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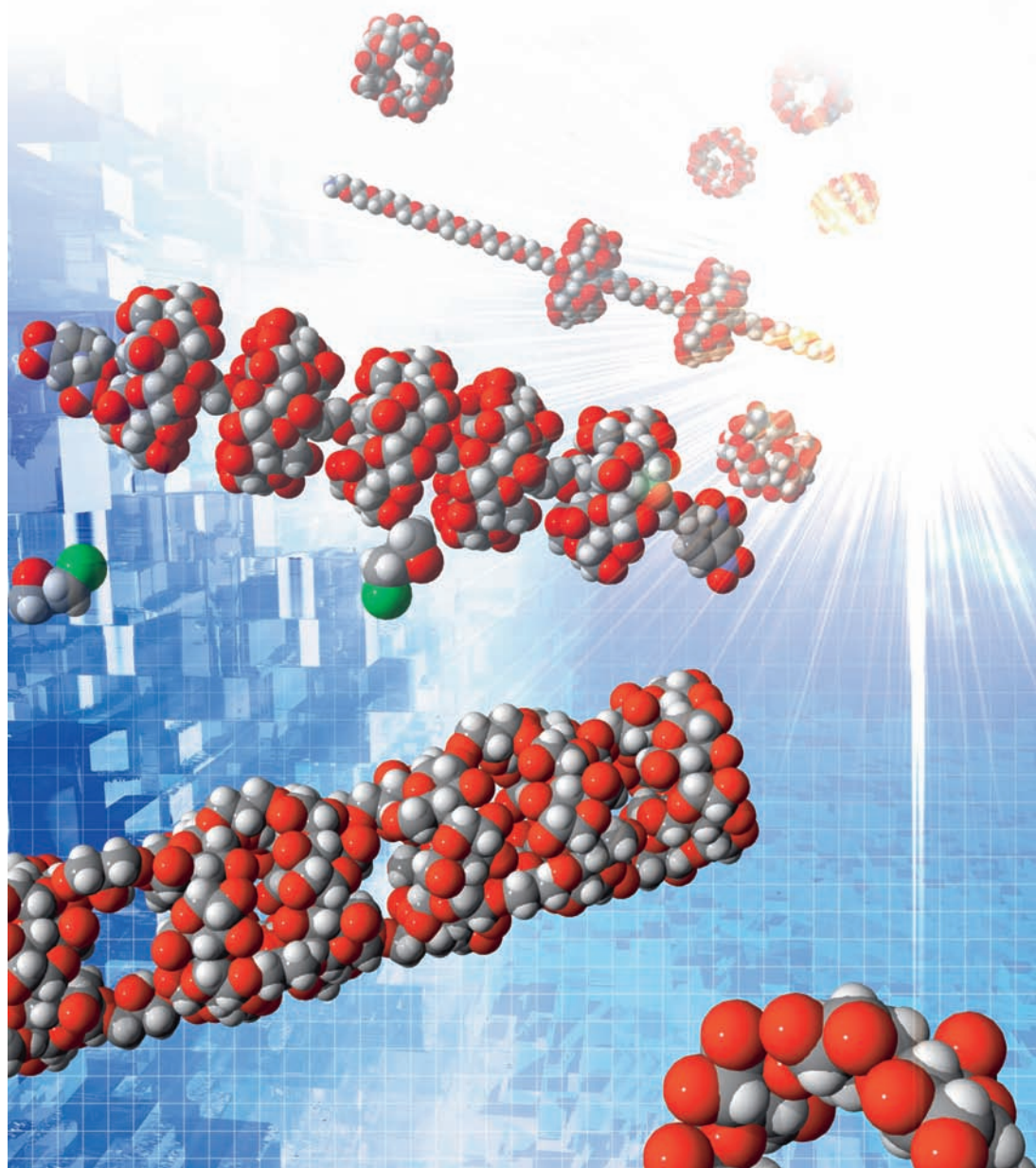
Supramolecular Polymer Chemistry

Edited by Akira Harada

**Supramolecular Polymer
Chemistry**

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Contents

Preface

The chemistry of molecular recognition began more than 50 years ago with the discovery of crown ethers as selective host molecules for alkali metal ions by Dr. Pedersen. In the last 30 years, the chemistry of molecular recognition has greatly expanded. For example, Cram *et al.* incorporated host–guest chemistry and Lehn created supramolecular chemistry. To date, numerous studies have been published on supramolecular complexes.

