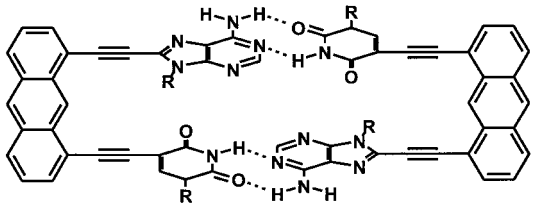
A structurally related module with an AADD H-bond array was reported by Corbin and Zimmerman.[105] In this case, analysis of the assembly process was also complicated by the presence of different tautomeric forms. In addition to this, heterodimerization of two different tautomers was observed as a result of their structural complementarity. The dimeric assemblies are highly stable in $CHCl_3$. Only a lower limit of $10^7\ M^{-1}$ could be estimated for the dimerization constant from ^{1}H NMR measurements. Davis et al. designed a compact module (AADD·DDAA) based on the squaramide unit.[106] The first heteromeric dimer involving four H-bonds (DAAD·ADDA) was reported by Lüning and Kühl.[107] The stability constant of $2000\ M^{-1}$ in $CHCl_3$ is fully in line with the expected value based on Schneider's rule. It must be noted though that the dimerization constant dropped to $16\ M^{-1}$ when bulky substituents were introduced.

Very recently, Corbin and Zimmerman reported a recognition motif (DDAADD·AADDAA) that involves six H-bonds.[108] Both monomers exist as intramolecularly H-bonded conformers which mutually unfold in solution to form a robust heterodimer with an association constant of around $5 \times 10^5\ M^{-1}$.

2.4. Motifs Inspired by Nature

Nature offers three sets of H-bonded dimers that are formed by complementary nucleobases, namely, the base pairs adenine·thymine (A·T), adenine·uracil (A·U), and guanine·cytosine (G·C). The specific interactions within these

base pairs are typically referred to as Watson – Crick type and they play a key role in the storage and decoding of genetic information. In an alternative mode, H-bonding may occur on the Hoogsteen edge. Consequently, the thermodynamic stabilities and related binding characteristics of these naturally occurring dimers have been studied extensively.[109–111] Other research groups have studied synthetic nucleotide base analogues with other H-bond patterns, such as the 6-aminopyrazin-2-one ring system,[112, 113] or transition metal complexes of synthetic or natural bases.[114, 115] These compounds have mainly received interest as potential drugs that can induce DNA mismatching. The relatively low binding constants of individual nucleotide base pairs strongly hampers their potential utility as noncovalent synthetic platforms. Sessler et al. employed the same strategy as used for synthetic motifs to develop a series of artificial dinucleotide modules with the ultimate objective of introducing sequence specifity in the self-assembly process.[116] ^{1}H NMR titrations in DMSO showed that the homodimers of the self-complementary AU dinucleotide **15**, in which the A and U nucleobases are connected through the very rigid 1,8-diethynylanthracene spacer (Scheme 8), have a dramatically improved stability



15$_2$

Scheme 8. Sessler and Wang's artificial dinucleotide complex **15**$_2$.

compared to the monomeric base pairs, whereas the use of flexible spacers hardly improves the dimer stability.[117, 118] It was also found that the presence of bulky protecting groups causes severe steric hindrance in the dimers, which leads to a significant reduction in their stability. Recently, the same research group reported a structurally very similar dinucleotide based on chemically modified guanine moieties which self-associates through the formation of eight H-bonds.[119] The corresponding homodimer was found to be stable in pure DMSO, whereas the unmodified G·G dimer, which forms only four H-bonds, is completely dissociated in DMSO/$CHCl_3$ (3/7). These results once again emphasize the importance of structural rigidity and positive cooperativity for the thermodynamic stability of noncovalent assemblies.

There is a currently growing interest in the use of DNA itself as a building block for noncovalent synthesis, as pioneered by the work of Seeman and co-workers.[120, 121] The key advantage of using DNA is the ability to specify intermolecular interactions by means of "sticky ends" technology. Short pieces of DNA, two or three turns, can be regarded as stiff building blocks, a feature essential for the formation of well-defined assemblies. Other attractive properties of DNA-based self-assembly are the readily automated synthesis, the easy modification with functional groups, and the mild conditions under which self-assembly occurs. Chen and Seeman synthesized geometrically complex structures, such as a cube[122] and a truncated octahedron,[123] fully composed of polynucleotides. Other research groups have exploited a similar approach, but used DNA only to link the components, and used synthetic molecules as branching points.[124] For example, von Kiedrowski and co-workers reported a DNA analogue of acetylene: a dimer held together by three double-stranded DNA linkages.[125]

2.5. Ion-pair-Reinforced Motifs

H-bonded assemblies in which the individual components carry opposite charges usually have increased stabilities relative to assemblies consisting of neutral components. In particular, the complexation of guanidinium cations with a variety of different anions, such as carboxylates,[126–129] sulfonates,[130] phosphates,[131, 132] and nitrates,[133] has been studied extensively. Such complexes can have association constants as high as $10^6\,\text{M}^{-1}$ in polar solvents such as DMSO. Recently, a K_{ass} value of $10^3\,\text{M}^{-1}$ in H_2O/DMSO (4/6) was reported for 2-(guanidiniocarbonyl)-1*H*-pyrrole carboxylate complexes.[134] These complexes have an increased stability relative to complexes of the guanidinium cation, because of the presence of additional H-bonds. 3-Acylaminopyridinium ions are also used instead of guanidinium ions to form tight H-bonded complexes with carboxylates.[135] Imidazolines,[136] tetrahydropyrimidines,[137] and amidines[138, 139] form very tight complexes with carboxylic acids as a result of proton transfer. Metzger and Lippert reported the dimerization of the zwitterionic 7,9-dimethylguanine, which exists as a 1:1 mixture of its neutral and cationic form at physiological pH values ($pK_a = 7.19$). The H-bond arrays of both forms are complementary, which results in the formation of a monocationic homodimer.[140] A cationic AAA·DDD complex with a K_{ass} value of $> 5 \times 10^5\,\text{M}^{-1}$ as determined from fluorescence measurements was reported by Bell and Anslyn.[141] Finally, Schneider and Wang studied a large variety of 1:1 complexes formed between tetrasubstituted porphyrins (with pyridinium, anilinium, or benzoate moieties) and negatively or positively charged ligands.[142]

3. Self-Assembly of H-bonded Multimers

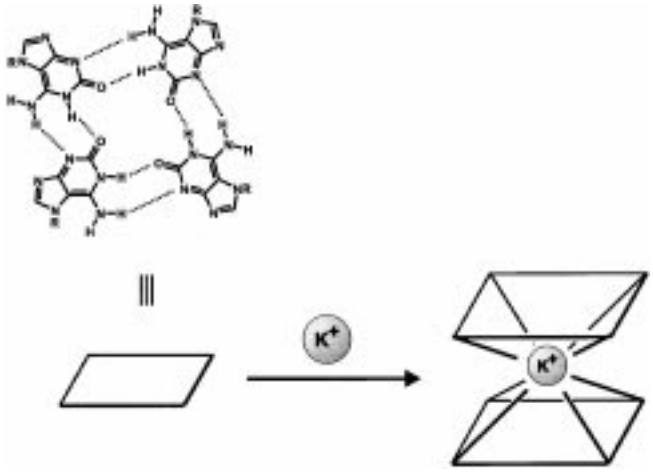
"The chemist finds illustration, inspiration, and stimulation in natural processes, as well as confidence and reassurance since they are proof that such highly complex systems can indeed be achieved on the basis of molecular components."

Jean-Marie Lehn, 1995

3.1. Introduction

Nature offers many examples of self-assembled nanostructures and therefore provides a rich source of inspiration for the design of synthetic assemblies. One such example involves the multicomponent assembly of the G_4 motif found in DNA

(Scheme 9). The ends of eukaryotic chromosomes, the telomeres, are composed of simple repeating sequences in which the 5′-3′ DNA strand contains tracts of four guanine residues alternating with short tracts of A/T-rich sequences. This strand is extended to produce a 3′-overhang containing additional sequences of guanine. It has been shown that tetramerization of the guanine sequences and subsequent stacking of the tetramers is responsible for the dimerization of telomeric DNA.[143]

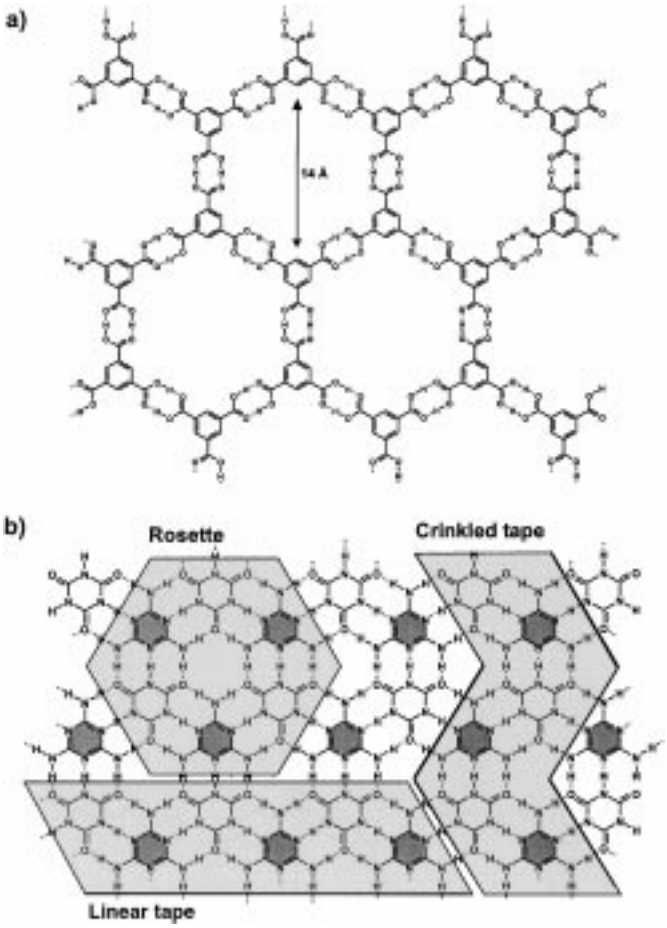


Scheme 9. Metal-induced stacking of the G-quartet.

Like guanine, synthetic molecules will only assemble into well-defined structural motifs if they are encoded with the appropiate H-bonding information and geometry. Most frequently, derivatized (hetero)aromatic molecules are used as modules, since their flat shape and rigidity optimally ensures the formation of 2D assemblies that are more easy to handle than 3D structures. The fixed geometry of aromatic six-membered rings ensures that the angle between two H-bonding sites is fixed either at 60° or 120°, which preferentially leads to trimeric or hexameric assemblies. This section reviews a number of multicomponent H-bonded assemblies that have been extensively studied with respect to their use in noncovalent synthesis.

3.2. Trimesic Acid and Isophthalic Acid Assemblies

Benzene-1,3,5-tricarboxylic acid (trimesic acid) crystallizes in a two-dimensional lattice, in which six trimesic acid units form a cyclic hexamer with an internal cavity of 14 Å (Scheme 10a).[144] X-ray studies revealed that the formation of channels, through which guest molecules can diffuse, is not observed even in the presence of guest molecules, such as *n*-tetradecane or isooctane, which can efficiently fill the channels.[145] Studies by Zimmerman and co-workers showed that the third carboxylic acid moiety is involved in non-standard H-bonding, which results in a lack of long-range ordering in the crystal. The crystallization of isophthalic acid (benzene 1,3-dicarboxylic acid) derivatives coupled through a rigid covalent linker resulted in the formation of zeolite-like channels inside the crystals.[146–148] In contrast to trimesic acid,



Scheme 10. Crystal lattices of trimesic acid (a) and isocyanuric acid and melamine (b).

isophthalic acid crystallizes in infinite chains.[149] The preference for the chain structure is most likely the consequence of subtle packing forces in the crystal, since 5-decylisophthalic acid selectively crystallizes as the cyclic hexamer.[150] However, a further increase in the alkyl chain length again results in the formation of infinite chains as a result of favorable interdigitation of the alkyl chains.[151, 152]

The assembly of isophthalic acid in solution has received very little attention. Although vapor-pressure osmometry (VPO) and ^{1}H NMR experiments suggest the formation of multicomponent assemblies above a concentration of 15 mM in toluene,[150, 152] quantitative data for the single hexamer have never been reported. A dendritic structure utilizing the self-assembly of cyclic hexamers based on isophthalic acid is discussed in Section 6.

3.3. Isocyanuric Acid · Melamine Assemblies

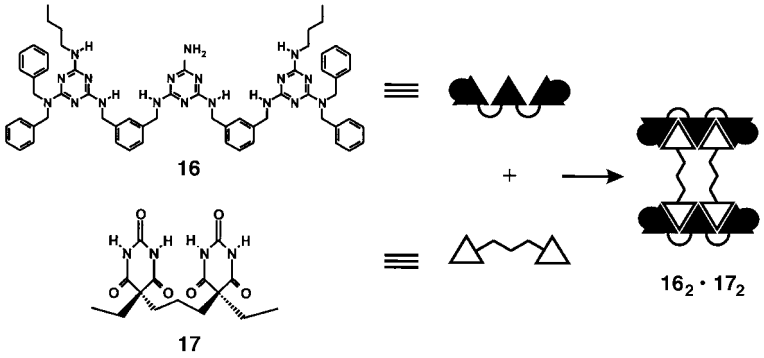
3.3.1. The Isocyanuric Acid · Melamine (CA · M) Lattice

Cyanuric acid can exist in two tautomeric forms of which the one with all protons residing on the nitrogen atoms, called isocyanuric acid (CA), is the thermodynamically most favored.[153] The three orthogonal ADA H-bonding arrays of isocyanuric acid are mutually complementary with the three

DAD arrays of melamine (M). Both compounds are rigid and the solid-state structure of the 1:1 complex of CA and M was therefore expected to be an infinite 2D lattice of alternating CA and M molecules connected through extensive H-bonds (Scheme 10b). Only recently was this prediction confirmed by X-ray crystallographic analysis.[154]

Similar to the lattice of trimesic acid (Section 3.2), three submotifs are discernible in the CA · M lattice, namely, the infinite linear and crinkled tapes, and a finite cyclic rosette motif (Scheme 10b). The research groups of Whitesides and Lehn showed that blocking one of the H-bonding arrays of both the cyanuric acid and melamine component gives either one of the submotifs.[155–157] Detailed crystallographic studies on a variety of 1:1 complexes of melamine[156] or 2,4,6-triaminopyrimidine derivatives[155] with either cyanuric or barbituric acid derivatives revealed that subtle structural changes in either the melamine or barbiturate component strongly affect the stability of the linear or crinkled tapes in an unpredictable manner.[158] Recently, Timmerman and co-workers reported the first synthesis of well-defined tapelike structures that are stable in solution.[159] They described the selective self-assembly of linear trimelamine **16** and bis(barbituric acid) derivative **17** into the [2 × 2] grid $\mathbf{16}_2 \cdot \mathbf{17}_2$ through the cooperative formation of 24 H-bonds (Scheme 11). The modular approach employed here can in principle be extended to much larger grids and provides access to well-defined oligomeric tapelike structures in solution.

Proton transfer of the highly acidic cyanurate NH proton to the relatively basic pyrimidine nitrogen atom was observed by Mascal et al. in pyrimidine – cyanurate cocrystals.[160, 161] Consequently, the tape structures, which consist of alternating

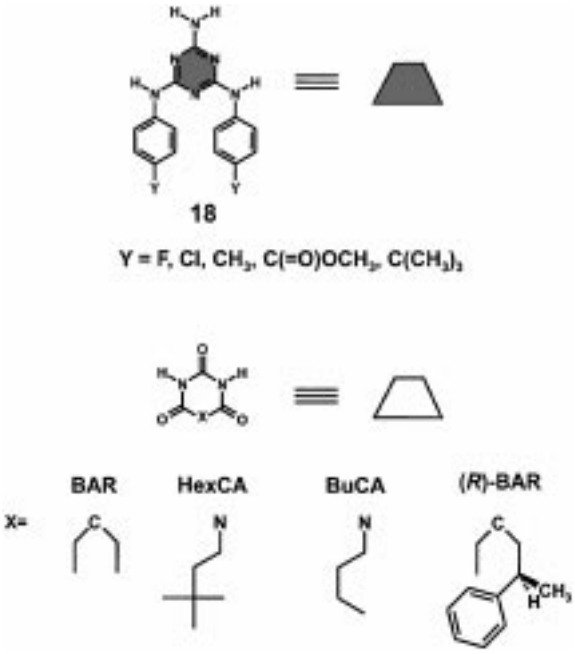


Scheme 11. Self-assembly of the tapelike structure $\mathbf{16}_2 \cdot \mathbf{17}_2$.

ADA · DAD and AAA · DDD arrays should exhibit increased stability according to Jorgenson's model of secondary interactions (see Section 2.2).

3.3.2. The Rosette Motif

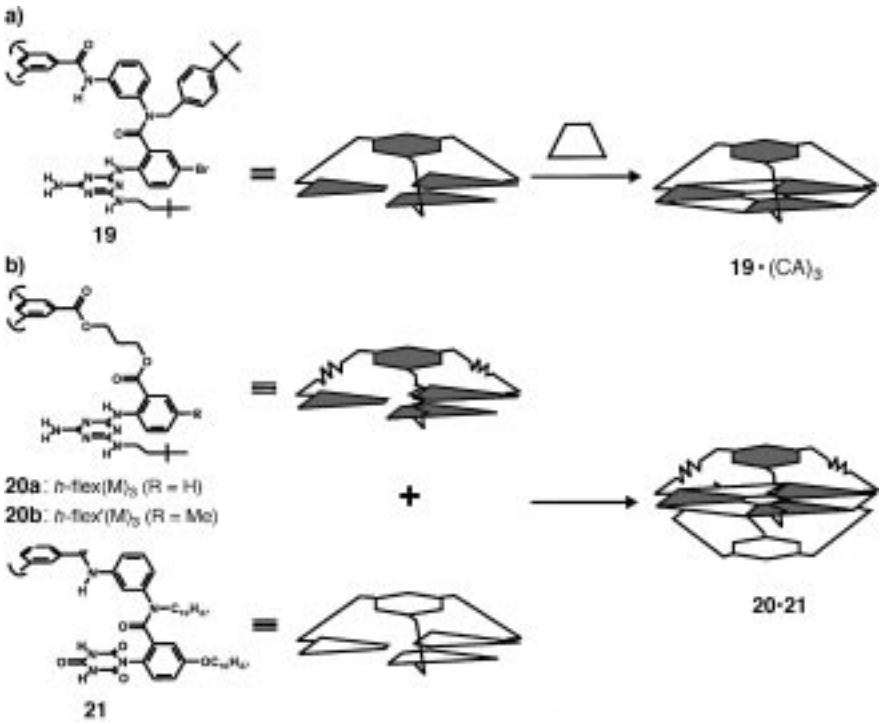
The tapelike structures are less useful for the noncovalent synthesis of nanostructures in solution as a result of their undefined shape and size, as well as their limited solubility. However, the rosette motif does not suffer from these disadvantages, and consequently has been studied extensively. Whitesides and co-workers developed two different strategies to promote the selective formation of rosette assemblies: peripheral crowding and covalent preorganization. The concept of peripheral crowding can best be illustrated by comparing the crystal structures of a series of 1:1 complexes of *N*,*N*′-bis(*p*-Y-phenyl)melamine **18** and 5,5-diethylbarbituric acid (BAR) (Scheme 12).[162, 163] Linear tapes are formed



Scheme 12. Melamines **18** used by Whitesides and co-workers to study the effect of peripheral crowding and the molecular structure of frequently employed barbiturates and cyanurates.

preferentially with melamines with small substituents Y, such as F, Cl, or CH_3. Increasing the size of substituent Y, for example, $C(=O)OCH_3$, promotes the selective formation of crinkled tapes, primarily as a result of the relief of unfavorable steric interactions between the Y substituents on adjacent melamine units that are present in the corresponding linear tapes. A further increase in size, for example, when Y is $C(CH_3)_3$, finally gives exclusively the rosette structure, in which all the repulsive steric interactions are minimized relative to those in the corresponding tapelike structures.

Covalent preorganization of the melamine and cyanurate units provides an alternative way to promote the exclusive formation of rosettes. In addition to this, the resulting assembly exhibits a higher thermodynamic stability as a result of the reduced number of separate components (from six to four or even two) and consequently a larger I_{Tm} value (see Section 3.3.4).[164] The first example involves the assembly of trismelamine hub(M)$_3$ **19**, in which three melamine units are covalently preorganized through semirigid spacers ("spokes") onto a C_3-symmetrical central hub, with three equivalents of a single cyanurate or barbiturate molecule (Scheme 13a).[157, 165] A sufficient degree of rigidity in the spokes is essential since analogues lacking one of the phenylene moieties exhibit a much lower thermody-



Scheme 13. Self-assembly of $\mathbf{19}\cdot(CA)_3$ (a) and $\mathbf{20}\cdot\mathbf{21}$ (b).

namic stability (for example, **20**). Moreover, complex formation was not observed at all for frameworks that do not contain any rigid element, such as a phenylene or amide moiety, in the spokes. ^{1}H NMR competition experiments clearly proved the increase in the thermodynamic stability of the preorganized rosette $\mathbf{19}\cdot(CA)_3$. This assembly was formed quantitatively upon addition of **19** to a solution of the six-component single-rosette assembly $(\mathbf{18})_3\cdot(CA)_3$. A further reduction of the number of particles consequently stabilizes the assembly even more, for example, when the three cyanurate units are covalently preorganized in a similar manner as the three melamine units.[166] The two-component assembly consisting of *h*-flex(M)$_3$ **20** and hub(CA)$_3$ **21** (1:1 ratio; Scheme 13b) is among the thermodynamically most stable assemblies synthesized which also exhibits a very high kinetic stability (see Section 3.3.6).