Moreover, in biological systems, macromolecular recognition by other macromolecules plays an important role in maintaining life (e.g., DNA duplication as well as enzyme–substrate and antigen–antibody interactions). Supramolecular polymer complexes are crucial for the construction of biological structures such as microtubules, microfilaments, and cell–cell interactions.

Synthetic supramolecular polymers have great potential in the construction of new materials with unique structures and functions, because polymers contain vast amounts of information on their main-chains and side-chains. For example, in 1990, supramolecular polymers consisting of cyclodextrins and synthetic polymers were reported. Prof. Lehn's textbook, *Supramolecular Chemistry*, which was published in 1995, mentions supramolecular polymers. Prof. Meijer and Prof. Zimmerman reported supramolecular polymers linked by multiple hydrogen bonds. Since then numerous other reports on supramolecular polymers have been published.

This book is geared toward current supramolecular polymer researchers as well as other interested individuals, including young researchers and students. Each chapter is written by experts who are actively engaged in supramolecular polymer research and have published important papers in the field.

I am honored to be a part of this project, and have eagerly anticipated receiving each chapter. They have all exceeded my expectations, and together they form a book that will become a cornerstone in the field of supramolecular polymer research and, I believe, will help to shape research in the future.

Finally, I would like to express my sincere appreciation to the authors and to all who have assisted in the preparation of this book.

Osaka   *Akira Harada*
May 2011

List of Contributors

Tomoko Abe
Tokyo Institute of Technology
Chemical Resources Laboratory
R1-3, 4259 Nagatsuta, Midori-ku
Yokohama 226-8503
Japan

Wilco P.J. Appel
Eindhoven University of Technology
Institute for Complex Molecular
Systems, Laboratory of Macromolecular
and Organic Chemistry
Den Dolech 2
5612 AZ Eindhoven
The Netherlands

Takayuki Arai
Tokyo Institute of Technology
Department of Organic and Polymeric
Materials
2-12-1 (H-126), Ookayama, Meguro-ku
Tokyo 152-8552
Japan

Eriko Chihara
Tokyo Institute of Technology
Chemical Resources Laboratory
R1-3, 4259 Nagatsuta, Midori-ku
Yokohama 226-8503
Japan

Stephen L. Craig
Duke University
Center for Biologically Inspired
Materials and Material Systems
Department of Chemistry
3221 FFSC
124 Science Drive
Durham, NC 27708-0346
USA

Enrico Dalcanale
University of Parma
Department of Organic and Industrial
Chemistry
Viale G. P. Usberti 17/A
43124 Parma
Italy

Johannes A.A.W. Elemans
Radboud University Nijmegen
Cluster for Molecular Chemistry
Heyendaalseweg 135
6525 AJ Nijmegen
The Netherlands

Harry W. Gibson
Virginia Polytechnic Institute & State
University
Department of Chemistry
2105 Hahn Hall
Blacksburg, VA 24061-0001
USA

Akira Harada
Osaka University
Graduate School of Science
Department of Macromolecular Science
1-1 Machikaneyama-cho, Toyonaka
Osaka 560-0043
Japan

Akihito Hashidzume
Osaka University
Graduate School of Science
Department of Macromolecular Science
1-1 Machikaneyama-cho, Toyonaka
Osaka 560-0043
Japan

Masaki Horie
National Tsing Hua University
Department of Chemical Engineering
Hsinchu, 30013
Taiwan

Kohzo Ito
The University of Tokyo
Graduate School of Frontier Sciences
Department of Advanced Materials
Science, Group of New Materials and
Interfaces
5-1-5 Kashiwanoha, Kashiwa
Chiba 277-8561
Japan

Kazuaki Kato
The University of Tokyo
Graduate School of Frontier Sciences
Department of Advanced Materials
Science, Group of New Materials and
Interfaces
5-1-5 Kashiwanoha, Kashiwa
Chiba 277-8561
Japan

Yasuhiro Kohsaka
Tokyo Institute of Technology
Department of Organic and Polymeric
Materials
2-12-1 (H-126), Ookayama, Meguro-ku
Tokyo 152-8552
Japan

Yasuhito Koyama
Tokyo Institute of Technology
Department of Organic and Polymeric
Materials
2-12-1 (H-126), Ookayama, Meguro-ku
Tokyo 152-8552
Japan

E.W. Bert Meijer
Eindhoven University of Technology
Institute for Complex Molecular
Systems, Laboratory of Macromolecular
and Organic Chemistry
Den Dolech 2
5612 AZ Eindhoven
The Netherlands

Bernd-Kristof Müller
Pharmpur GmbH
Messerschmittring 33
86343 Königsbrunn
Germany

Shintaro Murata
Tokyo Institute of Technology
Chemical Resources Laboratory
R1-3, 4259 Nagatsuta, Midori-ku
Yokohama 226-8503
Japan

Marko M.L. Nieuwenhuizen
Eindhoven University of Technology
Institute for Complex Molecular
Systems, Laboratory of Macromolecular
and Organic Chemistry
Den Dolech 2
5612 AZ Eindhoven
The Netherlands

Roeland J.M. Nolte
Radboud University Nijmegen
Cluster for Molecular Chemistry
Heyendaalseweg 135
6525 AJ Nijmegen
The Netherlands

Kohtaro Osakada
Tokyo Institute of Technology
Chemical Resources Laboratory
R1-3, 4259 Nagatsuta, Midori-ku
Yokohama 226-8503
Japan

Terry L. Price Jr.
Virginia Polytechnic Institute & State
University
Department of Chemistry
2105 Hahn Hall
Blacksburg, VA 24061-0001
USA

Helmut Ritter
Heinrich Heine University
Institute of Organic and
Macromolecular Chemistry
Universitätsstr. 1
40225 Düsseldorf
Germany

Alan E. Rowan
Radboud University Nijmegen
Institute for Molecules and Materials
Heyendaalseweg 135
6525 AJ Nijmegen
The Netherlands

Jean-Pierre Sauvage
University Louis Pasteur/CNRS
Institute of Chemistry, Laboratory of
Organic – Inorganic Chemistry
Institut Le Bel, U.M.R. 7177
67070 Strasbourg-Cedex
France

Seiji Shinkai
Fukuoka, Japan and Sojo University
Institute of Systems, Information
Technologies and Nanotechnologies
(ISIT)
Kumamoto
Japan

Masahiro Shioya
Tokyo Institute of Technology
Department of Organic and Polymeric
Materials
2-12-1 (H-126), Ookayama, Meguro-ku
Tokyo 152-8552
Japan

Kazunori Sugiyasu
National Institute for Materials Science
(NIMS)
Organic Nanomaterials Center
Macromolecules Group
1-2-1 Sengen
Tsukuba 305-0047
Japan

Yuji Suzaki
Tokyo Institute of Technology
Chemical Resources Laboratory
R1-3, 4259 Nagatsuta, Midori-ku
Yokohama 226-8503
Japan

Monir Tabatabai
Heinrich Heine University
Institute of Organic and
Macromolecular Chemistry
Universitätsstr. 1
40225 Düsseldorf
Germany

Yoshinori Takashima
Osaka University
Graduate School of Science
Department of Macromolecular Science
1-1 Machikaneyama-cho, Toyonaka
Osaka 560-0043
Japan

Toshikazu Takata
Tokyo Institute of Technology
Department of Organic and
Polymeric Materials
2-12-1 (H-126), Ookayama, Meguro-ku
Tokyo 152-8552
Japan

Francesca Tancini
University of Parma
Department of Organic and Industrial
Chemistry
Viale G. P. Usberti 17/A
43124 Parma
Italy

Yasuyuki Tezuka
Tokyo Institute of Technology
Department of Organic and
Polymeric Materials
2-12-1-S8-41 Ookayama, Meguro-ku
Tokyo 152-8552
Japan

Donghua Xu
Duke University
Center for Biologically Inspired
Materials and Material Systems
Department of Chemistry
3221 FFSC
124 Science Drive
Durham, NC 27708-0346
USA

Hiroyasu Yamaguchi
Osaka University
Graduate School of Science
Department of Macromolecular Science
1-1 Machikaneyama-cho, Toyonaka
Osaka 560-0043
Japan