3.3.3. Self-Assembly of Dynamic Nanostructures

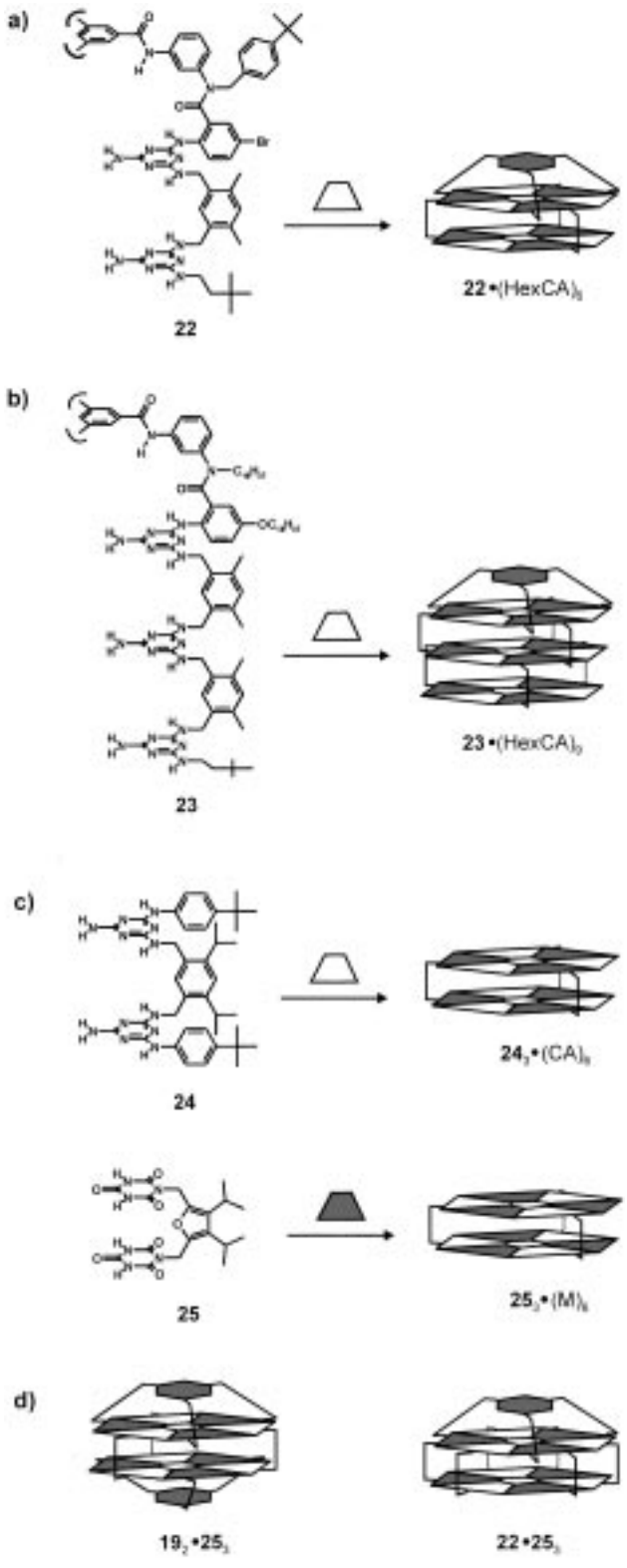
Having developed a general methodology for the exclusive formation of the rosette submotif, Whitesides and co-workers employed this motif as a module for the construction of larger assemblies, which had the potential for internal cavities.[167] The assembly of oligomelamine derivatives, such as hub(MM)$_3$ **22** (obtained by modular extension of hub(M)$_3$ **19** with three additional melamine units; Scheme 14a),[168] and six equivalents of neohexylCA (hexCA) leads to the quantitative formation of the seven-component assembly $\mathbf{22}\cdot(hexCA)_6$, which is held together by a total of 36 H-bonds. The assembly process displays positive cooperativity, since no partially formed assemblies but only the fully intact assembly $\mathbf{22}\cdot(hexCA)_6$ and free **22** are observed when less than six equivalents of neohexylCA are present. In a similar fashion the ten-component assembly $\mathbf{23}\cdot(hexCA)_9$, with three parallel rosette layers, can be assembled from hub(MMM)$_3$ **23** and nine molecules of neohexylCA (Scheme 14b). For multicomponent assemblies such as $\mathbf{23}\cdot(hexCA)_9$ it takes 48 h at room temperature before the assembly process has reached the thermodynamic equilibrium.[169]

A different approach towards noncovalent assemblies with improved stability involves the sideways connection of two rosette layers.[170] *m*-Xylylene- and furane-based linkers were found to provide sufficient preorganization of the melamine and cyanurate units while being flexible enough to adapt to local perturbations. The assembly of bis(M)$_2$ **24** or bis(CA)$_2$ **25** with two equivalents of a monomelamine or -cyanurate unit gives double rosette assemblies $\mathbf{24}_3\cdot(CA)_6$ and $\mathbf{25}_3\cdot(M)_6$, respectively, which have improved thermodynamic stability compared to single rosettes (Scheme 14c; see Section 3.3.4). However, the stability of these rosette assemblies depends critically on the peripheral crowding within the linkers and substituents. A combination of the two approaches has been used to obtain the two most stable assemblies of the rosette family, namely the five-component assembly $\mathbf{19}_2\cdot\mathbf{25}_3$ and the four-component assembly $\mathbf{22}\cdot\mathbf{25}_3$ (Scheme 14d).[168, 171]

Reinhoudt and co-workers showed that calix[4]arenes serve as excellent linkers for double-rosette assemblies.[172] Calix[4]arenes diametrically substituted with two melamine fragments at the upper rim were found to form the thermodynamically stable double rosettes $\mathbf{26}_3\cdot(BA)_6$ or $\mathbf{26}_3\cdot(CA)_6$ with a large variety of different barbiturates and cyanurates (Scheme 15).[173, 174] The conformation of the calixarene skeleton thereby plays an important role. Calix[4]arenes fixed either in the pinched cone or 1,3-*alternate* conformation perfectly preorganize the melamine units in the preferred planar orientation and consequently form stable assemblies, while assemblies based on the flexible tetramethoxycalix[4]arene skeleton are much less stable.[175] In addition to this, the calixarene module provides sufficient steric bulk to exclude the formation of tapelike structures and therefore enables the introduction of a wide variety of nonbulky functional groups. Recently, the quantitative formation of the 15-component tetrarosette assemblies $\mathbf{27a}_3\cdot(BAR)_{12}$ and $\mathbf{27b}_3\cdot(BAR)_{12}$, which consist of four parallel rosette layers that are held together by a total of 72 H-bonds, was reported by Reinhoudt and co-workers (Scheme 16).[176] The tetramelamine components **27a** and **27b** consist of two calix[4]arene dimelamine units that are covalently connected either through a rigid *m*-xylylene (**27a**) or a flexible hexyl spacer (**27b**).

3.3.4. Thermodynamic Stability

The large series of structurally related rosette assemblies available, which differ mainly in the number of H-bonds and



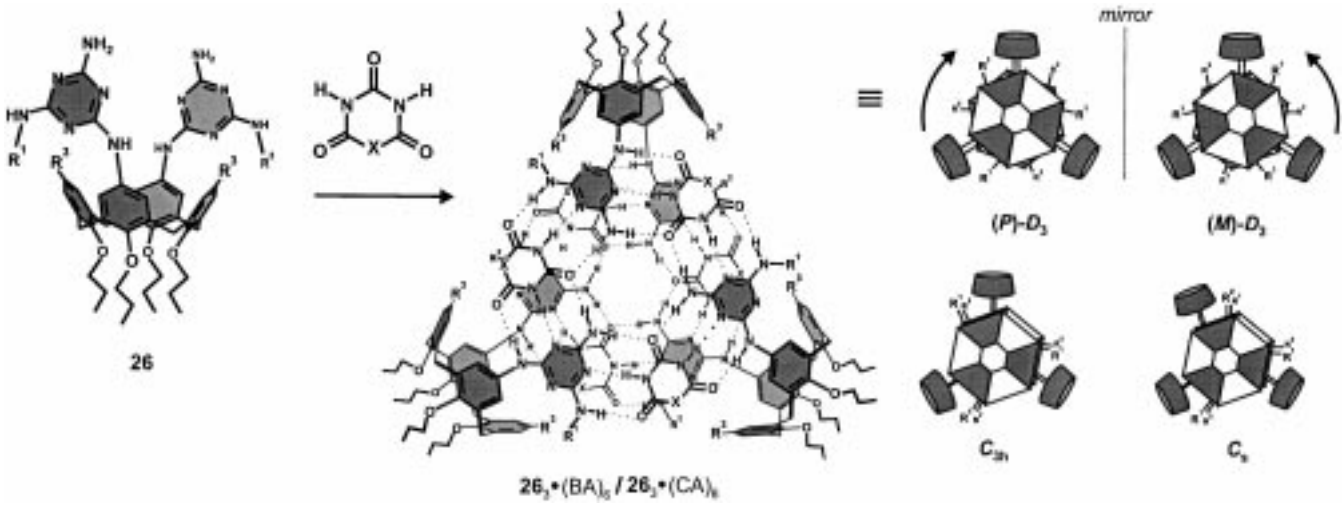
Scheme 14. Self-assembly of $\mathbf{22}\cdot(\mathrm{HexCA})_6$ (a), $\mathbf{23}\cdot(\mathrm{HexCA})_9$ (b), $\mathbf{24}_3\cdot(\mathrm{CA})_6$ and $\mathbf{25}_3\cdot(\mathrm{M})_6$ (c), and $\mathbf{19}_2\cdot\mathbf{25}_3$ and $\mathbf{22}\cdot\mathbf{25}_3$ (d).

the number of associating particles, has provided a unique opportunity to study their thermodynamic stability in a systematic way.[164] The thermodynamic stability reflects the difference in free energy ΔG between the assembly and the free components. The enthalpy term ΔH is mainly determined by the enthalpy of H-bond formation and is proportional to the number N_{HB} of H-bonds: $\Delta H = c_1 N_{HB}$. The entropy term ΔS is determined by changes in the translational, rotational, and conformational entropy, which all together are proportionally related to $N-1$, where N is the number of particles involved.[177] The entropy term is therefore written as $\Delta S = c_2(N-1)$. From this quantitative analysis it follows that $\Delta G = c_1 N_{HB} - c_2(N-1)T$. From this equation a melting point index $I_{\mathrm{Tm}} = N_{HB}/(N-1)$ was defined as a parameter that qualitatively predicts the stability of a particular H-bonded assembly. ^{1}H NMR titration experiments with polar solvents such as DMSO or methanol have been used to measure the stability in solution.[164] The χ value, that is, the amount of polar solvent at which only 50% of the assembly is present in solution, has been defined as a general indicator for the thermodynamic stability of an assembly. Comparison of the calculated (I_{Tm}) and experimentally determined stabilities (χ_{DMSO}) clearly exemplifies the predictive value of this relatively simple parameter. In principle, a thermodynamic evaluation such as this is not restricted to H-bonded rosette assemblies, but should be applicable to other noncovalent systems as well. However, it should be noted that comparison of I_{Tm} values for a series of assemblies is only meaningful when these are structurally related in terms of rigidity. For example, $\mathbf{19}\cdot(\mathrm{CA})_3$ and $\mathbf{20}\cdot(\mathrm{CA})_3$ (Scheme 13) have identical I_{Tm} values, but these values do not reflect the much lower thermodynamic stability of the latter that arises because of higher entropic costs. Similarly, replacement of the barbiturate for cyanurate units in an assembly does not change the I_{Tm} value, but is known to significantly increase the thermodynamic stability as a result of the increased H-bond strength of cyanurates.

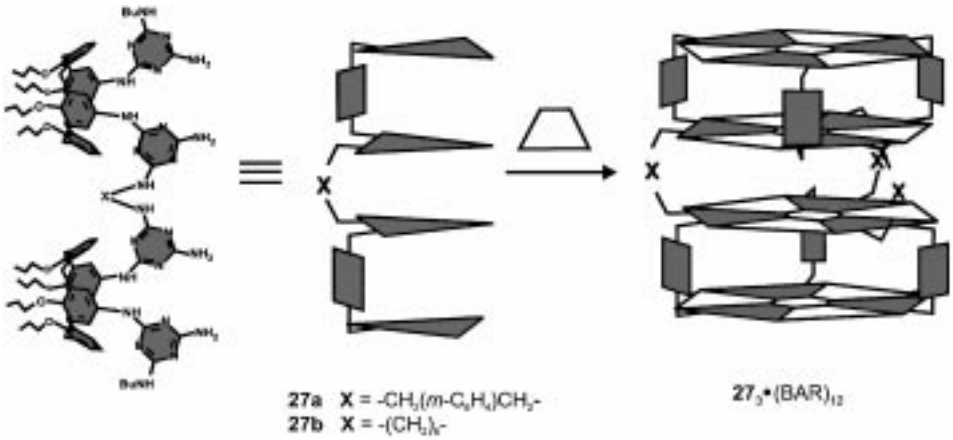
3.3.5. Kinetic Stability

One of the major differences between covalent and noncovalent synthesis concerns the fact that the thermodynamically stable noncovalent assemblies are kinetically not inert. This marks one of the most intriguing aspects of noncovalent assemblies and provides unique opportunities to study the mechanism of assembly formation (see Section 3.3.8). However, kinetic stability measurements are often complicated by the fact that exchange occurs too fast to be followed conveniently by ^{1}H NMR spectroscopy.

The dissociation rates of H-bonded assemblies rapidly decrease with the number of H-bonds that are broken in the dissociation of a particular component. For example, the dissociation rate constant of the 1-cyclohexyluracil dimer (cleavage of two H-bonds) is of the order of $10^8 - 10^9\ \mathrm{s}^{-1}$ in $CHCl_3$ at 20 °C,[39] while a rate constant of $21\ \mathrm{s}^{-1}$ in $CDCl_3$ at 20 °C was determined for the dissociation of the BAR units from assembly $\mathbf{26b}_3\cdot(\mathrm{BAR})_6$ (cleavage of six H-bonds).[178] Furthermore, it was found that exchange rates are particularly sensitive to the polarity and H-bond character of the solvent. For example, the exchange of dimelamines **26a** and **26b** (cleavage of 12 H-bonds) in a mixture of assemblies $\mathbf{26a}_3\cdot(\mathrm{BAR})_6$ and $\mathbf{26b}_3\cdot(\mathrm{BAR})_6$ to give the heteromeric assemblies $\mathbf{26a}_2\cdot\mathbf{26b}_1\cdot(\mathrm{BAR})_6$ and $\mathbf{26a}_1\cdot\mathbf{26b}_2\cdot(\mathrm{BAR})_6$ occurs within seconds in $CDCl_3$, even at −50 °C, while it takes 2.5 hours in toluene at 25 °C to reach the thermodynamic equilibrium

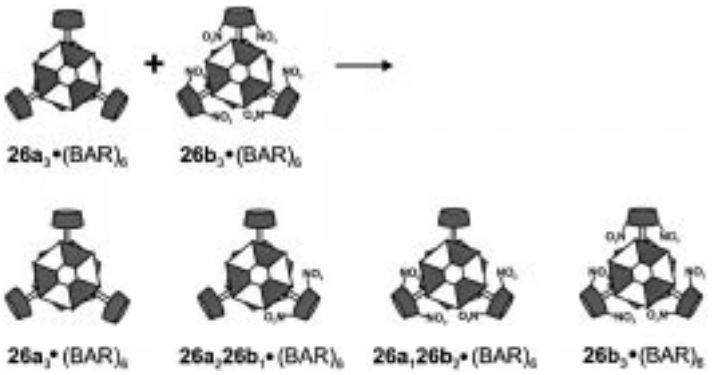


Scheme 15. Self-assembly of calix[4]arene double rosettes and the possible conformational isomers. **26a**: $R^1 = R^2 = (CH_2)_3CH_3$, $R^3 = H$; **26b**: $R^1 = R^2 = (CH_2)_3CH_3$, $R^3 = NO_2$; **26c**: $R^1 = R^2 = (R)$-$CH(C_6H_5)CH_3$, $R^3 = H$; **26d**: $R^1 = (R)$-$CH(C_6H_5)CH_3$, $R^2 = (S)$-$CH(C_6H_5)CH_3$, $R^3 = H$; **26e**: $R^1 = R^2 = (CH_2)_6CH{=}CH_2$, $R^{32} = H$.



Scheme 16. Self-assembly of calix[4]arene tetrarosettes.

(Scheme 17).[179] ^{1}H NMR measurements for the related assemblies **26a**$_3 \cdot$(BuCA)$_6$ and **26b**$_3 \cdot$(BuCA)$_6$ gave a rate constant of $7.0 \times 10^{-5}\,s^{-1}$ for the dissociation of the dimelamine fragments at 70 °C in [D$_6$]benzene, which clearly reflects the very high kinetic stability of these dynamic structures.[180]



Scheme 17. Exchange of calix[4]arene dimelamines **26a** and **26b** results in the formation of heteromeric assemblies **26a**$_2 \cdot$**26b**$_1 \cdot$(BAR)$_6$ and **26a**$_1 \cdot$ **26b**$_2 \cdot$(BAR)$_6$.

Seto and Whitesides have used kinetic measurements extensively to study the exchange mechanism of assemblies with very high stability, such as **20**$\cdot$**21** (see Scheme 13).[166] Analysis of the kinetic data for the exchange of **20a** with **20b**, a closely related structural analogue, in the assembly **20a**$\cdot$**21** gave a rate constant of $5.0 \times 10^{-7}\,s^{-1}$ for the exchange. On the basis of these data a mechanism was proposed in which assembly **20a**$\cdot$**21** completely dissociates into the free components **20a** and **21** through disruption of 18 H-bonds, followed by re-assembly of **21** and **20b** into the new assembly **20b**$\cdot$**21**.

In view of the data presented here, which show that the rate of exchange of assembly components tremendously decreases with the number of disrupted H-bonds ($10^8\,s^{-1}$ for 2 H-bonds versus $5.0 \times 10^{-7}\,s^{-1}$ for 18 H-bonds), it can readily be expected that H-bond-directed self-assembly processes will become kinetically rather than thermodynamically controlled; this phenomenon is well-known for covalent and coordinative bond-forming processes.[181] Recently, Reinhoudt et al. found such a case, namely the self-assembly of 3 calix[4]arene tetramelamine and 12 CYA units into a 15-component structure, in a similar way as the assembly of double rosettes. However, it turned out that the assembly is not formed even after extensive heating in chloroform for many hours, and is most likely the result of the initial formation of kinetically stable products that resist the subsequent reassembly into the thermodynamically more stable tetrarosettes.

3.3.6. Characterization of Rosette Assemblies

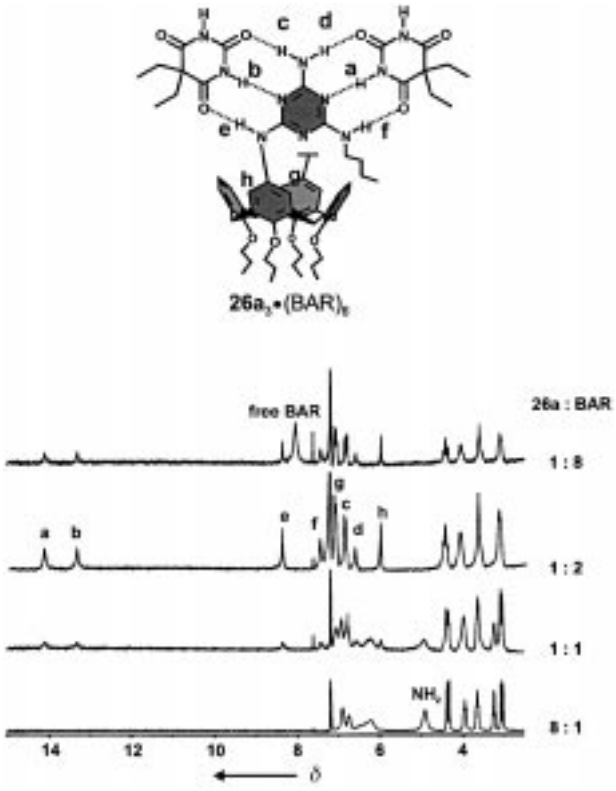
A solubility test often provides qualitative information about the assembly process. In general the individual compo-

nents with polar H-bonding sites are sparingly soluble in apolar solvents, such as chloroform or toluene. Upon formation of a well-defined assembly, such as the rosette, the solubility in apolar solvents dramatically increases, since all the polar sites are utilized in strong H-bonding interactions.[171] However, when nondefined tapelike assemblies containing polar end groups are formed, the solubility is often too low and the assemblies tend to precipitate.

Structural identification of H-bonded assemblies with low kinetic stability by ^{1}H NMR spectroscopy is troublesome when free components and assemblies are in fast exchange on the NMR time scale. In this case the proton signals represent an average resonance for all the species in solution and it is therefore impossible to decide whether rosette or tape assemblies are formed.[163] In cases where slow exchange between the assembly and components occurs ^{1}H NMR data provide a wealth of information about the assembly process. The spectra of well-defined assemblies usually display very sharp signals, while the spectra are often very broad for nondefined oligomeric assemblies. The H-bonded NH protons, which resonate between $\delta = 14$ and 16, are excellent probes for studying the structure and stability (both thermodynamic and kinetic) of the assemblies. The number of NH proton signals also provides important information regarding the structural symmetry of the assembly. For example, one of the assemblies of $\mathbf{19} \cdot (CA)_3$ shows eight different signals for the NH protons of the H-bonded cyanurates, two (high intensity) for the C_3-symmetrical isomer, and six for the less symmetrical C_1 isomer (see Section 3.3.7).[182] Similar evaluations have been worked out for larger assemblies, but the huge number of possible isomers and consequently the huge number of different signals may render analysis very complicated.[183] The presence of two different signals for the barbiturate NH protons in the ^{1}H NMR spectrum of assembly $\mathbf{26}_3 \cdot (BAR)_6$ first of all reveals that both protons reside in a chemically different environment within the assembly as a result of the dissymmetric substitution of the melamine units. Moreover, it shows that the assembly is exclusively present as the D_3 isomer (see Section 3.3.7).[173]

In cases of slow exchange ^{1}H NMR titration experiments are also used to obtain information regarding the stoichiometry and cooperativity of the assembly process. For example, the spectrum of a mixture of calix[4]arene dimelamine **26a** and BAR in $CDCl_3$ shows exclusively signals for assembly $\mathbf{26a}_3 \cdot (BAR)_6$ with a 1:2 ratio of the components, while below or beyond this ratio additional signals for free **26a** or BAR are observed (Scheme 18).[172] Signals for intermediate or partially formed $\mathbf{26}_3 \cdot (BAR)_6$ are not observed at any point of the titration, which indicates that assembly $\mathbf{26}_3 \cdot (BAR)_6$ is formed in a cooperative manner.

A variety of different techniques have been used to estimate the molecular weight of H-bonded assemblies. Vapor-pressure osmometry (VPO) studies by Seto and Whitesides showed that the VPO data generally correspond very well with calculated molecular weights for assemblies with very high stability.[171] However, the results for assemblies with low thermodynamic stability are strongly dependent on the assembly concentration,[163] which severely limits the general use of this technique. The results of gel permeation chromatography (GPC) studies are also strongly dependent on the assembly stability, since assemblies with low kinetic stability tend to show severe tailing as a result of (partial) decomposition on the column.



Scheme 18. NMR titration of calix[4]arene dimelamine **26a** with BAR.

Several research groups have investigated the identification of H-bonded aggregates by mass spectrometry. These studies reveal that ion-labeling techniques are usually required to observe the assemblies.[184] Lehn and co-workers reported ion-labeling electron-spray mass spectrometry (IL-ESMS) studies of single rosettes derivatized with [18]crown-6 moieties by using K^+ ions.[185] This labeling method enables the identification of intact rosette assemblies, but a significant amount of fragmented assemblies were observed as well. A very similar method was recently reported by Sessler and co-workers, who showed that H-bonded assemblies derivatized with ferrocene groups can be detected by ESMS after oxidation in air (O-ESMS).[186] Whitesides and co-workers employed a more pragmatic approach, in which ionization of the neutral assemblies occurs by labeling with Ph_4PCl.[187] Several different rosette assemblies were found to form strong complexes with chloride ions, most likely through cooperative binding to the three amide NH groups of the hub spacer. More recently, a Ag^+ labeling technique for the mass spectrometric identification of single, double, and tetrarosettes was reported by the Reinhoudt group.[53, 188] These studies show that assemblies with (aromatic) π-donor, cyano, or crown ether functionalities form strong complexes with Ag^+ ions which can be detected using MALDI-TOF MS (TOF = time-of-flight). The absence of signals for fragmented assemblies illustrates the unprecedented mildness of this technique.

Single-crystal X-ray diffraction studies have not been used very often for the structural characterization of rosette-type assemblies, because of difficulties in obtaining suitable crystals. So far, only two crystal structures of an isolated single rosette and one of a calix[4]arene-based double rosette have been reported.[162, 173, 189]

Computational simulations by Whitesides and co-workers showed that the DP parameter, that is, the average deviation from planarity, correlates well with the relative thermodynamic stabilities of a variety of hub-based single-rosette assemblies determined experimentally. Less preorganization in the spacers results in a larger deviation from planarity.[190, 191] Molecular dynamics (MD) simulations in chloroform solvent boxes revealed that one molecule of chloroform strongly stabilizes the assembly by filling the empty cavity between the hub spacer and the rosette motif. This fact could not be confirmed experimentally, most likely because of fast exchange with the bulk solvent. Similar solvent effects were also found by Reinhoudt and co-workers, who studied conformational isomerism (see Section 3.3.7) in a variety of different double-rosette assemblies using MD simulations.[174] In most cases the difference in the relative stability of the three isomers was determined by steric interactions between the components. However, it was also found that in certain cases chloroform molecules penetrated the assembly, which caused a distortion and eventually a complete destruction of the structure.

3.3.7. Regioselectivity in Noncovalent Synthesis

The products of noncovalent synthesis are often—as for covalent synthesis—not uniform as a result of tautomerism, stereoisomerism, or conformational isomerism (for an early example see Section 2.3.4). For example, assembly **19** · $(CA)_3$ is present in two conformers having either C_3 or C_1 symmetry, each of them being present as a mixture of enantiomers.[166] The observed isomerism is the result of the dissymmetrical substitution pattern of the melamine fragments. In the C_3 isomer all three melamine fragments have an identical orientation (depending on the enantiomer, either *P* (clockwise) or *M* (anticlockwise)). The orientation of one melamine fragment in the C_1 isomer is reversed, which lowers the symmetry of the assembly.

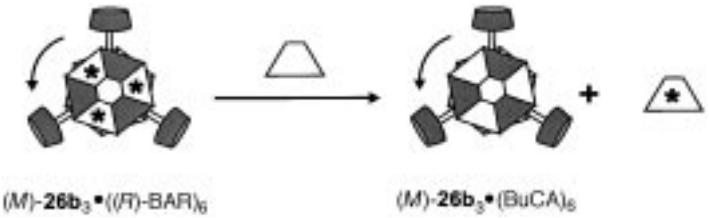
The double-rosette assemblies display a similar kind of regioisomerism and can be present in three different isomeric forms with either D_3, C_{3h}, or C_s symmetry (Scheme 15).[174] In the D_3 isomer the melamine units of each calix[4]arene adopt a staggered orientation, which causes the assembly to be chiral. The C_{3h} and C_s isomers, in which the melamine units are in an eclipsed orientation, have a plane of symmetry and are therefore achiral. The C_{3h} and C_s isomers are different in the sense that the C_s isomer lacks a C_3 axis as a result of a 180° rotation of one of the calix[4]arene moieties. In most cases one of the isomers is formed predominantly. However, small structural changes or solvent effects affect the isomer distribution in an unpredictable manner. Recently, it was shown that peripheral chiral groups in the assembly can be used to direct the regioselective formation of the isomers with D_3, C_{3h}, and C_s symmetry.[174] For example, assembly **26a**$_3$ · $(hexCA)_6$ is formed as a mixture of all three isomers in a 5:2:3 ratio as apparent from the presence of 10 different signals for the NH protons of hexCA. When the achiral butyl substituents in **26a** are replaced by (*R*)-1-phenylethyl groups, as in **26c**, the D_3 isomer is formed exclusively, as evident from the presence of only two signals for the NH protons of hexCA. The reason for the observed selectivity is that the chiral substituents have a strongly preferred orientation with respect to the rosette core which can only be adopted when the assembly is present in the D_3 form. For similar reasons, the C_{3h} and C_s isomers are formed exclusively when dimelamine **26d**, which carries one (*R*)- and one (*S*)-1-phenylethyl substituent, is used. In this case the chiral substituents can only adopt their preferred orientation when the melamine fragments assemble in the eclipsed isomeric form.

3.3.8. Stereoselectivity in Noncovalent Synthesis

Assemblies composed of achiral components express supramolecular chirality when the building blocks are arranged in an unsymmetrical fashion. Yang et al. showed that an achiral barbiturate and melamine assemble into an enantiomeric pair of supermolecules as a result of the presence of a double bond in the barbiturate component.[192] Further assembly results in the formation of mesoscopic supercoiled structures. Since the components themselves are achiral, both left- and right-handed supercoils are observed.

As mentioned before, assembly **26a**$_3$ · $(BAR)_6$ is exclusively present as the D_3 isomer, as was proven both by ^{1}H NMR spectroscopic and X-ray crystallographic analysis.[173] The assembly is chiral and consequently forms a racemic mixture of *M* and *P* enantiomers, since none of the individual components (**26a** or BAR) contains a chiral center (Scheme 15). The Reinhoudt group found that the use of chiral dimelamines or cyanurates strongly induces the helicity of the assembly, and results in the *diastereoselective* formation of assemblies with either *M* or *P* helicity, depending on the configuration of the chiral substituent (*R* or *S*) used. The asssembly process occurs with an unprecedentedly high diastereoselectivity ($de > 98\,\%$) according to ^{1}H NMR and CD measurements.[193] The assemblies exhibit a high CD intensity ($\Delta\varepsilon \approx 100\ cm^2\,m\,mol^{-1}$), in contrast to the free chiral components that are hardly CD active ($\Delta\varepsilon < 8\ cm^2\,m\,mol^{-1}$). The assembly of trismelamine **19** with optically active cyanurates also displays diastereoselectivity, but the *de* value is only 35 % in this case.[194]

Recently, the same group reported the first example of an enantiomerically pure H-bonded assembly (*M*)-**26b**$_3$ · $(BuCA)_6$ which does not contain any chiral carbon centers.[180] The enantioselective synthesis of assembly (*M*)-**26b**$_3$ · $(BuCA)_6$ is a two-step procedure that starts with the diastereoselective assembly ($de > 98\,\%$) of achiral dimelamine **26b** and enantiomerically pure barbiturate (*R*)-BAR to give exclusively (*M*)-**26b**$_3$ · $((R)\text{-BAR})_6$. In the second step, the chiral (*R*)-BAR units are quantitatively replaced by achiral BuCA units, to give assembly (*M*)-**26b**$_3$ · $(BuCA)_6$ in the enantiomerically pure form (Scheme 19). This assembly turns out to be surprisingly stable towards racemization ($E_{act} =$



Scheme 19. Noncovalent synthesis of an enantiomerically pure H-bonded assembly.

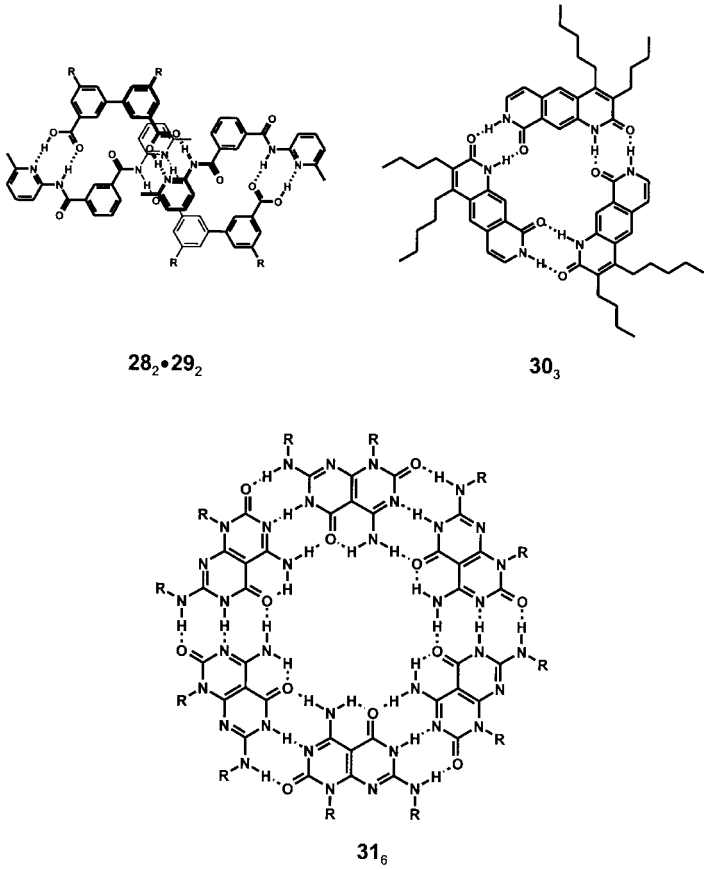
25.3 kcal mol^{-1}), with a half-life of 4.5 days in benzene at 18 °C. Detailed kinetic studies revealed that racemization of assembly (M)-**26b**$_3 \cdot$(BuCA)$_6$ occurs by a dissociative mechanism, with a rate constant of 1.1×10^{-5} s^{-1}, in which the expelled (R)-BAR acts as a catalyst.

3.4. Miscellaneous motifs

H-bonding between simple dicarboxylic acids and diacylaminopyridines can result in a variety of structures, which subtly depend on the spacers that separate the functional groups. Initial solid-state studies by Hamilton and co-workers revealed that 1:1 complexes are formed when the spacers of both components are comparible in size. However, when the spacer of the diacid is much longer than the spacer of the diacylaminopyridine component, the molecules arrange themselves into infinite linear arrays.[82] Changing the bite angle between the two acylaminopyridine rings by using a 1,3- instead of a 1,4-functionalized phenylene unit results in the formation of a H-bonded helix with heptanedioic acid as the complementary component.[195, 196] Interestingly, when the size and conformational flexibility of the diacid substrate was restricted, the compounds assembled as the discrete $[2 \times 2]$ aggregate **28**$_2 \cdot$**29**$_2$ both in the solid state and in solution (Scheme 20).[197]

An early example of the assembly of self-complementary components involves the noncovalent cyclotrimerization of pyrido[4,3-*g*]-quinoline **30** (Scheme 20). The cyclic trimer is formed in a cooperative way through the formation of six H-bonds.[198] Both VPO and ^{1}H NMR dilution studies confirm the high stability of the assembly ($K_{ass} = 20000\,\text{M}^{-2}$ in $CDCl_3$). Phthalhydrazides exist as an equilibrium of three tautomeric forms, of which the lactim–lactam tautomer can self-assemble into a trimer through the formation of six H-bonds. This motif has been found in the crystal structure of luminol and has been used as a module for supramolecular liquid crystals (see Section 6).[199]

The groups of Lehn and Mascal both reported the assembly behavior of the self-complementary compound **31**, which is designed in such a way that it can only assemble into a cyclic hexameric motif (Scheme 20).[200, 201] These Janus-type molecules, named after the Roman doubly faced god, possess complementary AAD and DDA H-bonding arrays at an angle of 120°. Assembly studies of **31** in apolar solvents were hampered by solubility problems, but ^{1}H NMR spectroscopic and VPO measurements indicated that the desired hexamer is indeed formed in solution.[200] Moreover, X-ray crystallographic studies confirmed the presence of the cyclic hexamer in the solid state.[201] Recently, Kolotuchin and Zimmerman described the synthesis of a very similar molecule with complementary AAD and DDA H-bonding sites.[202] The increased solubility of this assembly strongly facilitated the characterization using 2D NMR techniques and size-exclusion chromatography (SEC).



Scheme 20. Miscellaneous multimeric assemblies.

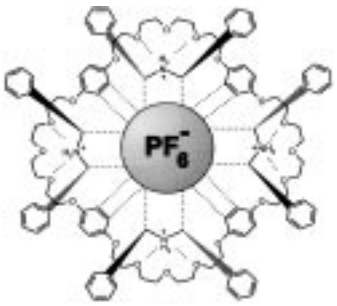
3.5. Self-Assembled Ionophores by H-Bonding

H-bonded assemblies often show interaction with ionic guest molecules, but this type of recognition has not been studied in detail, presumably since higher order aggregates are usually formed. The main contributions in this area come from the groups of Davis and Gottarelli, who studied the cation-binding properties of the well-known G-quartet and related self-assembled structures (see Scheme 9).[203, 204] Earlier studies in the 1970s and 1980s by the Pinnavaia and Laszlo groups already revealed that isolated 5′-guanosine monophosphates also form H-bonded tetramers that have a large tendency to stack.[205, 206] These studies revealed the crucial role of cations such as Na^+, K^+, and Rb^+ in stabilizing the guanosine tetramer through ion–dipole interactions with the inner carbonyl moieties.[207, 208] Furthermore, K^+ ions were shown to induce the stacking of two tetramers into an octameric structure, the exact molecular structure of which was recently confirmed by NMR spectroscopy.[208–211] The

molecular structure of the G-quartet itself has also been unraveled by NMR detection of the N−H···O=C H-bonds in the ^{13}C- and ^{15}N-labeled nucleic acid strand d(GGGTTCAGG), which forms a dimeric quadruplex containing two G-quartets.[212] The binding of monovalent metal ions could be directly detected using ^{205}Tl NMR spectrometry[213] and ESI-MS.[214] Recently, Sessler et al. reported the formation of a G-quartet even in the absence of templating metal cations. In this case, peripheral aryl moieties are presumed to stabilize the tetramer over ribbonlike structures.[215]

Both Gottarelli and Davis envisioned the potential utility of the G-quartet for the extraction of metal cations into organic media. Gottarelli et al. studied the ability of 3′,5′-didecanoyl-2′-deoxyguanosine to extract metal picrates into organic solvents. The binding selectivity of the assembly for cations decreased in the order of $K^+ > Na^+ > Cs^+$.[203] Similar results were obtained by Davis et al.[204] with self-assembled ionophores derived from isoguanosine derivatives.[216] They showed that the self-assembled ionophores act as a phase-transfer catalyst by transporting a nucleophilic counterion either from the solid or the aqueous phase.[217] The selectivity of the assembly for Cs^+ ions is comparable to the best synthetic covalent ionophores.[218] Remarkably, while exploring the properties of the Cs^+ complex Davis and co-workers found that this cation induces the formation of a duplex of pentamers, rather than a duplex of tetramers as observed for the K^+ ion.[219] Self-assembled ionophores can have significant advantages over covalent ionophores, such as calixarene crown ethers or cryptands, in terms of recovery of the host molecules from the complexes, which is an important step in the isolation of radioactive ^{137}Cs isotopes from nuclear aqueous waste. Recovery is relatively simple for noncovalent ionophores since the ion complexes can be strongly destabilized upon the addition of agents that disrupt H-bonds.

Stoddart and co-workers reported the self-assembly of H-bonded assembly **32**, which exhibits an affinity for anions (Scheme 21).[220] They found that macrocyclic polyethers form inclusion complexes of varying stoichiometries with secondary dibenzylammonium ions. The driving force for this assembly process is the formation of charged H-bonds and, occasionally, $\pi-\pi$ stacking interactions. The charged nitrogen atoms of the dibenzylammonium ions are directed towards the center of the assembly, which leads to complexation of one of the three PF_6^- counterions inside this cavity through



32

Scheme 21. Complexation of a PF_6^- ion in a self-assembled cavity.

C−H···F H-bond formation and Coulombic interactions. Increasing the size of the crown ether results in a more complete encapsulation of the anion.

Another example of anion-templated self-assembly by H-bonding was reported by de Mendoza and co-workers.[221] Two or more chiral guanidinium salts were covalently connected through a small spacer in such a way that the individual guanidium sites cannot interact with the same anion. Polysulfate anions were then added to induce the formation of a double-helical structure, which was confirmed. The chirality of the helix is induced as a result of the presence of chiral centers in the individual strands, which makes it possible to study the assembly process by circular dichroism. Later studies revealed that the tetraguanidinium strand interacts both in water and aqueous methanol with an oligopeptide containing anionic aspartate residues at matching positions.[222]

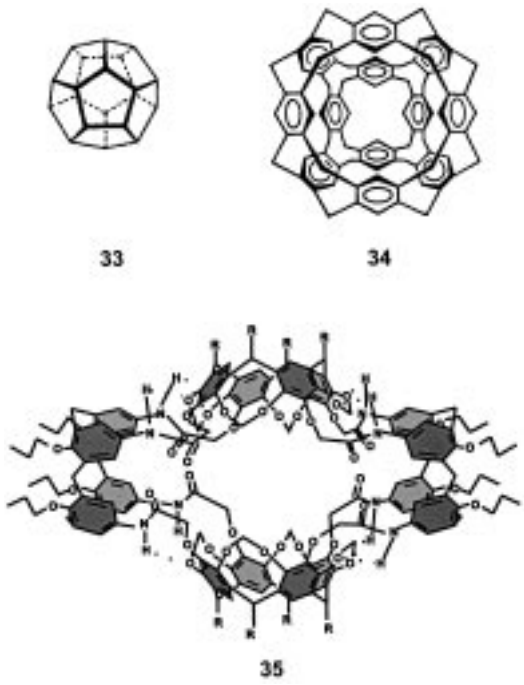
4. Molecular Containers by H-Bond-Directed Self-Assembly

"Simple objects with concave surfaces can be arranged in order of their increasing concavity, for example, saucers, bowls, pots, vases, and spheres. If organic compounds are to resemble such objects, provision must be made to enforce their shapes by limiting their conformational mobility. In principle, spheres can be assembled from rigid saucers by simple connecting groups. Once the concept of spherical compounds is in mind, fascinating questions about possible occupancy of their interiors seeks answers, and a new field of research is born."
Donald Cram, 1994

4.1. Introduction

Closed-surface compounds have always intrigued chemists because of their synthetic complexity and their aesthetically pleasing shape. The synthesis of dodecahedron (**33**; Scheme 22), one of the five Platonic solids and regarded as the "Mount Everest of Alicyclic Chemistry", remained elusive for more than 20 years, until Paquette et al. reported its 23-step synthesis in 1983.[223] These and other early examples mainly involved molecular cages too small to encapsulate guest molecules. In 1983, Cram proposed the synthesis of hydrocarbon sphere **34** (Scheme 22) that is large enough to accommodate simple organic compounds, inorganic ions, or gases.[224] This hypothetical molecule has formed the scientific basis for most of the synthetic work in the field of molecular encapsulation.

The first successful syntheses of molecular capsules, named carcerands and cryptophanes, were reported in 1985 by the groups of Cram and Collet.[225, 226] In general, capsules are always filled with one or more solvent molecules (DMF, EtOAc, DMSO, etc.) that act as a template during their formation. A severe drawback of carceplexes (carcerands with encapsulated guests) is that the encapsulated guest molecules are physically entrapped and can only be expelled after breakage of one or more covalent bonds. This feature



Scheme 22. Covalent cavity-containing molecules.

limits their potential application in catalysis and drug-delivery systems. Cram et al. developed new cages—named hemicarcerands—that have portals through which guest molecules can be exchanged.[227] The solvent molecule that is initially encapsulated during the synthesis is liberated at elevated temperatures to give the empty cage. Subsequently, the guest of choice enters the cavity and becomes kinetically trapped inside the hemicarcerand upon lowering the temperature.

The synthesis of rigid cavities with large internal voids, such as holand **35** (Scheme 22) becomes increasingly demanding and poses limits to what is synthetically achievable.[228] Practical limitations such as these have mainly initiated research activities on noncovalent container systems, which form in a reversible manner with concomitant self-correcting behavior. Guest encapsulation in reversible systems occurs spontaneously upon the addition of the appropriate guest molecule, provided that the host–guest complex is thermodynamically stable. Therefore, covalent synthesis remains restricted to the preparation of simple modules that are programmed for their own assembly, which makes structural modifications on the capsules far easier.