Nobuhiko Yui
Tokyo Medical and Dental University
Institute of Biomaterials and
Bioengineering
2-3-10, Kanda-Surugadai, Chiyoda
Tokyo 101-0062
Japan

and

JST CREST
Tokyo 102-0075
Japan

Part One
Formation of Supramolecular Polymers

1
Multiple Hydrogen-Bonded Supramolecular Polymers

Wilco P.J. Appel, Marko M.L. Nieuwenhuizen, and E.W. Meijer

1.1
Introduction

1.1.1
Historical Background

Since the introduction of the first synthetic polymer more than a hundred years ago by Leo Hendrik Baekeland, covalent polymers have become indispensable in everyday life. The term 'polymeric' was first introduced in 1832 by Jöns Jacob Berzelius to describe a compound with a higher molecular weight than that of the normal compound but with an identical empirical formula as a result of the repetition of equal units [1]. In 1920, Hermann Staudinger defined polymers, which he called macromolecules, to be multiple covalently bound monomers. For this work he was awarded with the Nobel Prize in 1953 [2]. Today, our knowledge of organic synthesis and polymer chemistry allows the preparation of virtually any monomer and its associated polymer. In addition, an in-depth understanding of 'living' types of polymerization facilitates tuning of the molecular weight and molecular weight distribution, at the same time creating the possibility to synthesize a wide variety of copolymers [3].

The macroscopic properties of polymers are directly linked to their molecular structure. As a result, polymer chemists devised synthetic approaches to control the sequence architecture. More recently, the importance of introducing supramolecular interactions between macromolecular chains has become evident, and many new options have been introduced. The final step in this development would be to develop polymers entirely based on reversible, noncovalent interactions. Rather than linking the monomers in the desired arrangement via a series of polymerization reactions, the monomers are designed in such a way that they autonomously self-assemble into the desired structure. As with covalent polymers, a variety of structures of these so-called supramolecular polymers are possible. Block or graft copolymers, as well as polymer networks, can be created in this way.

The first reports on supramolecular polymers date back to the time when many scientists studied the mechanism by which aggregates of small molecules gave rise to

increased viscosities. To the best of our knowledge it was Louise Henry who proposed the idea of molecular polymerization by associative interactions in 1878, approximately at the same time that van der Waals proposed his famous equation of state, which took intermolecular interactions in liquids into account, and was only 50 years after Berzelius coined the term polymers. Stadler and coworkers were the first to recognize that hydrogen bonds can be used to bring polymers together [4]. Lehn and coworkers synthesized the first main-chain supramolecular polymer based on hydrogen bonding [5]. In our group, we introduced the self-complementary ureido-pyrimidinone (UPy) quadruple hydrogen-bonding motif that shows a high dimerization constant and a long lifetime. In this chapter, we review the field of supramolecular polymers based on multiple hydrogen bonds and discuss some general approaches to the creation of supramolecular materials based on multiple hydrogen-bonded supramolecular polymers.

1.1.2
Supramolecular Chemistry

Jean-Marie Lehn defined supramolecular chemistry as '... *a highly interdisciplinary field of science covering the chemical, physical, and biological features of chemical species of higher complexity, which are held together and organized by means of intermolecular (noncovalent) binding interactions* [5].' This exciting new field introduced the possibility of self-sorting of subunits during the self-assembly process. At the same time large, complex structures can be created by the assembly of small supramolecular building blocks, thereby allowing the elimination of elaborate synthetic procedures. Complex self-assembly processes are widely recognized to have played an important part in different elements of the origin of life. As a result, many researchers explored different aspects of the field of supramolecular chemistry, using noncovalent interactions to self-assemble molecules into well-defined structures. Noncovalent interactions can vary in type and strength, ranging from very weak dipole-dipole interactions to very strong metal-ligand or ion-ion interactions with binding energies that can approach that of covalent bonds [6]. The most obvious benefits of noncovalent interactions are their reversible nature and their response to external factors such as temperature, concentration, and the polarity of the medium. A subtle interplay between these external factors allows precise control of the self-assembly process. Due to their directionality and the possibility to tune the dynamics and lifetime, hydrogen bonds are among the most interesting assembly units for supramolecular polymers. Before focusing on hydrogen bonding, we shall first address the different mechanisms for the formation of supramolecular polymers.