This section reviews recent achievements on the self-assembly of molecular capsules through H-bonding. The emphasis will be on novel principles and concepts that have emerged from these studies. For more detailed information the reader is referred to previous reviews on this topic.[229–233]

4.2. Structural Design of H-Bonded Capsules

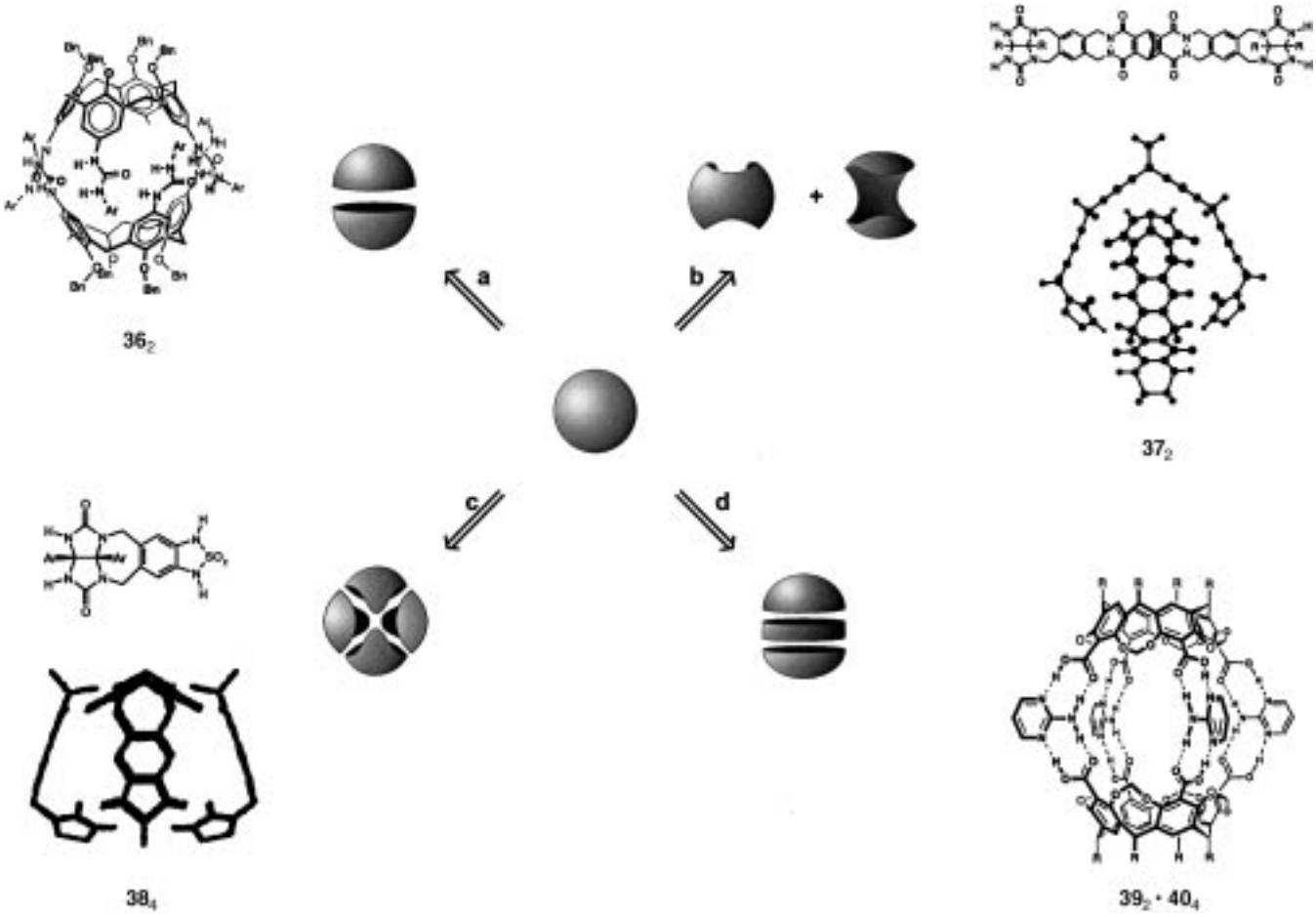
Molecular design of the building blocks is an essential element in the successful formation of thermodynamically stable noncovalent capsules.[234] The individual components must be curved and complementary in size in order to form a spherical object. The simplest way to bisect a sphere is to cut it in two halves along the equator (Scheme 23a). Kim and Gokel reported the very first attempt to form a molecular box by noncovalent synthesis using H-bonding interactions.[235] 4,13-Diaza-[18]crown-6 was derivatized with two side arms terminated with adenine or thymine residues. In the proposed structure the roof and floor of the box were constituted of crown ethers, while the A-T base pairs functioned as side walls. VPO and ^{1}H NMR studies revealed some kind of aggregation, but the monomers were too flexible and consequently failed to form well-defined assemblies.[236] These findings strongly emphasize the importance of rigidity in the modules. From this perspective, macrocyclic structures such as cyclodextrins, calixarenes, resorcinarenes, and cavitands were subsequently identified as ideal for the discrete self-assembly of molecular capsules, because they are curved and rigid. Moreover, ample procedures for the selective introduction of directive functional groups have been developed over the last ten years for these molecules.

Aoyama and co-workers were the first to recognize these advantages and reported on a boxlike structure in which methyl glucoside forms a sandwich-type complex with two molecules of resorcinarene.[237] It is disputable, however, whether the ternary complex can be regarded as a true H-bonded capsule, since H-bonding does not seem to occur between the capsule halves themselves, but only between the self-assembled host and the guest.

As a direct result of the studies of Cram et al. towards the properties of carcerands, Sherman and co-workers focused their attention on the noncovalent intermediate complex preceding the formation of these covalent capsules.[238, 239] The two resorcinarene parts in this complex are held together by four charged H-bonds that are formed between the anionic phenolate and phenol groups. Böhmer and co-workers reported on a related resorcinarene dimer that is formed through eightfold H-bonding between phenolic hydroxyl groups and ester carbonyl groups.[240] Reinhoudt and co-workers reported the heterodimerization of two cavitands through fourfold pyridine–carboxylic acid interactions with an association constant of $> 10^7\,\mathrm{M}^{-1}$ in chloroform.[241]

Calix[4]arenes are part of the same class of compounds as resorcinarenes and cavitands. However, their general use as a module for H-bonded capsules is in some cases hampered by the much higher conformational flexibility of the macrocycle, which causes either a collapse of the cavity,[242–244] or the formation of undefined assemblies.[245] Only calix[4]arenes that are substituted at the upper rim with four urea moieties form the well-defined capsule $\mathbf{36}_2$ in solution (Scheme 23a).[246–248] The reason is that the urea H-bonds are directed sideways, which allows H-bonding between the two parts when the calix[4]arenes adopt the cone conformation. Recently, the larger calix[6]arenes substituted either with three carboxylic acid or three urea moieties were found to dimerize. The resulting capsules have small cavities that allow entrapment of guests such as *N*-methyl-4-picolinium iodide and solvent molecules, respectively.[249, 250]

Other H-bonded capsules constructed by this design principle include the homodimers from cyclocholates,[251]



Scheme 23. Four strategies for the noncovalent synthesis of molecular containers.

cyclotriveratrylenes,[252] and a heterodimer from a complementary cyclodextrin and porphyrin.[253, 254] In other cases the formation of H-bonded capsules based on resorcinarenes was only observed in the solid state. The low thermodynamic stability of these capsules is a consequence of the relatively weak H-bonds and the fact that cocrystallized solvent molecules are part of the cage.[255–257]

Two examples of capsules with a cylindrical shape were recently reported by Rudkevich, Rebek, and co-workers.[184, 258] In one of these cases, deep-cavity cavitands with extended aromatic walls dimerize by the formation of eight bifurcated H-bonds between imide functionalities. The cylindrical shape of the capsule, with outer dimensions of roughly 1.0×1.8 nm, gives the cavity unique guest-binding properties (see Section 4.3.4).

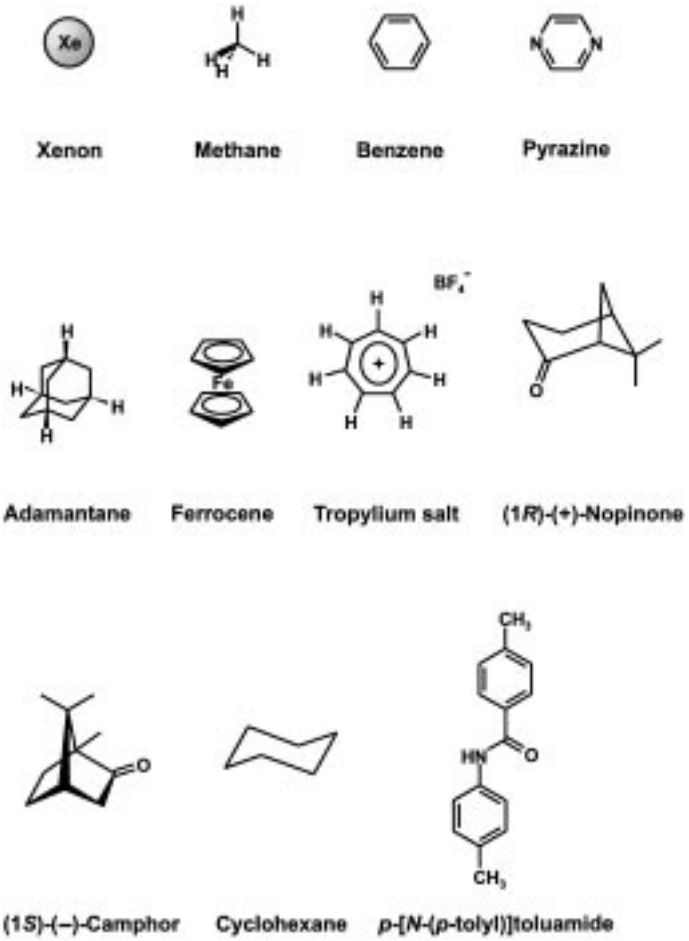
A second class of capsules is formed from modules with D_{2d} symmetry—analogous to the way a tennis ball is formed from two identical halves (Scheme 23b). All these systems make use of the H-bonding properties of glycoluril.[259] Connecting two glycoluril moieties through a benzene spacer results in a rigid, concave monomer with C_{2v} symmetry that meets all the requirements to form a capsule on dimerization.[260] The first "molecular tennis ball" assembled in this way possesses a cavity size of 61 Å^3, which decreases to 37 Å^3 when the benzene spacer is substituted with an ethylene spacer. Much bigger capsules, such as "softball" $\mathbf{37}_2$ with a cavity size of 313 Å^3, were obtained by using larger spacers containing functionalities that form H-bonds with the glycoluril moieties (Figure 23b).[261] However, the information in these modules is not unique for dimerization to occur, since higher order aggregates were observed in the absence of suitable templates. The thermodynamic stability of these capsules was further improved upon the introduction of additional H-bonding sites in the spacer.[262] An enhanced stability can also be achieved by using multidentate modules. Assemblies such as the so-called "jelly doughnut" and phthalocyanine dimer (not shown) with C_{3v} and C_{4v} symmetry, respectively, have an increased stability as a result of the larger number of H-bonds that are formed upon capsule formation.[263, 264] The flattened cavity shape allows the encapsulation of disklike guests.

Recently, Rebek and co-workers reported an alternative capsule that is chemically related to the tennis ball structures, but is constructed by using a new design principle (Figure 23c). Capsule $\mathbf{38}_4$ is formed from four different fragments, with the driving force for assembly being H-bond formation between the sulfamide and glycoluril moieties.[265] Previously, MacGillivray and Atwood reported a molecular box constructed from six resorcinarenes, but the thermodynamic stability of this six-component capsule in solution has so far remained unclear, most likely because the presence of eight water molecules is crucial for its assembly.[266]

Yet another method for constructing molecular boxes was very recently demonstrated by Kobayashi et al. (Figure 23 d), who followed an approach used earlier by Lehn and co-workers to construct bisporphyrin cages.[267] Instead of bisecting a sphere along the equatorial plane, they cut it two times along both the "tropic of Capricorn and Cancer". Chemically, this translates into assembly $\mathbf{39}_2 \cdot \mathbf{40}_4$, in which two cavitands with four carboxylic acid groups **39** act as end-caps, and four 2-aminopyrimidine molecules **40** act as "connectors". Conceptually, this approach is very interesting, since it allows for a wide variation in size and structural diversity inside the capsule simply by varying the spacer units. MacGillivray et al. reported the crystal structure of a capsule with similar architecture obtained from cocrystallization of *C*-methylcalix[4]resorcinarene and 4,4′-bipyridine in the presence of nitrobenzene.[268]

4.3. Guest Encapsulation

Most noncovalent capsules, like their covalent counterparts, are formed only when suitable guest molecules are present to fill the interior. For instance, the glycoluril-based monomers of Morgan Conn and Rebek form nondefined aggregates in the absence of suitable guest molecules that can act as a template.[230] In this way, the addition of small amounts of guest molecules to solvents, which are themselves poor guests, can spontaneously induce the formation of well-defined capsules with the desired guest inside. Alternatively, guests that are sparingly soluble in organic media can be encapsulated by solid–liquid extractions.[240] A selection of guests that have been used in encapsulation studies is shown in Scheme 24. A special example are the supramolecular Matroschka dolls consisting of cryptates encapsulated in cavitand-based dimers.[269]



Scheme 24. Typical examples of guest molecules.

4.3.1. Characterization

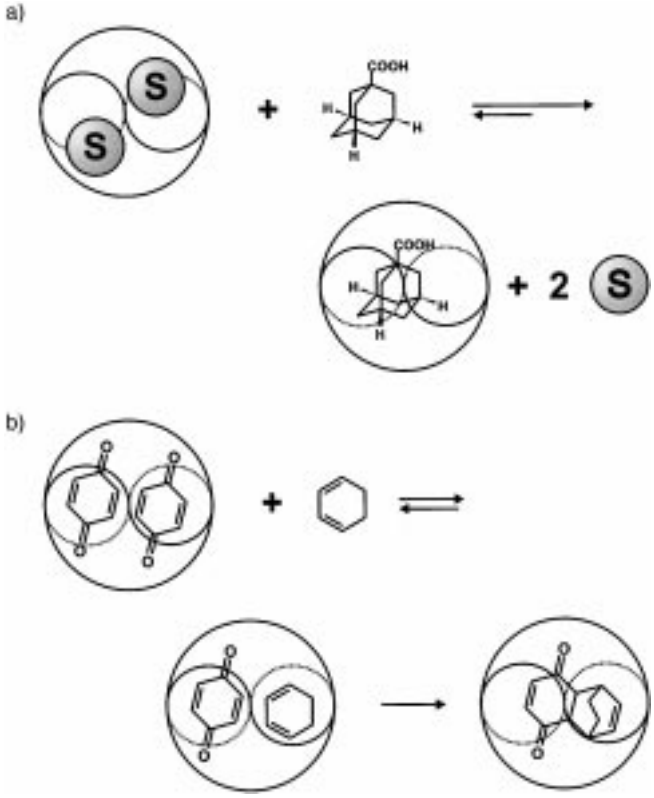
NMR spectroscopy provides valuable information regarding molecular structure, guest inclusion, and the thermodynamic and kinetic parameters of the assembly process. In general, the proton signals of encapsulated guests experience upfield chemical shifts resulting from anisotropic shielding effects of the capsule. The magnitude of this chemical shift provides useful information about the orientation of the specific guest inside the capsule. Parts of the guest that are directed towards the apolar hemispheres of the capsule experience a larger anisotropic shielding than protons located in the polar equator and hence exhibit a larger chemical shift.[270, 271] Cohen and co-workers utilized pulsed-field gradient (PFG) NMR spectroscopy to show that the diffusion coefficient of encapsulated benzene in tetraureacalix[4]arene capsules is similar to the diffusion coefficient of the capsule itself, thus providing supporting evidence for its encapsulation.[272] Recently, ESI-MS was also used to characterize capsular complexes.[273, 274] The inclusion of ionic guest molecules gives charged complexes that can be readily detected by mass spectrometry. In certain cases it has been possible to identify the capsules by X-ray crystallography.[240, 255, 256, 266, 275–277] This technique, however, provides only structural information, and gives no thermodynamic or kinetic information.

4.3.2. Thermodynamics of Guest Encapsulation

Naturally, the size of the capsules poses restrictions to what kind of guest molecules can be encapsulated. Guests that are significantly larger than the cavity simply cannot fit without disrupting the structure of the capsule. On the other hand, the encapsulation of guests that are too small becomes unfavorable from an entropic point of view, since large voids remain inside the capsules. Mecozzi and Rebek studied a large collection of capsules with their guests and observed that the highest association constants are typically found for guests that fill the cavity to $55 \pm 9\,\%$.[278] This number corresponds remarkably well to the volume occupied by molecules in the liquid state. These guests have the appropiate size and shape for optimal van der Waals interactions with the cage. Deviations may occur as a result of specific functional groups on the guests, such as H-bond acceptors or donors, which cause additional stabilizing interactions. For instance, tetraureacalix[4]arene capsule $\mathbf{36}_2$ with a cavity of approximately 190 Å^3 binds a small guest, such as pyrazine, despite the fact that this guest only fills the cavity to 38 %.[247] The unexpected stability of this complex is attributed to stabilizing interactions

of the C–H bonds of pyrazine with the aromatic π surfaces of the calix[4]arenes and of the partially negative nitrogen atom with the polar H-bonded seam of the urea moieties. Pyrazine is also one of the best guests for the capsules reported by Sherman and co-workers, for which a similar evaluation holds.[279]

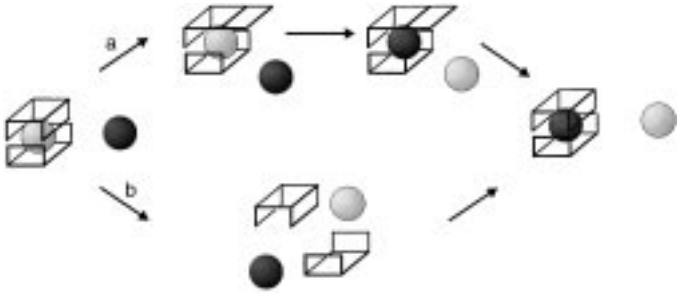
This study makes it clear that in most cases the driving force for the encapsulation process is strictly of enthalpic origin. A conceptual breakthrough was accomplished by Kang and Rebek, who observed that guest inclusion can also be entropically driven.[262] The thermodynamic stability of softball $\mathbf{37}_2$ with encapsulated adamantane and ferrocene derivatives was found to increase with temperature, which correlates with a positive entropy term. The positive entropy term results form the replacement of two molecules by one larger guest (Scheme 25a).



Scheme 25. a) Entropy-driven encapsulation in the softball (S = solvent molecule) and b) the softball as a mini-reactor for a Diels–Alder reaction.

4.3.3. Kinetics and Mechanism for Guest Exchange

Guest exchange in Cram's hemicarcerands occurs by an S_N1-type mechanism, which starts with the formation of an energetically highly unfavorable void that is subsequently filled with the new guest. The weak interactions that hold the H-bonded capsules together make alternative mechanisms for guest exchange possible that involve intermediates with significantly lower energies. Guest exchange may either occur through a dissociative mechanism, which involves full dissociation of the capsule, or a gating mechanism, which involves partial dissociation of the capsule, to create a portal (Scheme 26). Exchange studies by Rebek and co-workers with tennis ball complexes showed that the exchange rate for



Scheme 26. Guest exchange can occur either by a gating (a) or a dissociative mechanism (b).

methane and ethane encapsulation is a factor of 5–8 higher than the observed dissociation rate of the empty capsule.[280] On the basis of these results they proposed a mechanism in which the seven-membered ring connecting the glycoluril and the aromatic spacer undergoes inversion, thus creating a portal for guests to exchange by an S_N2-type mechanism. Calculations by Houk et al. showed that the energy barrier of the rate-determining step in the gating mechanism, that is, breaking four H-bonds and ring inversion, is equally as high as that for dissociation of the capsule (30 versus 29 kcal mol^{-1}). However, the positive entropy term of about 6–12 kcal mol^{-1} for the dissociative mechanism, which is absent in the gating mechanism, renders it energetically the most favorable pathway. The discrepancy between kinetic and computational data illustrates the difficulties for a fundamental understanding of these dynamic processes.

In the case of the softball, both kinetic and computational studies indicate that the gating mechanism occurs. The eight additional H-bonds in the softball decrease the dissociation rate of the capsule to days.[281] In contrast to this, the guest-exchange process occurs within several minutes, which indicates that in this case exchange must take place through a gating mechanism. Kinetic studies support this view, since they reveal the presence of intermediate structures, which most likely correspond to a softball with one or two arms flipped over. Computational studies also support the gating mechanism, with an energy preference of 46 kcal mol^{-1} over the dissociative mechanism.[282]

Guest (benzene) exchange in tetraureacalix[4]arene dimers proceeds with a rate constant of 0.47 s^{-1}, as determined by EXSY measurements.[283] Böhmer and co-workers showed that the half-life increases from about 1 s to 60 h upon increasing the steric bulkiness of the urea units.[284] This enormous increase in kinetic stability results from a mechanical entanglement of the bulky residues which hinders "dethreading" of the monomers, similar to the process observed in rotaxanes.