1.1.3
Supramolecular Polymerization Mechanisms

The mechanism of noncovalent polymerization in supramolecular chemistry is highly dependent on the interactions that play their part in the self-assembly process.
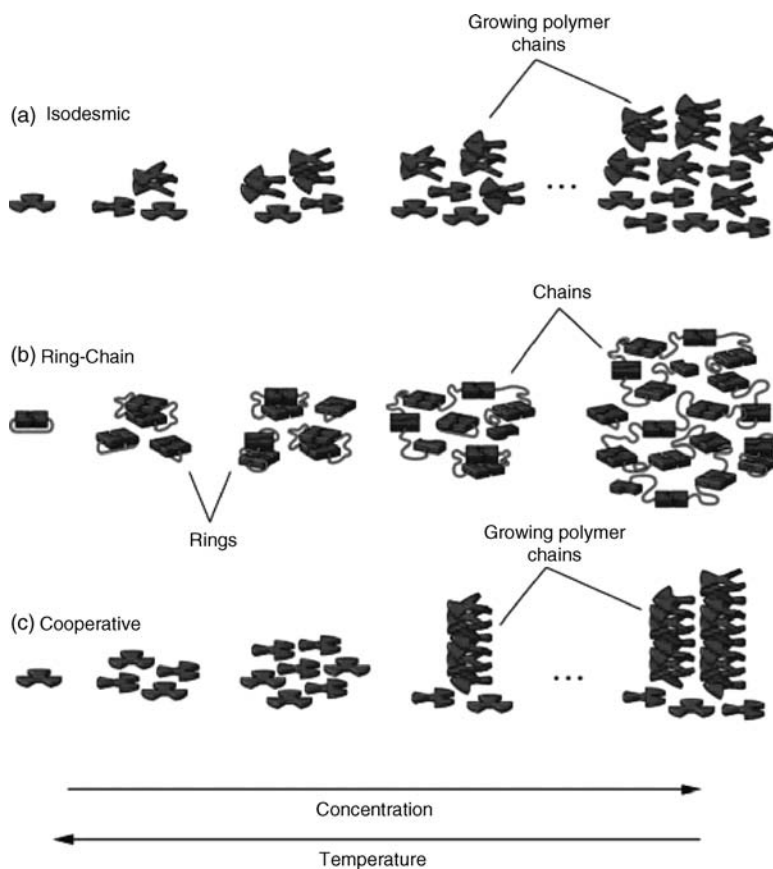
Figure 1.1 Schematic representation of the major supramolecular polymerization mechanisms. Reprinted with permission from Nature Publishing Group [7].

In contrast to covalent bonds, noncovalent interactions depend on temperature and concentration, thereby affecting the degree of polymerization. The mechanisms of supramolecular polymerizations can be divided in three major classes, these being isodesmic, cooperative, or ring-chain equilibria (Figure 1.1) [7].

Isodesmic polymerizations occur when the strength of noncovalent interactions between monomers is unaffected by the length of the chain. Because each addition is equivalent, no critical temperature or concentration of monomers is required for the polymerization to occur. Instead, the length of the polymer chains rises as the concentration of monomers in the solution is increased, or as the temperature decreases.

The ring-chain mechanism is characterized by an equilibrium between closed rings and linear polymer chains. In this mechanism, below a certain monomer concentration the ends of any small polymer chain react with each other to generate closed rings. Above this critical concentration, linear chain formation becomes more

favored, and polymer growth is initiated. The degree of polymerization changes abruptly once the critical conditions are reached. The critical polymerization concentration is largely dependent on the length and rigidity of the monomers. Especially at low concentrations, the presence of cyclic oligomers can drastically influence the macroscopic properties.

Cooperative polymerizations occur in the growth of ordered supramolecular polymers in which there are additional interactions present besides the formation of linear polymers, such as those that form helices. This involves two distinct phases of self-assembly: a less favored nucleation phase followed by a favored polymerization phase. In this mechanism, the noncovalent bonds between monomers are weak, hindering the initial polymerization. After the formation of a nucleus of a certain size, the association constant is increased, and further monomer addition becomes more favored, at which point the polymer growth is initiated. Long polymer chains will form only above a minimum concentration of monomer and below a certain temperature, resulting in a sharp transition from a regime dominated by free monomers and small aggregates to a regime where almost all of the material is present as large polymers. For further details about supramolecular polymerization mechanisms we would refer the reader to a recent review by our group [7].

1.2
General Concepts of Hydrogen-Bonding Motifs

The existence of the hydrogen bond was first suggested by Moore and Winmill in 1912 [8], and it was defined in 1920 by Latimer and Rodebush as '*a hydrogen nucleus held between 2 octets, constituting a weak bond*' [9]. In that time the concept of hydrogen bonding was used to explain physical properties and chemical reactivities due to intramolecular and intermolecular hydrogen bonding. Nowadays, we interpret hydrogen bonds as highly directional electrostatic attractions between positive dipoles or charges on hydrogen and other electronegative atoms. In the field of supramolecular chemistry, hydrogen bonding is currently one of the most widely applied noncovalent interactions.

1.2.1
Arrays of Multiple Hydrogen Bonds

Hydrogen bonding is especially suitable as a noncovalent interaction because of the high directionality of the hydrogen bonds. In general, the strength of a single hydrogen bond depends on the strength of the hydrogen bond donor (D) and acceptor (A) involved, and can range from weak $CH - \pi$ interactions to very strong $FH - F^-$ interactions. When multiple hydrogen bonds are arrayed to create linear hydrogen-bonding motifs, both their strength and directionality are increased. However, the binding strength of the motif is dependent not only on the type and number of hydrogen bonds, but also on the order of the hydrogen bonds in the motif.

$K_a = 10^2\ M^{-1}$

$K_a = 10^4\text{-}10^5\ M^{-1}$

$K_a = >10^5\ M^{-1}$
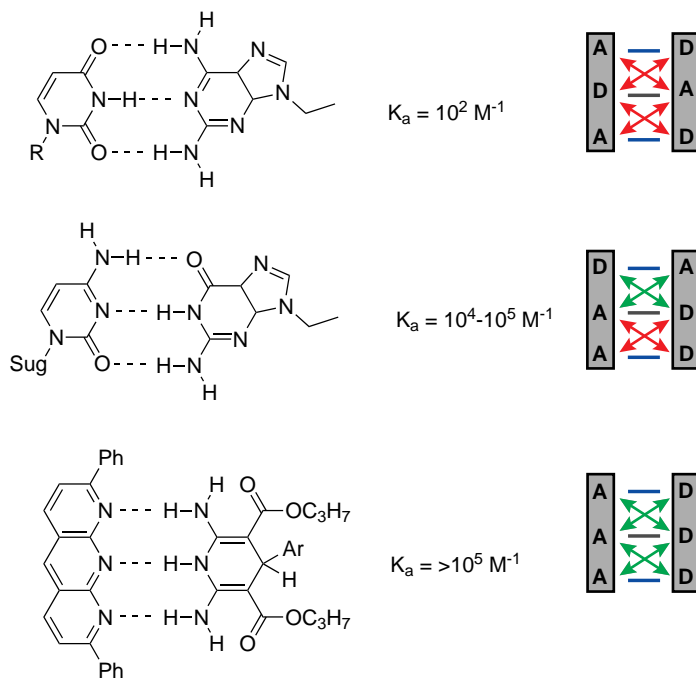
Figure 1.2 Influence of attractive and repulsive secondary interactions on the association constant of threefold hydrogen-bonding motifs [10, 11]. Reprinted with permission from The Royal Society of Chemistry [13].

This important aspect of linear hydrogen-bonding motifs was pointed out by Jorgensen *et al.,* who found a large variation in the association constants of threefold hydrogen-bonding motifs. Although the ADA – DAD and DAA – ADD arrays exhibit an equal amount of hydrogen bonds, the association constants of these motifs were significantly different. This was attributed to the different order of the hydrogen bonds [10]. Since the hydrogen bonds in the motifs are in close proximity, the distance of a hydrogen-bonding donor or acceptor to the neighbor of its counterpart is also relatively small, creating attractive or repulsive electrostatic secondary cross-interactions (Figure 1.2). This theory was later confirmed by Zimmerman *et al.,* who completed the series with the AAA – DDD array and indeed found a significantly higher dimerization constant due to the presence of solely attractive secondary interactions [11].