4.3.4. New Physical Properties of Encapsulated Guests

The isolation of individual molecules inside molecular capsules can significantly change their chemical and physical properties. For this reason, Cram et al. characterized the interior of (hemi)carcerands as "a new phase of matter", which has unique properties that are different from the gas, liquid, or solid phase. This was most convincingly illustrated

by the successful isolation of cyclobutadiene inside a hemicarcerand. This extremely reactive molecule can normally only be isolated in an argon matrix at 8 K.[285]

Encapsulated guests in H-bonded capsules also exhibit novel physical properties as a result of the new chemical environment that they experience inside the capsule. One particular example involves the slightly increased barrier for ring inversion of cyclohexane ($\Delta\Delta G^{*} = 0.30$ kcal mol^{-1}) encapsulated inside the "jelly doughnut" assembly.[286] The energy difference is attributed to favorable C-H-π interactions that stabilize the ground-state chair conformation (D_{6h}) relative to intermediate conformations of higher energy. Similar stabilizing interactions are responsible for the constrained rotation of pyrazine inside Sherman's capsule.[270]

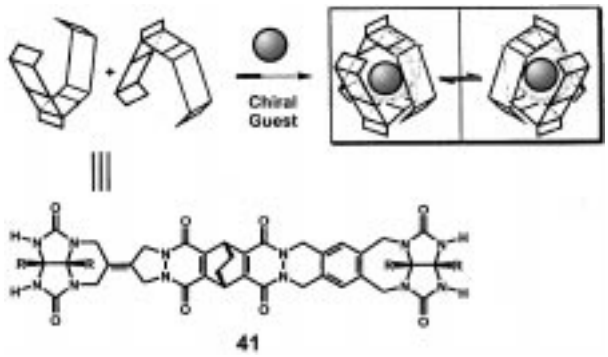
The cylindrical capsule recently described by Rudkevich and co-workers deserves special attention in regard to novel guest properties.[258] This capsule has an internal space of 5.7×14.7 Å that is well suited for guests with complementary shapes, such as bibenzyl and terphenyl. The relationship between the shape of the cavity and the guest becomes apparent from encapsulation studies of (*E*)- and (*Z*)-stilbene. Competition experiments reveal that the capsule has a selectivity for the *E* isomer of at least 50:1.[287] Unstable molecules, such as benzoyl peroxide, or noncovalent complexes, such as the H-bonded pyridone dimer, can be stabilized inside the capsule as well, a phenomenon that is reminiscent of the stabilization of cyclobutadiene inside Cram's carcerands. The noncovalent nature of these capsules enables an induced release of the guest molecules, for example, by the addition of polar solvents or competing guests, whereas the guests in covalent cages are kinetically trapped.[288]

4.4. Self-Assembled Capsules as Mini-Reactors

The encapsulation of two molecules inside a self-assembled cavity offers great potential with regard to catalysis. The catalytic effect results from a dramatic increase in the effective molarity of the reagents upon encapsulation. The use of molecular containers as mini-reactor vessels was first reported by Kang and Rebek following their discovery that the softball $\mathbf{37}_2$ can encapsulate two different guest molecules.[262] Subsequently, they studied the effect of the capsule on the Diels–Alder reaction between quinone and cyclohexadiene. When a mixture of the reactants was added to the capsule, only encapsulation of quinone was observed. Cyclohexadiene was apparently encapsulated also in very small, but sufficient, amounts, because the encapsulated product of the Diels–Alder reaction was formed slowly over time (Scheme 25b).[289, 290] A 200-fold rate acceleration was observed in the presence of the capsule over the control reaction. Product inhibition prevented real turnover and therefore this capsule does not truly act as a catalyst. True catalysis was subsequently observed when cyclohexadiene was replaced by the sterically more-demanding thiophene dioxide derivative. In this case the product of the Diels–Alder reaction with benzoquinone is expelled from the cavity as a result of its lowered affinity for the capsule.[291]

4.5. Chiral Capsules

Capsules display supramolecular chirality when the monomers are arranged in a dissymmetrical fashion upon formation of the assembly.[292] This phenomenon poses a new and intriguing question: do chiral capsules discriminate in the binding of chiral guest molecules? Recent work by the Rebek group reveals some of the answers. When a dissymetric spacer is used to connect two glycoluril moieties (C_s symmetry), for example, in **41**, the resulting capsule is formed as a pair of enantiomers (C_1 symmetry).[293] The inclusion of chiral guests gives rise to diastereomeric complexes, which are clearly observable by a doubling of the host and guest signals in the ^{1}H NMR spectra (Scheme 27). A maximum *de* value of 35% was observed, with a corresponding $\Delta\Delta G^{0}$ value of



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Scheme 27. Dissymmetrization of the monomer results in the formation of an enantiomeric pair of softballs. Encapsulation of chiral guests causes the complexes to be diastereomers.

0.4 kcal mol^{-1}. The selectivity increases with guest size as a result of increased van der Waals contacts of the guest with the capsule walls. Recent studies show that these capsules memorize the induced chirality after the chiral guest is exchanged with an achiral guest.[294] In another approach, the monomers were desymmetrized by substituting the two glycoluril moieties with different side groups.[295] Again, the capsules were formed as a pair of enantiomers, but in contrast to the previous study no diastereoselectivity was observed upon the addition of chiral guests. Apparently, diastereoselective guest encapsulation is only observed if the chiral information in the capsule is directed inwards, that is, influences the interior of the capsule.

The tetraureacalix[4]arene capsules exhibit supramolecular chirality as a result of the directionality of the H-bonded seam of the urea moieties, provided that the northern and southern hemisphere of the capsule are different. Böhmer and co-workers showed that the mixing of two symmetrical homomeric capsules spontaneously results in the formation of statistical amounts of the asymmetrical heterodimeric capsule.[248, 283] Surprisingly, Rebek and co-workers discovered that the asymmetrical heterodimer is formed exclusively when two symmetrical ureido- and sulfonylureido-functionalized calix[4]arenes were combined.[296] Subsequent studies with a variety of heterodimers with chiral α-methylbenzylamino or amino acid side chains revealed that heterodimerization was not quantitative in all cases, but the amount of heterodimer

present was sufficient to study the complexation behavior of chiral guests. Addition of (−)-nopinone to heterodimers of opposite handedness indeed gave diastereomeric complexes. However, these chiral capsules exhibit modest enantioselectivities in the binding of chiral guests (1.3:1).[297]

Carceroisomerism, the new type of isomerism resulting from two different alignments of asymmetrical guests in capsules with different hemispheres,[298] was also observed in H-bonded capsules. Chapman and Sherman found that pyrazine can adopt two different orientations inside their capsule, with an activation energy for rotation around the pseudo-C_1 axes of 18 kcal mol^{-1}. This value is almost identical to that found for the very similar covalent complex.[270] Rotation of the guest around the equatorial axes requires partial breakage of the assembly, which raises the energy barrier.

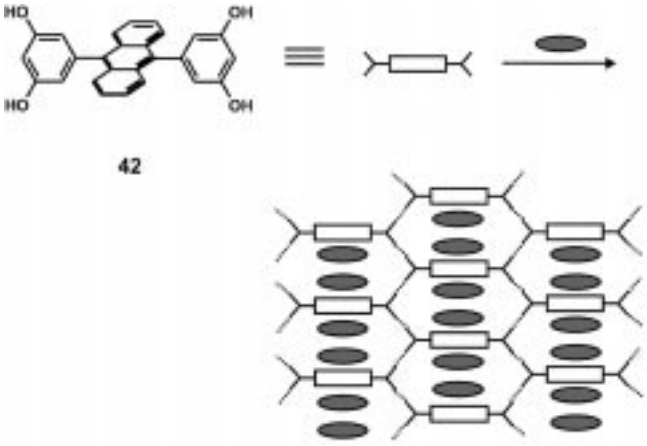
4.6. Inclusion Complexes in the Solid State

Crystal engineers aim to design solid-state structures by using functional building blocks. In this respect H-bonding interactions provide a unique tool because of their high directionality and easy synthetic access. It is beyond the scope of this review to give an exhaustive overview of all the crystal structures in which H-bonding plays an important role. However, the three examples presented here merely illustrate the potential of H-bonding in crystal engineering, especially regarding the formation of open "zeolite-like" materials.

As an extension of the study on the self-assembly of 2-pyridone dimers in solution (see Section 2.3.2) Wuest and co-workers covalently arranged four 2-pyridone moieties in a tetrahedral fashion around a central carbon atom to give multidentate modules called tectons.[299] Crystallization of this tecton from butyric acid/methanol/hexane mixtures gave diamondoid networks with large internal chambers occupied by butyric acid molecules. This very robust organic material displays zeolite-type properties in the sense that the network is sufficiently porous to permit exchange of guests.[300]

Russell and Ward made use of the H-bonding interactions between guanidinium cations and sulfonates for the construction of solid-state materials with guest-selective binding properties.[301] Initial studies addressed the question of structural diversity within the individual building blocks,[302, 303] while later work focussed on tailoring the solid-state structure to optimize guest recognition properties.[304, 305]

Aoyama and co-workers described the formation of crystals of anthracenediresorcinol derivatives, such as **42**, that are stabilized through extensive H-bonding networks (Scheme 28).[306] The cavities inside the crystals are occupied by a variety of different guest molecules, such as quinones, alkyl benzoates, aliphatic esters, and ketones, as well as nitrobenzene.[307] Moreover, the cocrystallized solvent molecules can be exchanged for a variety of other guests without destroying the crystals.[308] These organic solids can promote stereoselectivity in the Diels–Alder reaction between acrolein and cyclohexadiene, unfortunately not in a catalytic manner.[309]



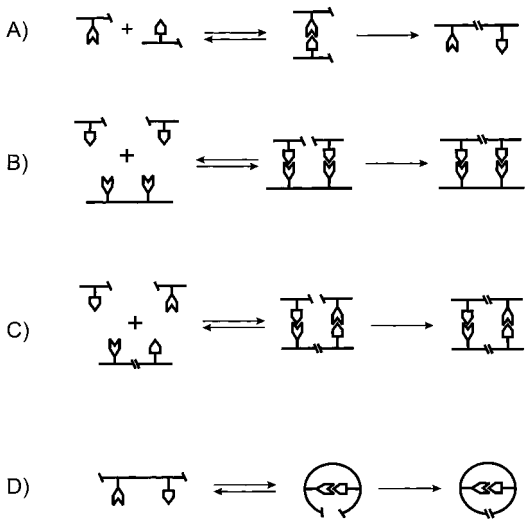
Scheme 28. Crystallization of anthracene-bis(resorcinol) derivatives, such as **42**, results in the formation of porous networks.

5. Templated Synthesis

"The use of one molecule as a template to guide and facilitate the synthesis of another […] has not hitherto been attempted in laboratory synthesis, although it seems probable that it is common in living systems. It represents a challenge which must, and surely can, be met by organic chemistry."
Alexander Todd, 1956

5.1. Introduction

Template-directed synthesis uses noncovalent interactions to enhance the rate and/or selectivity of a particular chemical reaction.[310–313] The catalytic effect can be the direct result of complex formation between (self-)complementary reactants (Scheme 29A), or can be exerted by an external template that is (self-)complementary to the reactants (Figure 29B and C). Self-replication (Scheme 29C) involves a special type of templating, in which molecules catalyze their own formation by formation of complexes with both the reactants. This type



Scheme 29. Types of template effects: in bimolecular reactions (A and B), self-replicating systems (C), and macrocyclization reactions (D).

of catalysis is commonly observed in any system that bears self-complementary recognition sites, but its occurrence can be strongly attenuated by intramolecular complexation as a direct result of insufficient structural rigidity of the linker unit.[314] Finally, intramolecular template effects frequently occur in macrocyclization reactions (Scheme 29 D), and are commonly used to promote the formation of large macrocycles or mechanically interlocked systems.

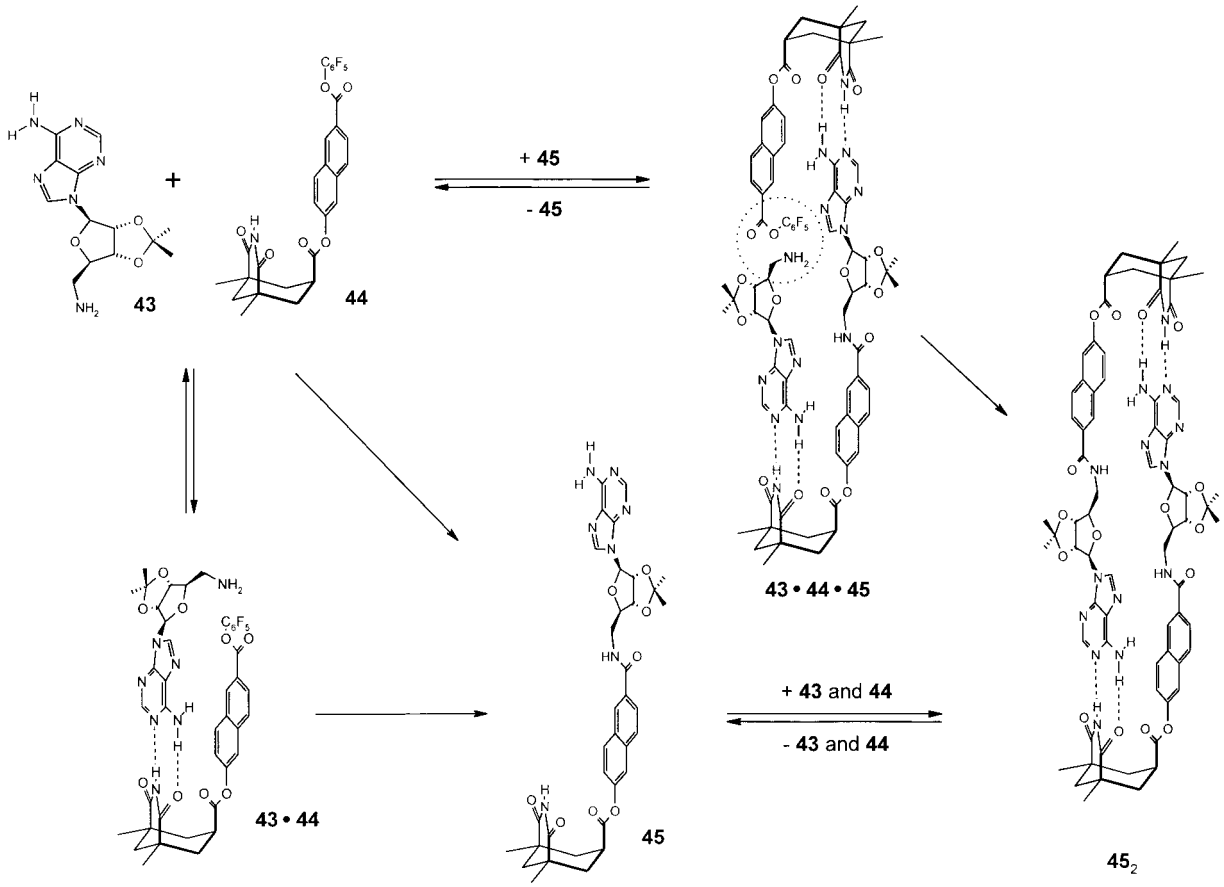
The majority of template effects are positive and consequently lead to a decrease in the activation energy for the reaction. The observed effects, which are entropic in nature, are the result of a higher effective concentration of the substrates within the complex, and can be best expressed in terms of an effective molarity—the ratio of the rate constants for the templated and the nontemplated reaction.[315] In addition to this, the template can lower the energy of the transition state through stabilizing enthalpic interactions.[316] Template effects can also be negative, which means that the template increases the energy barrier for the reaction by reducing the effective concentration of the reactants.[310]

This section summarizes recent efforts in templated synthesis that involve the formation of H-bonded complexes. A special example of templated synthesis was discussed in Section 4.4, in which the binding of two reactive molecules inside a hydrogen-bonded molecular capsule was found to catalyze their chemical reaction. Since many reviews cover the early work in this field, we will mainly focus on developments during the last decade.[317–321]

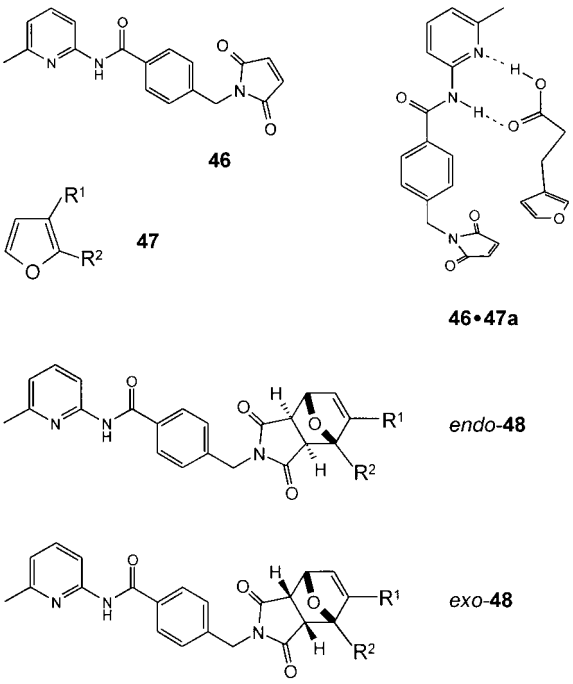
5.2. Reaction of Molecules with Complementary Binding Sites

To date, there has been relatively little interest in the occurrence of internal template effects, most likely because of the overwhelming attention paid to the self-replicative effects that are usually observed in these systems (see Section 5.4). Rebek and co-workers reported a tenfold rate increase for the reaction between amine **43** and active ester **44** (8.2 mM in $CHCl_3$) to give **45**, which arises as a direct result of the formation of Watson–Crick H-bonds ($K_{ass} = 60\,M^{-1}$) between the adenine and Kemp's triacid moieties (Scheme 30).[322] Rate enhancements as large as 3500 were observed in a more elaborate system in which the flexibility of the linkers allows a much better approach of the reactive groups.[323]

Philp and co-workers studied the recognition-induced control of Diels–Alder reactions using the 2-amidopyridine · carboxylic acid motif ($K_{ass} \sim 170\,M^{-1}$; Scheme 31).[324, 325] A drastic increase in the *endo*/*exo* product selectivity ($\Delta\Delta G^0 = 21.9\,kJ\,mol^{-1}$ for the recognition-mediated reaction and $4.7\,kJ\,mol^{-1}$ for the control reaction) was observed for the reaction between **46** and **47a**, while for the reaction between **46** and **47b** the selectivity was hardly different to that of the control reaction ($\Delta\Delta G^0 = 6.2\,kJ\,mol^{-1}$ for the recognition-mediated process and $6.1\,kJ\,mol^{-1}$ for the control reaction). Selective formation of the *exo* product was observed in a structurally analogous system, and occurred most likely as the result of intramolecular H-bonding.[326] Only the formation of



Scheme 30. Self-replication cycle for the templated synthesis of template **45**.



Scheme 31. Recognition-induced control of the Diels–Alder reaction between diene **47** and dienophile **46**.

endo-**48a** showed a positive template effect (kinetic effective molarity 63 mM), while for all other products the activation barrier for formation had increased as a result of the formation of H-bonds. Similar studies for a [2+3] dipolar cycloaddition reaction showed a much larger rate acceleration (kinetic effective molarity 2.16 M), although the stability of the reactive complex was much lower ($K_{ass} \approx 28\,M^{-1}$). These results clearly illustrate that the strength of the association of the reactive partners does not seem to correlate with the observed rate effects.[327]

5.3. External Template Effects

Template-directed reactions which model DNA replication have received a great deal of attention. Early work by Orgel demonstrated that the template-directed ligations of most activated nucleotides are inefficient and nonregiospecific (preference of natural 3′-5′ over unnatural 2′-5′ ligation), except for the 5′-phosphoro-2-methylimidazolides, which show relatively high efficiency and regioselectivity in the coupling reactions.[320] Moreover, it was found that pyrimidine-rich oligo- and polynucleotides efficiently act as templates for the polycondensation of activated mononucleotides, while purine-rich oligonucleotides do not.[328, 329] For example, the pentamer d(pGGCGG) was obtained in 18% yield by using d(pCCGCC) as a template. Under enzyme-free conditions the templated synthesis of an oligonucleotide 14-mer was achieved in 2% yield; the main problems were the limited regiospecificity and efficiency of the coupling reaction.[330] Significantly higher yields were obtained in coupling reactions with oligonucleotide fragments of three or more base pairs. Goodwin and Lynn reported a fourfold increase in the yield of the reversible imine formed between the trimers d(CGT)-CHO and H_2N-d(TGC) in the presence of the template hexamer d(GCAACG) at 0 °C, while at 30 °C the yield was hardly different.[331] Moreover, it was found that the selectivity for trimer H_2N-d(TGC) and tetramer H_2N-d(TTTT) in this reaction also showed a large temperature dependance (about 2:1 at 30 °C and >30:1 at 0 °C). Both findings reflect the improved stability of the ternary complex at lower temperatures.

Ross Kelly et al. described the first example of template effects in truly synthetic systems involving H-bonding.[332] The template contains two identical noncomplementary ADD recognition sites where two substrate molecules with DAA recognition sites can be bound. A sixfold rate increase was observed at reactant and template concentrations of 4.0 mM. Product inhibition was not observed in this case since the product precipitated as a salt after formation. A second template with nonidentical binding sites (DAA-ADA) turned out to be more effective, most likely because nonproductive complexes with two identical substrates are not formed in this case.[333]

Rebek and co-workers extensively studied the role of geometrical factors on the template effect in acyl transfer reactions by using the recognition of adenosines by synthetic receptors based on Kemp's triacid.[316, 334] These studies showed that rate enhancements can differ by a factor of 160 depending on the geometrical orientation of the two recognition sites. The observed differences are not solely entropic, but also seem to be the result of geometry-dependent formation of internal H-bonds that can stabilize the transition state for acylation. Another study by the same research group showed that template effects can be further improved by two orders of magnitude when additional stabilizing functionalities are incorporated.[323] Interestingly, the template can be turned "on" and "off" when a light-switchable diazobenzene spacer is used.[335] While the *E* isomer of the template has a negligable effect on the reaction rate, irradiation with light of 366 nm wavelength causes nearly a tenfold rate enhancement, which is clearly attributed to the presence of 50% of the active *Z* isomer.