These so-called secondary interactions have a significant influence on the association constant of the corresponding motif, changing the association constant of the triple hydrogen-bonding motif by at least three orders of magnitude. Based on these results, Schneider *et al.* developed a method to calculate the free association energy for linear hydrogen-bonding motifs taking into account the secondary interactions, each contributing $2.9\ kJ\ mol^{-1}$ to the binding energy, and expanded it to quadruple hydrogen-bonding motifs [12].
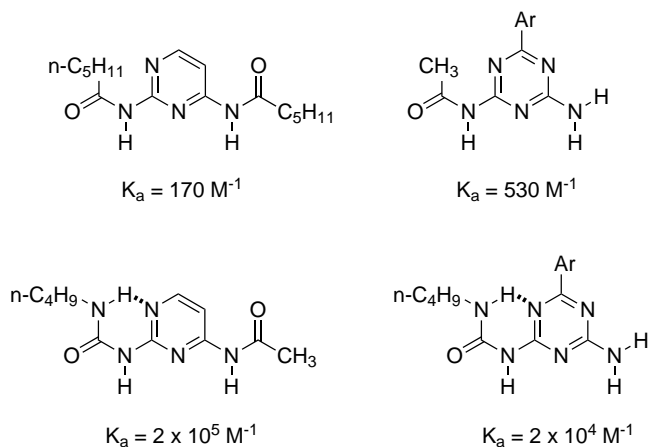
Figure 1.3 Quadruple hydrogen-bonding motifs with their corresponding dimerization constants, revealing the effect of the intramolecular hydrogen bond on the dimerization constant [14].

1.2.2
Preorganization through Intramolecular Hydrogen Bonding

Throughout the development of supramolecular chemistry, our knowledge of hydrogen-bonding motifs expanded rapidly. To attain high association constants, multiple hydrogen-bonding motifs were developed. Our group developed quadruple hydrogen-bonding motifs based on diaminotriazines and diaminopyrimidines in which a remarkably high dimerization constant was achieved when an amide moiety was replaced by a ureido moiety (Figure 1.3) [14]. A large deviation in the values of the experimentally determined dimerization constants of the ureido molecules was observed when compared to the calculations as proposed by Scheider *et al.* However, the experimental values for the amide molecules were in agreement with the calculated values. The large difference between the experimental and the predicted dimerization constants was attributed to the presence of an intramolecular hydrogen bond between the ureido NH and the nitrogen in the ring. This intramolecular hydrogen bond stabilizes the cis conformation of the ureido moiety and forces the carbonyl in plane with the aromatic ring. This causes prearrangement of the DADA hydrogen-bonding motif and results in an increase in the association constant by two or three orders of magnitude.

To reduce the number of repulsive secondary interactions, thereby increasing the association constant, our group introduced the self-complementary 2-ureido-4[1H]-pyrimidinone (UPy) quadruple hydrogen-bonding DDAA motif [15]. The intramolecular hydrogen bond prearranges the motif, resulting in a nearly planar DDAA motif (Figure 1.4) [16]. Due to the reduced number of repulsive secondary interactions and the intramolecular hydrogen bond, the dimerization constant was found to be $6 \times 10^7 \, M^{-1}$ in chloroform, with a long lifetime of 0.1 s [17].
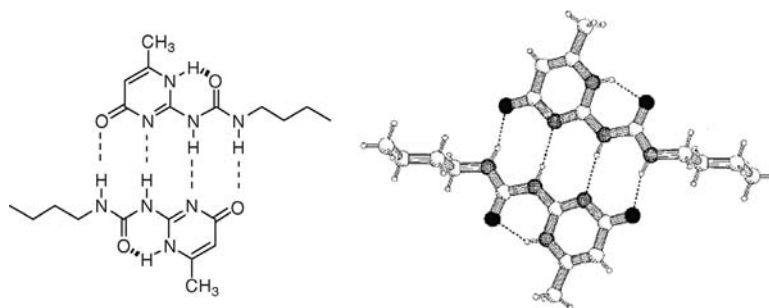
Figure 1.4 2-Ureido-4[1H]-pyrimidinone dimer and its corresponding single-crystal structure. Reprinted with permission from the American Chemical Society [16].