Very recently, Krische and co-workers used similar template effects in the covalent casting of one-dimensional H-bonding motifs for the preparation of duplex molecular strands.[336]

5.4. Self-Replication

When Watson and Crick discovered the DNA double helix in 1953, they realized immediately that its replication involved a templated synthesis, in which a single strand of DNA acts as a template for the formation of the double strand. An autocatalytic process in which the reaction product serves as the specific catalyst for its own synthesis by recognizing and promoting coupling of the reactants is the most basic form of molecular self-replication. In fact, the realization that self-replication can be regarded as a primitive sign of a living

system has inspired many different research groups to investigate this type of catalysis in synthetic systems.[318–320, 337, 338]

5.4.1. Synthetically Modified DNA and RNA

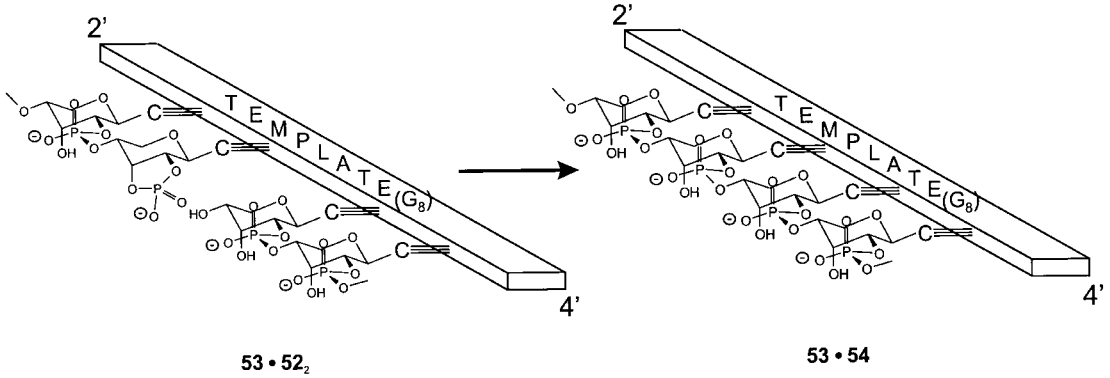
In 1986 von Kiedrowski reported the first example of nonenzymatic self-replication in the chemical ligation of the self-complementary trinucleotides d(^{Me}CCGp) (**49**) and d(oCGG^{ClPh}) (**50**; o = hydroxyl; ClPh = 3′-(2-chlorophenyl) phosphate).[339] As expected, the addition of various amounts of the template product d(^{Me}CCGpoCGG^{ClPh}) (**51**) increased the rate of product formation according to the empirical square-root law for template autocatalysis: $d[\mathbf{51}]/dt = [\mathbf{49}][\mathbf{50}](k_a[\mathbf{51}]^{1/2} + k_b)$, where k_a and k_b are the rate constants for the autocatalytic and the noninstructed process, respectively. Sequence-variation studies of **51** showed that the self-complementary product is formed faster than any of the other sequences, which indicates that the observed autocatalysis is indeed the result of a template effect.[340] Luisi and co-workers found that the kinetics for self-replication of **51** inside vesicles are comparable to bulk-phase conditions.[341]

Autocatalytic behavior was also reported by Zielinski and Orgel for the synthesis of tetranucleotide triphosphoamidates, in which chemical ligation involves phospoamidate bond formation.[342] This work provides the first evidence for the self-replication of synthetically modified biomolecules. Parabolic growth, a characteristic of self-replicating systems that suffer from product inhibition, was observed by von Kiedrowski in a similar replicating system involving the synthesis of d(^{MTM}CCGpnCGG^{ClPh}) (MTM = 5′-*O*-methylthiomethyl; pn = 3′-5′phosphoamidate).[343] Parabolic growth is usually only observed for replicators with a high catalytic efficiency ($k_a/k_b = 300-400$). The same system even showed characteristics of information transfer and selection, though very concealed, when the template molecule was synthesized from three different components.[344]

Cross-catalytic self-replication of complementary templates proceeds with efficiencies similar to those of self-complementary replicators. In this case, the template does not catalyze its own formation, but rather a complementary template that subsequently catalyzes the original template's synthesis. Sievers and von Kiedrowski performed a study in which the two self-complementary templates d(^{MTM}CGGpnCCG^{ClPh}) (AB) and d(^{N3}CCGpnCGG^{ClPh}) (BA; N3 = 5′-azido-5′deoxy) and the two complementary templates d(^{MTM}CGGpnCGG^{ClPh}) (AA) and d(^{N3}CCGpnCCG^{ClPh}) (BB) compete in a combinatorial synthesis with four common trinucleotide precursors. This study revealed that selective stimulation of template synthesis, and thus information transfer, occurs on seeding the reactions with one of the four templates.[345, 346] One year later, Orgel and co-workers showed that RNA oligonucleotides can also template the synthesis of complementary PNA strands (and vice versa). Moreover, they showed that ligation to form chimeras proceeds efficiently both on PNA and on DNA templates. The efficiency of the ligation is primarily determined by the number of backbone bonds at the ligation site and the relative orientation of the template and substrate strands.[347] These experiments demonstrate that takeovers of this kind can occur without the loss of genetic information, which supports the idea that other genetic systems might have preceded RNA.[348]

The self-replication of duplex DNA by means of triple-helix formation was reported by Li and Nicolaou.[349] Initially, the duplex DNA strand binds two complementary single-strand DNA fragments and catalyzes their chemical ligation. Upon raising the pH the single-strand DNA is released and now can serve as a template for the synthesis of the complementary strand, thus giving a copy of the original duplex DNA. This scheme of stepwise replication has the potential of overcoming the problem of product inhibition. Recently, the surface-promoted replication and exponential amplification of DNA analogues (SPREAD) was reported.[350] The role of the solid support is to separate complementary templates which would otherwise form stable duplexes. Similar processes might also have played a role in the origin of life on Earth, since the earliest replicating systems may have proliferated by spreading on mineral surfaces.

Eschenmoser and co-workers studied the replicating behavior of pyranosyl-RNAs, synthetic analogues of the natural furanosyl-RNAs, which display exceptional base-pairing behavior as a result of their much higher rigidity.[351] It was found that the tetramer-2′-phosphate p-ribo(C_4)-2′-p (**52**) regioselectively (4′-2′) ligates to form higher oligomers **54** in the presence of template p-ribo(G_8) (**53**; Scheme 32). No ligation was observed in the absence of the template or in the presence of "wrong" templates (four mismatched pairs in the product octamer), which shows that the template effect is sequence selective. Similarly, the template p-ribo(C_8) (**55**) catalyzes the ligation of p-ribo(G_4)-2′-p (**56**) with comparable efficiency,



53 • 52$_2$ **53 • 54**

Scheme 32. Ligation of p-RNA tetranucleotide-2′,3′-cyclophosphate **52** on p-RNA template **53**.

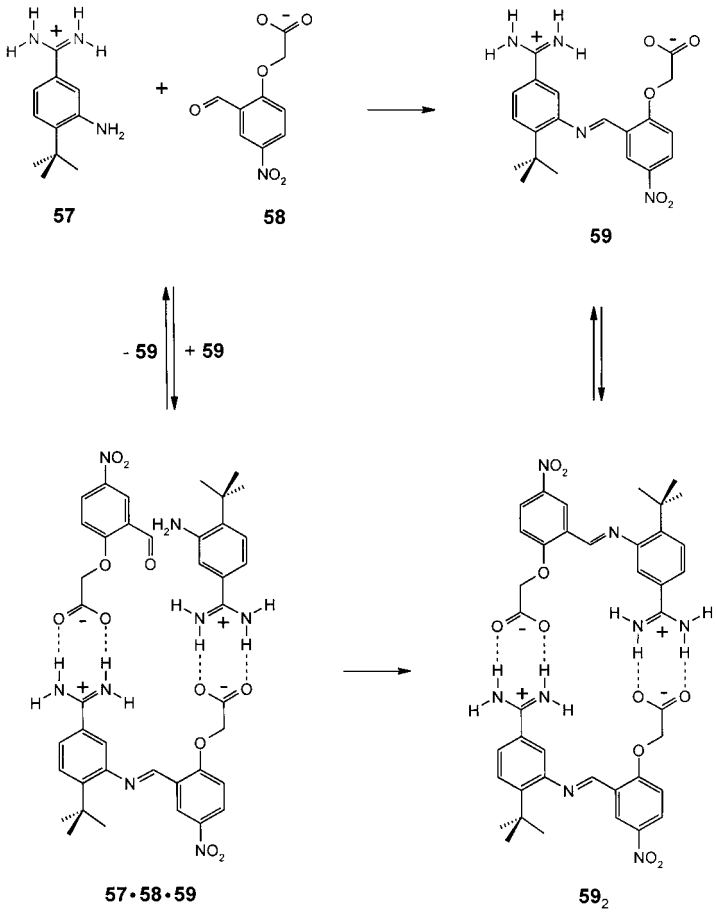
which shows that the C_8 and G_8 octamers **53** and **55** can self-replicate by a double replication cycle. Further experiments showed that the template effects are highly stereoselective, namely, templates containing a single *enantio*-ribopyranosyl are not active at all.[352] The main difference to the natural furanosyl-RNAs is the remarkable absence of self-deactivation for G-rich templates in the p-RNA series.

5.4.2. Other Synthetic Systems

In living systems, single strands often act as templates during phosphate transfer reactions. Rebek and co-workers showed that self-replication also occurs in the acyl transfer reaction between adenosine amine **43** and the activated ester **44** to give the self-complementary product **45** (Scheme 30).[322] The self-replicative activity of product **45** is the result of the careful design of the molecules;[353] steric interaction between the two ribose "bulges" keeps the dimer $\mathbf{45}_2$ apart ($K_{dim} = 630\,M^{-1}$) so that it is available for the desired templation. It was found that the initial rate of this reaction at 8.2 mM increases by 40–70% upon addition of 0.2–0.5 equivalents of product **45**.[314] A similar rate effect was not observed with crippled analogues of **45**, in which one of the recognition sites was blocked. Simple "amide-catalysis" as suggested by Menger et al. cannot explain the observed rate enhancement at this low concentration.[338, 354, 355] Furthermore, Menger et al. claimed that an alternative mechanism in which recognition of only one reactant is required could also explain the observed effects.[356] However, detailed analysis of the reaction kinetics by Reinhoudt's group clearly revealed that self-replication as defined by Rebek and co-workers operates in this system.[357] Other pathways, such as the (bimolecular) pathways described by Menger et al., obscure the simple picture of the ternary complex **43**·**44**·**45** being the only explanation for the observed rate enhancement. Simulations by Reinhoudt et al. showed that reaction of **43** and **44** in the ternary complex is 6.8 times faster than for the uncatalyzed bimolecular reaction, which illustrates the efficiency of the template **45**. Sigmoidal growth was observed in a structurally optimized system in which the naphthyl spacer was replaced by a dibenzyl spacer to suppress the bimolecular reaction.[358–360]

A xanthene-based replicator that utilizes the recognition between thymine and diaminotriazine residues also shows autocatalytic behavior.[361] Crossover or recombination experiments between different replicators gives both active and inactive mutants, the activity of which entirely depends on their molecular shape.[361] Competition experiments using several different replicators revealed that the more effective replicator rapidly takes over the system's resources.[362] In a primitive way these experiments resemble mutations in nature which form the basis for biological evolution. Quite recently, Rebek and co-workers showed that the formation of hydrogen-bonded molecular capsules (Section 4) also exhibit recognition features that are characteristic of self-replication.[363]

Terfort and von Kiedrowski reported the only synthetic system that replicates in a polar solvent.[364] The system explores the relatively strong association between amidinium **57** and carboxylate **58** ($K_{ass} = 350\,M^{-1}$ in DMSO) to self-organize the reactants in the reactive termolecular complex **57**·**58**·**59** (Scheme 33). The system exhibits an autocatalytic efficiency (factor by which the template is built faster by the autocatalytic way than by the nonautocatalytic way) of $16.4\,M^{-1/2}$, which is comparable to that of the hexanucleotide **51** ($24\,M^{-1/2}$) and Rebek's system ($22\,M^{-1/2}$).



Scheme 33. Self-replication as observed in polar solvents by formation of the ternary complex **57**·**58**·**59**.

Persico and Wuest studied self-replicative effects in the copper-induced oxidative coupling of 3- and 6-ethynylpyridones.[365] A purely statistical product distribution was found, despite the fact that only one of the three products was complementary to itself. This observation prompted the authors to conclude that self-replication was not operative in their system, either because of rigidity in the system or because of strong dimerization of the template ($K_{dim} > 6.0 \times 10^4\,M^{-1}$ in $CHCl_3$). However, an alternative explanation could be that a template effect is indeed present, but that it is obscured by the fact that the two non-self-complementary products form a replication cycle because they are complementary to each other and therefore can catalyze each others formation.

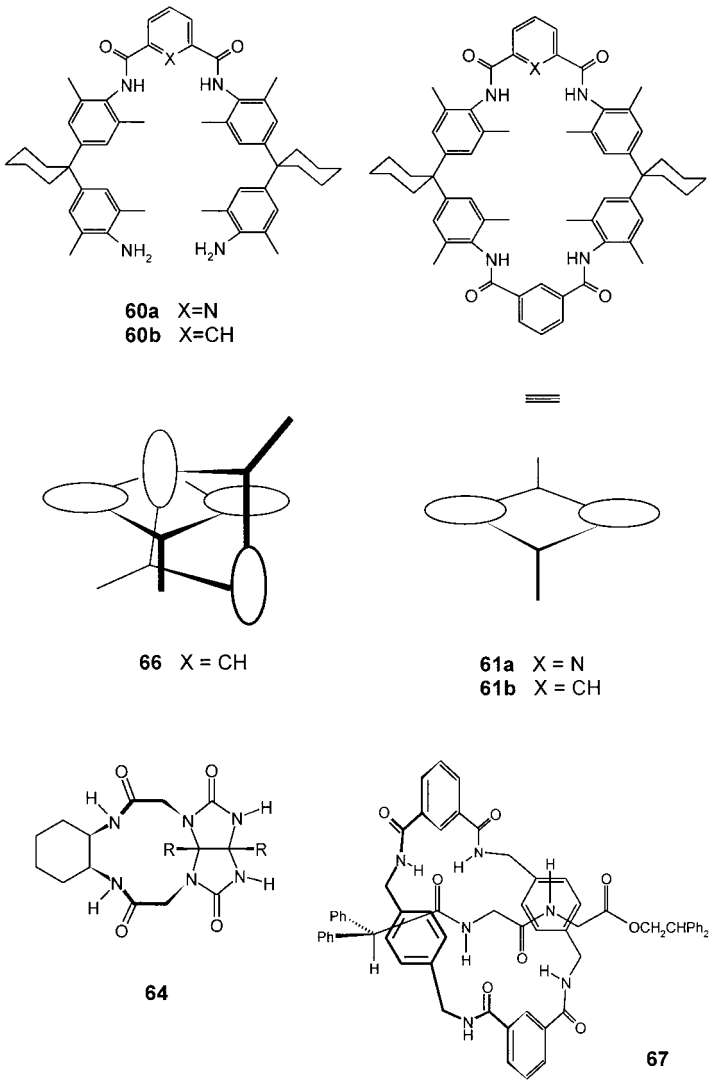
Wang and Sutherland reported the first example of self-replication in a Diels–Alder reaction by utilizing the H-bond mediated recognition between 6-acylamino-2-pyridone and

2-acylamino-1,8-naphthyridine.[366] Although transition-state binding to the template is reasonably effective (effective molarity about 4 M), no attempts were made to study the effect of added template on the *endo*/*exo* product ratio.

5.5. Templated Cyclizations

5.5.1. Macrocyclization Reactions

Template effects can drastically alter the course of macrocyclization reactions and consequently promote the formation of one particular product.[367] For example, intramolecular H-bond formation is responsible for the observed template effects in amide-based macrocyclization reactions as studied by Hunter and co-workers. It was found that the reaction between isophthaloyl dichloride and diamine **60a** yields 88% of the cyclic tetramer **61a**, while higher oligomers were not found (Scheme 34).[368] In their studies of the covalent capture of noncovalent peptide ensembles Clark and Ghadiri observed template effects that result from intermolecular H-bonding.[369, 370] Olefin metathesis of homoallylglycine-bearing octapeptide dimer $\mathbf{62_2}$ smoothly yielded the corresponding covalent cyclic dimer **63** in 65% yield, whereas no product was formed in the absence of the H-bonded dimer (Scheme 35).



Scheme 34. Templated-directed synthesis of macrocycle **61** and **64**, catenane **66**, and peptide rotaxane **67**.

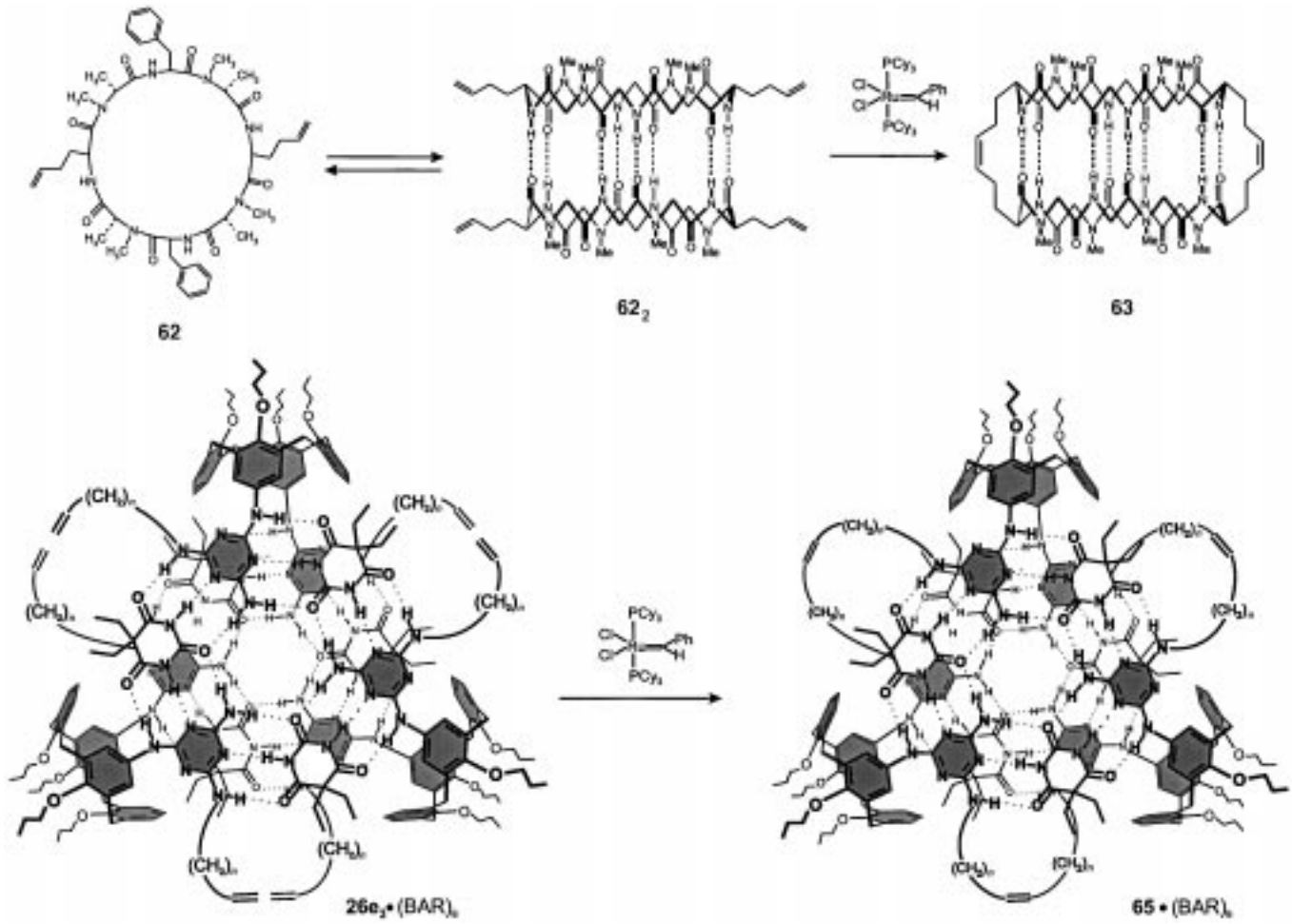
Rudkevich and Rebek reported a cyclization reaction that was templated by the product (**64**) of the reaction (Scheme 34).[363] The observed template effect strongly resembles that of the self-replicating systems as discussed in Section 5.4, but differs in the sense that in this case the product catalyzes the *intra*molecular cyclization of an intermediate (unimolecular reaction) rather than the *inter*molecular reaction between the reactants (bimolecular reaction). The template both increases the yield of the reaction (from 20 to 55%) as well as the rate (more than threefold) of its own formation. Whether the reaction exhibits true autocatalytic behavior awaits further kinetic studies.

Recently, Reinhoudt's group reported one of the most spectacular examples of templated synthesis in which H-bond formation is involved (Scheme 35). Reaction of assembly $\mathbf{26e}_3 \cdot (\mathrm{BAR})_6$, which carries 1-octenyl side chains, with Grubbs catalyst in CD_2Cl_2 resulted in the covalent linkage of the three calix[4]arene units **26e** through a threefold metathesis reaction to give the 123-membered macrocycle **65** as the corresponding hydrogen-bonded assembly $\mathbf{65} \cdot (\mathrm{BAR})_6$ in 96% yield.[371] Not a single trace of **65** was formed in the absence of BAR as a template. Moreover, the reaction turned out to be extremely sensitive to the length of the alkenyl spacer: with 1-hexenyl side chains the reaction did not give any of the desired trimer, while for 1-decenyl spacers the yield was reduced to 71% yield.

5.5.2. Catenane and Rotaxane Formation

Catenane formation involves a special type of template effect, one in which an empty macrocycle (one half of the catenane) complexes its linear precursor and subsequently templates the formation of the catenane.[372–374] The clear difference with most self-replicating systems is the nonreversibility of the dimer formation. Therefore, reversibly formed catenanes could potentially exhibit self-replicating behavior.[375]

Significant amounts of the catenated product **66** (29%) were formed in the reaction between **60b** and isophthaloyl dichloride as a direct result of the formation of strong intermolecular H-bonds between the empty macrocycle **61b** and its linear precursor (Scheme 34).[376] Very similar catenanes were reported shortly after by the group of Vögtle,[377] who extended the concept further to the synthesis of amide-linked rotaxanes by using anion complexation.[378] Later, Leigh and co-workers found similar template effects in the formation of catenanes obtained from isophthaloyl dichloride and benzylic diamines.[379, 380] Moreover, this research group reported that linear amides[381] or peptides[382] can also act as templates in the synthesis of amide-based rotaxanes such as **67** with yields as high as 62% (Scheme 34).[375] A novel class of pseudorotaxanes that were stabilized largely by H-bonding interactions between secondary dialkylammonium salts and crown ethers, was recently reported by Stoddart and co-



Scheme 35. Covalent capture of octapeptide dimer $\mathbf{62}_2$ and double-rosette assembly $\mathbf{26e}_3 \cdot (BAR)_6$.

workers.[383] This recognition motif was also used for the preparation of [2]rotaxanes as pH-controllable molecular shuttles.[384]

6. Properties and Applications of H-bonded Assemblies

"The most fundamental and lasting objective of synthesis is not production of new compounds, but production of new properties"
George Hammond, 1968

6.1. Introduction

A lot of work on self-assembly through H-bonding is aimed at a particular application, such as in Section 4 where H-bonded molecular capsules for guest complexation and molecular catalysis were described. This section reviews H-bonded assemblies that exhibit novel properties *as a direct result* of the H-bonding interactions. A full coverage of all the literature would certainly be beyond the scope of this review and therefore only a representative selection of important developments is given, which adequately illustrates where the field is moving.