1.2.3
Tautomeric Equilibria

Although the UPy motif exhibits a high dimerization constant, the type of aggregate that is obtained during self-assembly is highly dependent on the substituent on the 6-position of the pyrimidinone ring, since different tautomeric forms can be present [16]. With electron-withdrawing or -donating substituents, the tautomeric equilibrium is shifted to the pyrimidin-4-ol tautomer, which is self-complementary as a DADA hydrogen-bonding motif (Figure 1.5). Due to more repulsive secondary
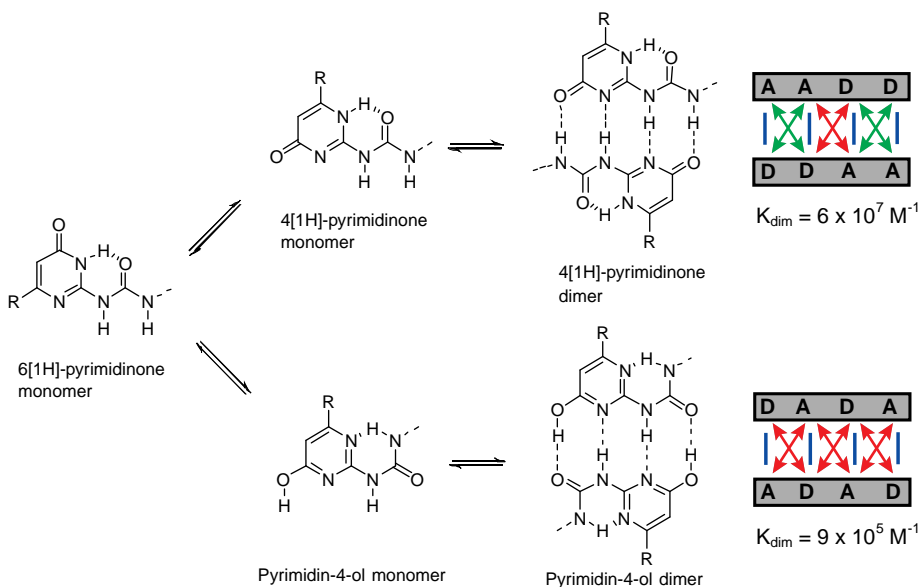
Figure 1.5 Tautomeric equilibria in the 2-ureido-pyrimidinone motif. Reprinted with permission from The Royal Society of Chemistry [13].

interactions, the dimerization constant of this DADA motif is lowered to $9 \times 10^5\,M^{-1}$ in chloroform [18]. The tautomeric equilibrium showed a high dependence on the solvent, and also showed concentration dependence. This illustrates that understanding the tautomeric equilibria is crucial for predicting the properties of hydrogen-bonding motifs.

Nowadays, the synthesis of new hydrogen-bonding motifs is almost unrestricted. Current hydrogen-bonding motifs used in supramolecular chemistry are not only purely derived from organic chemistry, but are also derived from hydrogen bonding as found in nature, for example by using the hydrogen-bonding motifs found in DNA base pairs [19] or using peptide mimics (Figure 1.6) [20, 21]. Since the start of supramolecular chemistry, many different hydrogen-bonding motifs have been reported, ranging from monovalent up to dodecavalent hydrogen bonds [21], with dimerization constants up to $7 \times 10^9\,M^{-1}$ [22]. However, it has to be noted that some of the reported hydrogen-bonding motifs require a multistep synthetic pathway, which lowers the overall yield tremendously, thereby making them less attractive to use.

1.3
Hydrogen-Bonded Main-Chain Supramolecular Polymers

1.3.1
The Establishment of Supramolecular Polymers

In macromolecular chemistry, the monomeric units are held together by covalent bonds. In 1990, Jean-Marie Lehn introduced a new area within the field of polymer chemistry by creating a polymer in which the monomeric units were held together by hydrogen bonds, resulting in a liquid crystalline supramolecular polymer (Figure 1.7) [23]. This initiated the field of supramolecular polymer chemistry, generating materials with reversible interactions, and thereby introducing the opportunity to produce materials with properties that otherwise would have been impossible or difficult to obtain.

Inspired by this work, Griffin *et al.* developed main-chain supramolecular polymers based on pyridine/benzoic acid hydrogen bonding, also obtaining liquid crystalline supramolecular polymers [24]. Our group introduced supramolecular polymers based on the ureido-pyrimidinone motif. Due to the high dimerization constant present in the UPy motif, supramolecular polymers were formed with a high degree of polymerization even *in semi-dilute solution* [15].

We have defined supramolecular polymers as '...*polymeric arrays of monomeric units that are brought together by reversible and highly directional secondary interactions, resulting in polymeric properties in dilute and concentrated solutions, as well as in the bulk. The monomeric units of the supramolecular polymers themselves do not possess a repetition of chemical fragments. The directionality and strength of the supramolecular bonding are important features of these systems, that can be regarded as polymers and behave according to well-established theories of polymer physics. In the past the term "living polymers" has been used for this type of polymer. However, to exclude confusion with the important field of*