6.2. Photo- and Redox-Active Assemblies

6.2.1. Photoactive Assemblies

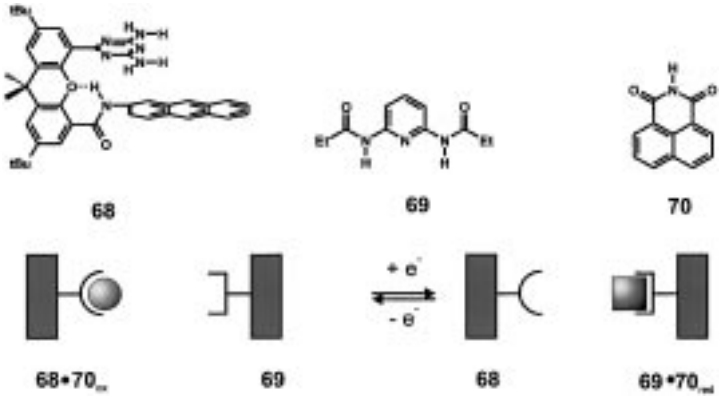
The mechanism of how energy and electrons are transferred over long distances in biological systems, such as DNA or in light harvesting systems, is currently not known. H-Bonded model systems have been studied to provide fundamental insight into these processes. Hamilton and co-workers showed that the fluorescence of a dansyl moiety (dansyl = 5-dimethylaminonaphthalene-1-sulfonyl) is quenched as a result of energy transfer to a free-base porphyrin connected by six H-bonds.[385] Sessler and co-workers studied the energy transfer in 1:1 H-bonded complexes of cytosine-substituted zinc and free-base porphyrins.[386] The time-resolved fluorescence measurements of the zinc porphyrin showed bi-exponential decay profiles as a result of significant dissociation of the cytosine dimer (cleavage of only two H-bonds) under the experimental conditions. The longer lifetimes, which account for $\geq 80\,\%$ of the total fluorescence, correspond to the monomeric zinc porphyrin present. The shorter lifetimes originate from quenching of the Zn-porphyrin fluorescence by energy transfer to the free-base porphyrin. Further studies on rigid analogues utilizing the G·C base-pair motif allowed the complete elucidation of the mechanism of energy transfer.[387]

Time-resolved fluorescence meaurements showed that singlet–singlet energy transfer occurs through a Förster-type mechanism (through-space) with a rate constant of $9 \times 10^8\ s^{-1}$ and a quantum efficiency of 60%. Transient absorption measurements showed that triplet–triplet energy transfer is very slow and occurs by a Dexter-type mechanism (through bond).

Photoinduced electron transfer (ET) occurs when the energy level of the excited state of the donor is high enough to reduce the acceptor.[388] Studies on complexes based on imide · diamidopyridine interactions[389, 390] and carboxylic acid dimerization[391] revealed that H-bonded interfaces hardly pose a barrier for ET, with rates only slightly lower (about $10^{10}\ s^{-1}$) than for covalently bound structures (about $10^{11}\ s^{-1}$). High-field EPR studies of noncovalent complexes of Zn-porphyrins with either quinone or dinitrobenzene units have shown that ET pathways are stabilized by multiple H-bonding interactions.[392, 393]

6.2.2. Redox-Active Assemblies

The research groups of Yano and Rotello have extensively studied the mechanism by which flavoenzymes change the redox properties of cofactors through a combination of H-bonding, electrostatic interactions, and $\pi-\pi$ interactions.[394, 395] Flavin binds to diamidopyridine derivatives through threefold H-bonding (DAD · ADA array) with $K_{ass} = 10^2 - 10^3\ M^{-1}$ in chloroform. Cyclic voltammetry measurements revealed that the flavin radical anion is significantly stabilized upon complexation with diamidopyridine.[396] The K_{ass} value of the complex increases by a factor of 500 upon reduction of the flavin unit as a result of increased electron density at the carbonyl groups. Similar increases in binding strength upon reduction have been reported for simple imide · amidopyridine and quinone · urea dimers.[397] On the basis of this principle, a three-component molecular switch that could be controlled electrochemically was constructed (Scheme 36).[398] The system is composed of two receptor molecules (**68** and **69**) that can both form a dimeric complex with naphthalimide **70**. In the oxidized state, guest molecule **70** has a higher affinity for receptor **68** as a result of favorable stacking interactions ($K_{ass} = 1840\ M^{-1}$ for $\mathbf{68} \cdot \mathbf{70}_{ox}$ and $150\ M^{-1}$ for $\mathbf{69} \cdot \mathbf{70}_{ox}$). In the reduced state, however, the electrostatic repulsion strongly destabilizes the $\mathbf{68} \cdot \mathbf{70}_{red}$ complex, while the K_{ass} value for dimer $\mathbf{69} \cdot \mathbf{70}_{red}$ increases to $41\,000\ M^{-1}$ as a result of stronger H-bonding interactions. Consequently, guest **70** "switches" from receptor **68** to receptor **69** upon reduction.

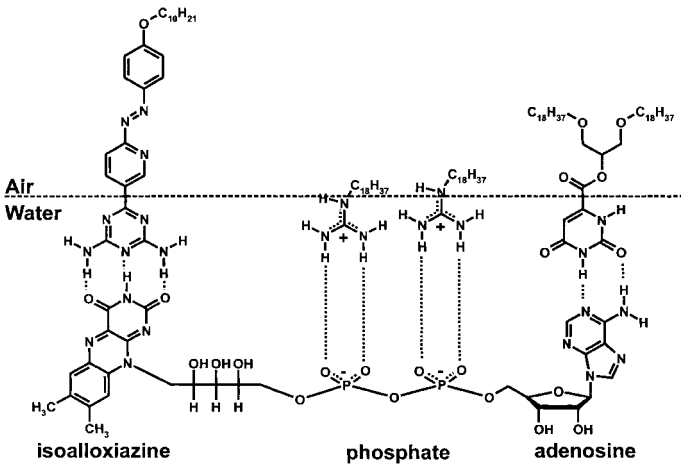


Scheme 36. A three-component electrochemically controlled switch.

6.3. Self-Assembly at Interfaces

6.3.1. Sensor Development: The Air–Water Interface

Ariga and Kunitake observed that monolayers of alkylated guanidinium at the air–water interface associate with phosphates present in the aqueous phase with a K_{ass} value of $10^6 - 10^7\ M^{-1}$.[399] This value contrasts strongly with the dimerization constant of $1.4\ M^{-1}$ in bulk water. The strong enhancement of the binding affinity is attributed to a dramatic decrease in the dielectric constant close to the hydrophobic phase. This effect offers the possibility of utilizing H-bonding interactions for molecular recognition purposes in Langmuir films at the air–water interface.[400–404] Since Langmuir monolayers are in a dynamic equilibrium, they can to some extent be regarded as a dynamic library of functionalities (see Section 6.6). Kunitake and co-workers showed that mixed monolayers displaying an ADA, a DA, and a guanidinium recognition motif selectively recognize FAD through a three-point interaction with the complementary isoalloxazine (DAD), adenosine (DA), and phosphate moieties (Scheme 37).[405] X-ray photoelectron



Scheme 37. Selective recognition of FAD by a mixed monolayer through a three-point interaction between complementary sites.

spectroscopic analysis of the Langmuir film transferred from an aqueous phase containing FAD revealed that one single FAD molecule was bound to the three recognition units. The same approach was applied to bind water-soluble dipeptides to monolayers of peptide-functionalized dialkyl amphiphiles. This study significantly widens the scope of this technique.[406] An interesting future development will be the use of interfacial molecular recognition to create patterns with molecular resolution in Langmuir films.

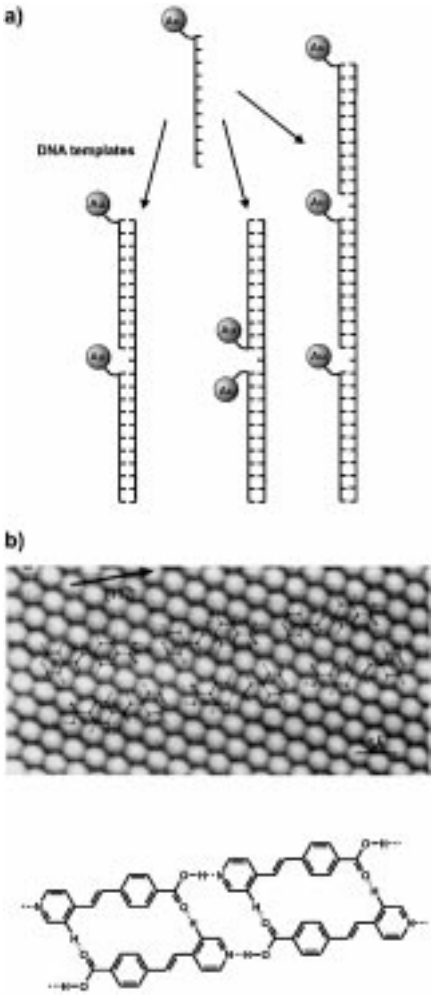
6.3.2. Nanotechnology: The Solid–Air Interface

Organic and inorganic structures of nanosize dimensions (1-100 nm) are at the focal point of current nanotechnological

developments. The controlled organization of nanoparticles into well-ordered two- and three-dimensional arrays is of crucial importance for the development of nanoelectronics. The directionality and reversibility of H-bonds make them perfectly suitable to serve as linkers between nanoparticles.[407] Mirkin et al. showed that the addition of "sticky" DNA strands to a solution of Au colloids functionalized with complementary single DNA strands resulted in the formation of well-defined 3D networks.[408] Transmission electron microscopy (TEM) studies showed close-packed assemblies of the colloids with a uniform separation of about 60 Å. Formation of the network causes a characteristic color change from red to purple as a consequence of a change in the surface plasmon resonance of Au. The color change reversed upon heating, which proved the reversibility of the network formation. In subsequent work this property was used for the colorimetric detection of polynucleotides.[409] The "melting" temperature T_m of a network formed between polynucleotide targets and Au colloids functionalized with DNA recognition elements is strongly dependent on the complementarity between the DNA strands. A mismatch of only one base pair reduces the T_m value by 5 K. The high sensitivity of the system is apparent from the detection limit of approximately 10 fmol for the unoptimized system.

Alivisatos, Schultz, and co-workers employed DNA hybridization to control the spatial position of individual nanoparticles.[410] The Au colloids were monofunctionalized with 18-base single DNA strands to prevent formation of a three-dimensional network. The addition of complementary single DNA strands containing 37 or 56 bases resulted in DNA strands containing two or three Au colloids, respectively, with the spatial position depending on the base-pair sequence (Scheme 38a). In a similar fashion, the spatial orientation of Au particles of different sizes can be controlled.[411] However, a uniform spatial separation of the particles was hampered by the relatively low rigidity of the DNA backbone. Besides DNA, biotin–streptavidin,[412] amidopyridine–imide,[413] and triazine–thymine interactions[414] have been employed for the same purpose.

The self-assembly of H-bonded structures also provides an efficient route to fabricate nanostructures on solid surfaces.[415] The research groups of Whitesides and Reinhoudt have shown that the mixing of dimelamines and dicyanurates (see Section 3.3) in a 1:1 ratio resulted in the formation of polymeric stacks of rosettes.[416, 417] Drop-casting solutions of these polymeric structures onto a graphite surface enabled the long-range ordering of the nanorods to be shown by atomic-force microscopy (AFM). Recently, Kern and co-workers showed that the self-assembly of regular patterns of 4-[*trans*-2-(pyrid-4-yl-vinyl)]benzoic acid units on a Ag(111) surface occurred as a result of strong pyridine·carboxylic acid and weak C=O···H–C H-bonding interactions (Scheme 38b).[418] Pattern formation turned out to be strongly affected by the substrate–surface interactions. Van Esch, Feringa, and co-workers employed H-bonding interactions between urea moieties to assemble fibers with regularly spaced thiophene groups, which results in a high charge mobility in these materials.[419] These fibers were shown to form highly elongated aggregates on solid substrates.[420]



Scheme 38. a) DNA hybridization to control the spatial orientation of Au nanoparticles. b) Regular patterns of 4-[*trans*-2-(pyrid-4-ylvinyl)]benzoic acid units on an Ag(111) surface.

6.4. Macromolecular Assemblies

6.4.1. Polymers

Supramolecular polymers can be defined as polymers in which the individual subunits are connected through non-covalent interactions. Polymers of this type are expected to display novel, interesting properties, for example, liquidlike behavior upon heating or dilution. After entanglement of the individual polymer strands, dissociation of single connector units should still be possible without losing the polymeric properties. For this purpose, H-bonding interactions provide an attractive option because of their directionality, reversibility, and the possibility of controlling the strength of the interactions by altering the number of H-bonds involved. Early attempts by the groups of Griffin and Lehn were based on 1-H-bond and 3-H-bond modules, such as the carboxylic acid·pyridine motif or the uracil·2,6-diacylaminopyridine motif.[421–423] Unfortunately, the stability of these complexes was not sufficient to induce polymeric properties in solution. Similar results were obtained for macromolecular structures composed of H-bonded complexes based on melamine·barbiturate,[192, 424] pyrimidine·isocyanuric acid,[425] melamine·

imide,[426, 427] or 2,6-diaminotriazine · imide interactions.[428] Cocrystallization of compounds with complementary H-bonding sites has often led to the formation of well-defined polymeric strands, but in general the stability was too low under dynamic conditions.[155, 195, 429–433]

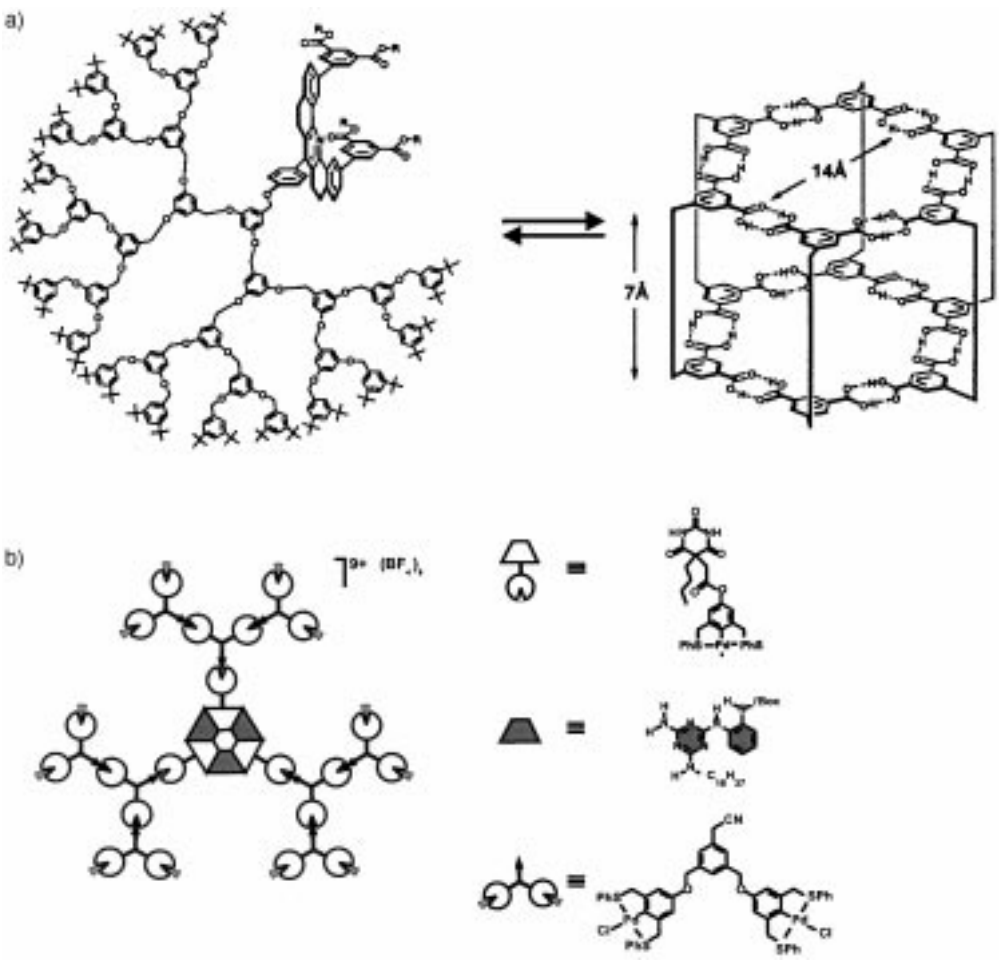
In order to generate polymer chains of sufficient length that exhibit true polymeric properties, the association constant of the individual H-bonding modules should be significantly higher than those of 3H-bond modules. This concept has initiated the search for novel building blocks that (self-)associate with $K_{ass} > 10^6\,M^{-1}$.[434] A breakthrough was achieved by Sijbesma, Meijer, and co-workers when they developed a quadruple H-bonded motif based on the dimerization of 2-ureido-4-pyrimidones (see Section 2.3.4).[435] It was found that ditopic monomers containing two 2-ureido-4-pyrimidone moieties that cannot interact in an intramolecular fashion spontaneously form polymers in chloroform. The number-average degree of polymerization of $P_n = 700$ at 40 mM corresponds to an average molecular weight of about 500 kDa. These H-bonded structures display the anticipated behavior of true polymers for the first time. The equilibrium is shifted in favor of the monomer units at low concentrations or elevated temperatures, which consequently causes liquidlike behavior of the polymer solution. The viscosity drops sharply when small amounts of monofunctional "stoppers" are added, which means that polymer formation is reversible. Interestingly, in situ generation of stopper molecules by photoinduced cleavage of an *o*-nitrobenzyl protecting group caused a large drop in the viscosity η_{rel} upon irradiation with light.[436] The same module has been used as end-caps of low molecular weight telechelic polymers to change their properties[437, 438] and also in three-dimensional polymer networks.[439]

Another type of H-bonded polymer was recently reported by Rebek and co-workers which employed two tetraureacalix[4]-arenes connected covalently by a rigid spacer.[440, 441] In these systems the addition of guest molecules induces the formation of polymer strands, while the H-bonded capsules serve as connector units. Recently, it was also shown that mesogeneity can be induced by incorporating long aliphatic chains.[442]

6.4.2. Dendrimers

Dendrimers are a special class of polymers with unique properties as a consequence of their uniform size and shape. There are only a few examples of using H-bonding for the self-assembly of well-defined dendritic structures of nanometer dimensions.[443, 444] Zimmerman et al. constructed dendritic wedges of different generations containing a rigid concave spacer that preorganizes two isophthalic acid moieties in a parallel fashion (Scheme 39a).[445] The self-association of these monomers through the formation of a double hexameric motif in the core resulted in the spontaneous formation of dendrimers with molecular weights up to 30 kDa. The dendritic wedges preferentially form a cyclic hexamer rather than a polymeric structure because steric repulsion between the wedges is minimized in the cycle. Molecular modeling studies showed that the structure of these assemblies is disk-shaped with a thickness of 2 nm and a diameter of 9 nm.

By using a similar approach, Reinhoudt and co-workers used the rosette motif for the self-assembly of noncovalent dendrimers.[446] In this case, metallodendrimer wedges were functionalized with a barbiturate moiety at the focal point. The addition of one equivalent of melamine resulted in the quantitative formation of dendritic structures that have a rosette moiety inside the core (Scheme 39b). The unique feature of this approach is that two orthogonal noncovalent interactions for self-assembly are employed: metal–ligand coordination (Pd–CN) in the wedges and H-bonding in the core.

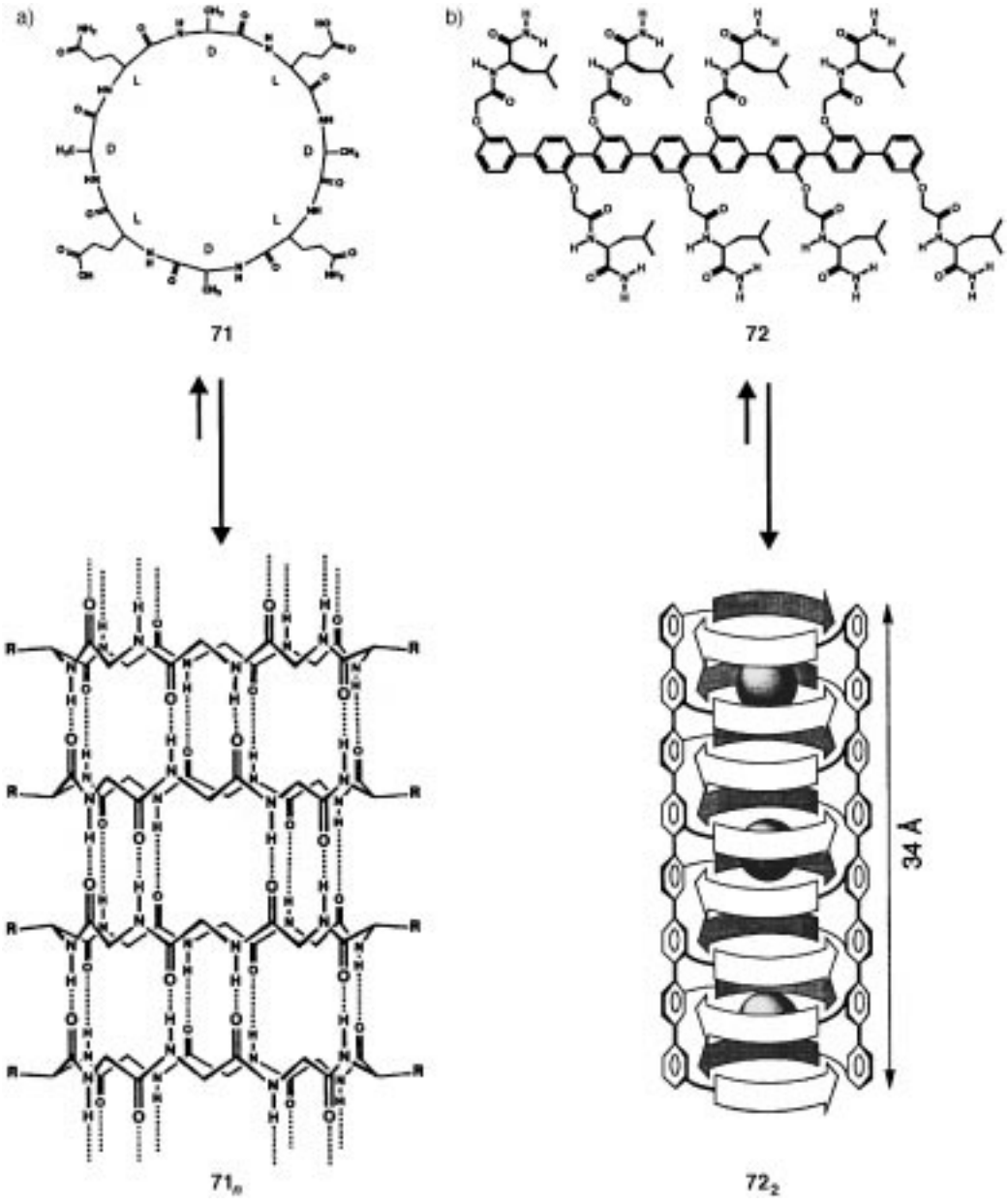


Scheme 39. Self-assembled dendrimers with H-bonded cores.

6.4.3. Self-Assembled Nanotubes

In 1974, De Santis et al. suggested that cyclic peptides composed of an even number of amino acids with alternating chirality should form tubelike stacks through backbone H-bonding.[447] However, it was not until 1993 that Ghadiri et al. reported the first assembly of organic nanotubes based on this design principle (Scheme 40 a).[448, 449] The first nanotubes were composed of eight-membered cyclic peptide **71** with the sequence (L-Gln-D-Ala-L-Glu-D-Ala)$_2$. The successful organization of these units into nanotubes relies on two issues. Firstly, the cycle is flat with all the backbone amide functionalities perpendicular to the plane of the ring, which allows orthogonal stacking through the formation of eight H-bonds. Secondly, the amino acid substituents point outwards, which creates an empty interior with an internal van der Waals diameter of roughly 7 Å.

The diameter of these nanotubes can be controlled simply by changing the number of amino acids in the cyclic peptide.[450] Not only are these structures aesthetically very appealing, they also serve as excellent transport channels in lipid bilayer membranes. Single-channel conductance measurements indicated channel activities for K^+ and Na^+ similar to naturally occurring channel-forming proteins, such as gramicidin A and amphotericin B, with rates exceeding 10^7 ions per second.[451] Nanotubes with larger internal diameters transport glucose across lipid bilayers.[452] The insertion of self-assembled nanotubes in self-assembled monolayers (SAMs) of thiols or thioethers on gold was also studied.[453] Cyclic voltammetry showed that the nanotubes act as selective ion channels, since only redox couples small enough to pass through the channels showed redox activity. The thermodynamic parameters for nanotube formation were inferred from studies on the isolated recognition motif.[454]



Scheme 40. Self-assembled nanotubes based on cyclic peptides (a) and oligo-anisoles (b).

Selective N-methylation of one side of the cyclic peptide only allows formation of dimeric structures. Variable temperature ^{1}H NMR studies revealed that the assembly process is enthalpy driven with $\Delta H^0_{298} = -11.0\,\mathrm{kcal\,mol^{-1}}$ and $\Delta S^0_{298} = -23.7\,\mathrm{cal\,K^{-1}\,mol^{-1}}$.

Other peptide nanotubes constructed from cysteine-based macrocyclic bisureas,[455] serine-based cyclodepsipeptides,[456] and cyclic tetramers of 3-aminobutanoic acid have been reported.[457] Recently, Matile and co-workers reported self-assembled ionophores **72** based on oligoanisoles that are functionalized with "sticky" peptide ends that self-assemble in water (Scheme 40b).[458–460] An intriguing aspect of these nanotubes is their ability to transport protons across lipid bilayers.

6.4.4. Liquid Crystalline Materials

H-bonded complexes with liquid crystalline properties can form from two different components that are not mesogenic by themselves.[461–464] H-bonding gives extended rigid aromatic mesogens, which strongly stabilize the mesophase. Kato and Fréchet used the formation of a single H-bond between pyridine and carboxylic acid to obtain a large variety of mesogenic complexes, such as 2:1 complexes between 4,4′-bipyridines and carboxylates.[465] These studies were followed by related systems based on phenol–stilbazole,[466] carboxylic acid–stilbazole,[467] phenol–pyridine,[468] alcohol–imidazole,[469] and carboxylic acid–amidopyridine interactions.[470] Liquid crystalline properties were introduced in covalent polymers by using a similar approach, for example, by the addition of stilbazole derivatives to a polyacrylate with 4-oxybenzoic acid side chains.[471]

Several examples of multicomponent assemblies that form discotic liquid crystals have been reported. X-Ray studies on fibres obtained from a guanosine 3′-phosphate gel revealed that the guanosine tetramers (see Section 3.5) are piled on top of one another, with the sugar moieties located on the periphery. Gottarelli, Spada, and co-workers showed that oligomers containing between two and six deoxyguanosine moieties form liquid crystalline phases in water at very low concentrations (2.5% w/w for d(GpG)).[472, 473] A strong stabilizing effect observed for different alkali cations in the order $K^+ > Rb^+ > Na^+ > Cs^+$ was attributed to intra- and interassembly binding to oxygen donors. Columnar aggregates were also observed for derivatives that could not form interassembly H-bonds. Other discotic liquid crystals were obtained from synthetic, disklike recognition motifs based on α-pyridone dimerization[474, 475] and lactim–lactam trimerization.[199] Meijer and co-workers showed that intramolecular H-bonding can be used to organize the core of a covalent molecule into a flat disk, which induced columnar liquid crystalline behavior.[476]

6.5. H-Bonding in Water

It is nowadays a generally accepted view that simple H-bonded complexes, such as a single A·T or C·G base pair, do not form in bulk water in the absence of additional stabilizing interactions, such as ion pairing and hydrophobic interactions.[477, 478] For example, Rebek and co-workers showed that the strength of binding of 9-ethyladenine to water-soluble derivatives of Kemp's triacid imide is correlated to the surface area of the hydrophobic group facing the binding pocket.[479] The formation of H-bonded complexes within the lipophilic core of micelles has been reported by Nowick et al.[480] Recently, Komiyama and co-workers found that poly(2-vinyl-4,6-diamino-1,3,5-triazine) (PVDAT) efficiently binds pyrimidine derivatives from aqueous solutions through the formation of complementary H-bonds,[481] as confirmed by ^{1}H NMR spectroscopy and ultrafiltration experiments.[482] The order of the binding activity (U, T > A ≫ C, G) coincides with the number of H-bonds formed between the host and guest. The corresponding monomers show virtually no activity, which indicates that the binding is predominantly the result of a polymer effect.

Recently, Meijer and co-workers described the first example of multicomponent H-bonded assemblies that are stable in water.[483] The structures form as a result of cooperative stacking and H-bonding interactions.

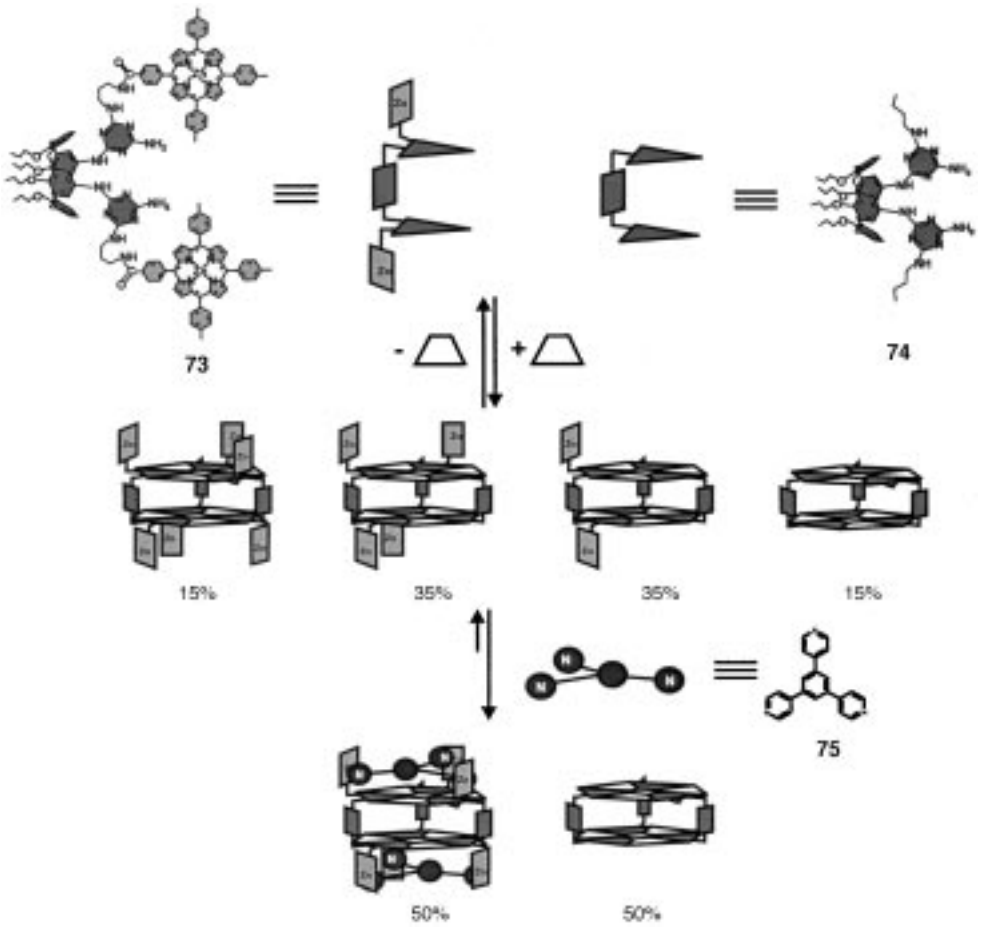
The formation of H-bonded complexes at the air–water interface has already been described in Section 6.3.1.

6.6. Self-Assembled Receptors: Dynamic Combinatorial Chemistry

6.6.1. Self-Assembly of Functionalities

The use of H-bonded assemblies as a molecular platform for guest recognition studies requires the introduction of compatible functional groups. The research groups of Lehn and Whitesides both showed that the presence of peripheral Zn-porphyrins is fully compatible with the formation of single-rosette assemblies.[484, 485] However, in both cases complexation of guest molecules to the apical binding site of the Zn center is prevented. Reinhoudt and co-workers constructed a bifunctional receptor that consists of a calix[4]arene binding site that is selective for Na^+ ions, and a Zn-porphyrin that is capable of binding SCN^- ions.[486] Both modules carry complementary H-bond recognition sites (DAD·ADA), and binding studies showed that the 1:1 H-bonded complex has an increased affinity for NaSCN as a direct result of H-bond formation.

Studies by Timmerman et al. on the assembly behavior of functionalized calix[4]arenes revealed that double-rosette assemblies are compatible with a large variety of functional groups, such as polar nitro and cyano groups.[173] Significant destabilization was only observed for functionalities that cause severe steric hindrance within the assembly or as a result of the formation of additional H-bonds. Guest binding does not occur in these assemblies, since the functionalities are located in between the rosette layers, an area inaccessible for guest molecules. In the next generation of receptor assemblies the binding functionalities, such as Zn-porphyrins or peptides, were located at the periphery of the assembly (Scheme 41).[487, 488] The C_3-symmetrical assembly $\mathbf{73}_3\cdot(\mathrm{BAR})_6$, which carries two circular arrays of three Zn-



Scheme 41. Guest-templated formation of the strongest receptor in a DCL.

porphyrin units, binds strongly to the trispyridine guest **75** through threefold coordination to the Zn centers.

6.6.2. Dynamic Combinatorial Chemistry

Dynamic combinatorial libraries (DCLs) have recently attracted a great deal of attention in the rapidly growing field of combinatorial chemistry.[489–491] The interest in DCLs relies mainly on two important features. First of all, structural diversity in DCLs is generated spontaneously by mixing single components of the library under reversible conditions. Secondly, the reversible character of DCLs permits target-driven amplification of selected library members by means of thermodynamic equilibria shifting as a result of molecular recognition phenomena. The high thermodynamic stability of H-bonded assemblies combined with their usually low kinetic stability renders them very suitable for the generation of dynamic libraries.[492] Moreover, H-bonding interactions have been used extensively to induce guest-templated amplification.

The first model study on H-bonded DCLs was reported by Timmerman and co-workers.[179] This study showed that a statistical mixture (1:3:3:1) of four possible double-rosette assemblies is formed instantaneously by mixing the components in $CHCl_3$ at room temperature (see also Section 3.3.5). Recently, the same group reported a four-component DCL of receptors $\mathbf{73}_n\mathbf{74}_{3-n}\cdot(BAR)_6$ ($n=0-3$) which was obtained by mixing the homomeric assemblies $\mathbf{73}_3\cdot(BAR)_6$ and $\mathbf{74}_3\cdot(BAR)_6$ in a 1:1 ratio (Scheme 41).[487] The various members of this library all contain a different number of Zn-porphyrin units and consequently exhibit different binding affinities for the trispyridine guest **75**. Subsequent addition of **75** induced a shift of the library composition from statistical (1:3:3:1) to an almost 1:1 mixture of assemblies $\mathbf{73}_3\cdot(BAR)_6\cdot\mathbf{75}_2$ and $\mathbf{74}_3\cdot(BAR)_6$ as a direct result of the preferential binding of **75** to the all-porphyrin assembly $\mathbf{73}_3\cdot(BAR)_6$. Recently, Rebek and co-workers showed the occurrence of guest-template effects in DCLs of H-bonded capsules.[493]

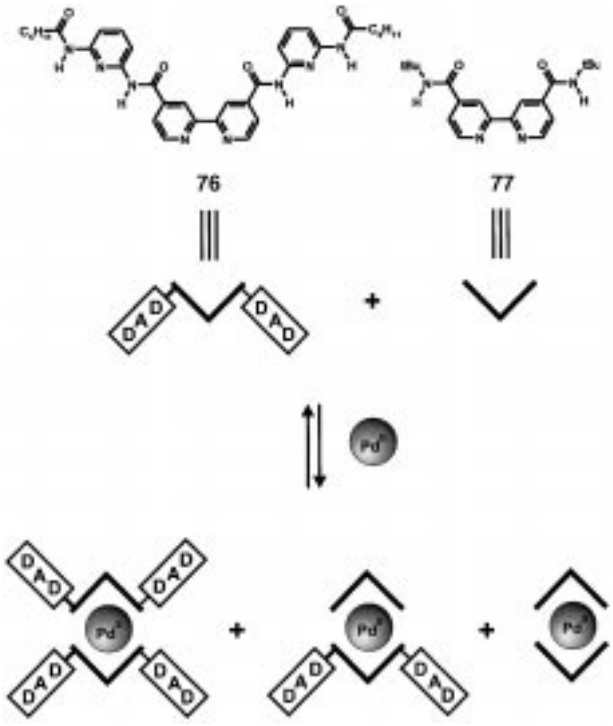
H-bonding interactions have been extensively employed to drive the chemical evolution of DCLs of potential receptors. The concept was first illustrated by Eliseev and Nelen in a study on the rapid interconversion of a dicarboxylate between three isomeric forms upon irradiation with UV light.[494] From the three receptors, only the *cis*–*cis* isomer, which has the ideal geometry to complex guanidinium, shows significant retention on an affinity column loaded with immobilized arginine. Repetitive isomerization–selection cycles have been used to generate the *cis*–*cis* receptor from the mixture in 85% yield.

Huc et al. reported DCLs that are formed by the coordination of Pd^{II} ions to bipyridines (Scheme 42).[495] Bipyridine ligands **76** and **77**, with and without additional H-bonding arrays, respectively, were used to generate a library of three different complexes, only one of which displays a DAD · DAD array that is complementary to a barbituric acid derivative (ADA · ADA). Addition of this guest to the library resulted in a small, but significant, shift of the equilibrium towards the complex with the highest affinity. Similar template effects were observed recently by the same group in DCLs of conformational isomers of di- and polytopic receptors.[496]

7. Conclusions and Perspectives

"Research is not to follow known tracks, but instead to crumble into the forest in the hope that one leaves a track behind."

Noncovalent synthesis has dramatically changed the way in which chemists approach the generation of molecular structures of nanosize dimensions. Whereas molecules tradition-



Scheme 42. A DCL based on bipyridine – Pd^{II} coordination.

ally were synthesized by the stepwise formation of covalent bonds, the use of multiple weak interactions to organize molecular components into supramolecular nanostructures is now a very attractive and fruitful alternative. In addition to this, the noncovalent assemblies display fundamentally different properties in comparison to purely covalent structures. What originally started as a curiosity has now developed into a mature field of research that will have a major impact on the way chemistry is conducted in the next decade. At the end of this review, we will give a short highlight of a number of new and promising developments that may initiate new research areas in the coming decade.

7.1. Catalyzed Noncovalent Synthesis

The majority of H-bond-directed self-assembly processes discussed in this review take place under thermodynamically controlled conditions. This means that such processes benefit from self-repairing as a direct result of the fact that the reverse process, namely, the breakdown of these assemblies, is rapid on the laboratory timescale. However, with the increase in the number of individual H-bonds that are involved in the assembly process, the rate of disassembly will rapidly decrease. Ultimately, this will lead to situations in which the self-assembly process becomes kinetically controlled and suffers from the same problems as those observed in covalent synthesis. Several examples of kinetic control in self-assembly processes have been described recently.[181, 497, 498] Whitesides and co-workers reported that the kinetic stability of multidentate complexes based on the vancomycin-D-Ala-D-Ala recognition motif can be drastically decreased by the addition of the monovalent ligand N^{α}-Ac-L-Lys-D-Ala-D-Ala.[499] In other words, the monovalent ligand "catalyzes" the intermolecular exchange process of the tripodal ligands in the complex by temporarily binding to the free binding sites of the fully or partially uncomplexed states that are formed during the exchange process.

Recently, Reinhoudt, Timmerman, and co-workers reported a similar form of catalysis in a hydrogen-bond-mediated self-assembly process.[180] It was found that the presence of free barbiturate (*R*)-BAR (Scheme 12) catalyzes the racemization of an enantiomerically pure assembly $\mathbf{26}_3 \cdot (\mathrm{BuCA})_6$ (Scheme 19) by activation of the assembly for the exchange of the melamine components. Kinetic analysis of the system revealed that about 80% of racemization occurs at 1 mM concentrations by the catalytic pathway, with a corresponding rate constant of $14.7 \times 10^{-3}\,\mathrm{M^{-1}s^{-1}}$. Other kinetically controlled self-assembly processes involving H-bonding have been identified which are subject to catalysis under certain conditions.[500] Without doubt, this type of catalysis in self-assembly processes will receive increasing interest in the near future and may ultimately determine the dimensions of nanostructures that we may be able to generate.

7.2. Combinatorial Libraries of Artificial Receptor Systems by Noncovalent Synthesis

The combinatorial philosophy, which has revolutionized the way in which covalent bond making processes are performed nowadays, is about to create a paradigm shift in noncovalent synthesis. Processes that form noncovalent bonds are ideally suited to be performed in combinatorial fashion for two reasons. First of all, such processes are clean, high-yielding, and (in most cases) take place under thermodynamic control. This means that combinatorial libraries of H-bonded assemblies are formed spontaneously upon mixing the individual components. Moreover, the resulting libraries are dynamic in nature, which means that guest-templating effects are applicable.[490–492]

At the moment, noncovalent combinatorial synthesis is still in its infancy. Initial studies are concerned with simple model systems,[179] in which strong guest-templating effects have already been observed.[487, 493] Future work in this area should therefore be directed at library characterization and lead/hit identification.[371] Once these problems have been solved, it seems beyond doubt that the combinatorial approach is going to provide the ultimate solution to the development of artificial receptor systems that mimic the binding properties of natural antibodies in terms of affinity and selectivity.[492] The high degree of control that can be achieved over chirality in noncovalent assemblies may pave the way to optically pure chiral cavities that encapsulate chiral guest molecules with high enantioselectivity, for example, for purification purposes or enantioselective catalysis inside capsules.

7.3. H-Bond-Directed Self-Assembly in Water

The majority of synthetic H-bonded assemblies are studied in apolar solvents, such as chloroform or toluene. Usually,

such structures do not assemble in water because the polar water molecules compete favorably in H-bond-forming processes and strongly destabilize the assemblies. But why then does nature provide ample examples of binding processes based on H-bonding, such as formation of the DNA duplex or substrate binding in enzyme pockets, even though such processes occur in the presence of water? The most likely answer to this question is that the formation of H-bonds in biological systems generally takes place within a hydrophobic microenvironment from which water molecules are excluded as a result of hydrophobic effects. The hydrophobic pockets are usually formed as a result of the clustering of multiple hydrophobic fragments that are in some way preorganized, either on a polymeric backbone or as a result of cooperative binding interactions. Only very recently, an example of a synthetic multicomponent H-bonded assembly that forms in an aqueous environment was reported.[483] However, it will not take long before many such structures will appear in the literature. Ultimately, a systematic study of the self-assembling properties of H-bonded assemblies that exist in water will help to unravel the underlying principles that govern self-assembling processes in this mysterious solvent.

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