FEATURE ARTICLE

ChemComm www.rsc.org/chemcomm

Quadruple hydrogen bonded systems

Rint P. Sijbesma* and E. W. Meijer

Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands. E-mail: r.p.sijbesma@tue.nl; Fax: +40-2472655; Tel: +40-2472655

Received (in Cambridge, UK) 18th June 2002, Accepted 13th August 2002
First published as an Advance Article on the web 30th August 2002

In this feature article, the development of linear quadruple hydrogen bonded systems is discussed, emphasizing applications in supramolecular chemistry and self-assembly.

Introduction

Hydrogen bonding is one of the most useful interactions in self-assembly,[1] and is widely used because hydrogen bonds are directional and moderately strong.[2] When stronger interactions are required than achievable with single hydrogen bonds, it is—at least conceptually—quite simple to increase the number of hydrogen bonds between components by using units that have arrays of hydrogen bonding sites. Like many concepts in supramolecular chemistry, the inspiration for this approach eventually comes from nature, where double and triple hydrogen bonds provide the means to read out and to replicate the information stored in DNA. Linear arrays of the kind found in nucleic acids—heterocyclic molecules with equidistant donor and acceptor sites—can be extended by adding rings or other functional units.[3] The binary character of hydrogen bonding (a hydrogen bonding site is either a donor (D), or an acceptor (A)) leads to an information content of this type of linear arrays, which increases with the number of sites.[4] While there are two different types of dimers for double hydrogen bond arrays, there are three triple hydrogen bonded dimers, and six different quadruple hydrogen bonded dimers, two of which contain self-complementary arrays [$(DDAA)_2$ and $(DADA)_2$]

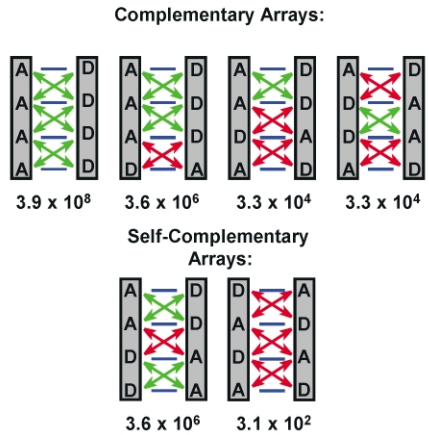


Fig. 1 Dimers formed by linear arrays of four hydrogen bonding sites, and their stability constants (in M^{-1}) in $CDCl_3$ as predicted in ref 11. Attractive and repulsive secondary interactions are indicated by green and red double headed arrows, respectively.

(Fig. 1). Obviously, when the spatial arrangement of sites in a hydrogen bonding unit is not restricted to be linear, the number of complementary pairs of arrays is unlimited. Multiple hydrogen bonding interactions between non-linear arrays of sites are very important in host–guest chemistry, *e.g.* for recognition of urea,[5] barbiturates[6] and other polar guests, and also plays a essential role in self-assembly of capsules[7] and tubules.[8] Self-assembly *via* double, triple and quadruple hydrogen bonds has been discussed recently,[9] and the use of heteroaromatic modules for self-assembly using multiple hydrogen bonds has been reviewed.[3] The present review will be restricted to linear quadruple hydrogen bonded arrays reported since 1988.

Several aspects contribute to the strength of quadruple hydrogen bonded complexes, and apart from the obvious effect of donor and acceptor strength of the individual sites, it has been suggested that there is a sizable contribution from secondary electrostatic interactions between adjacent sites in a complex, which are repulsive between like sites, while disparate sites attract each other.[10] These effects have been used by Schneider to set up a linear free energy relationship for the prediction of the strength of multiple hydrogen bonded complexes in $CHCl_3$.[11] When increments are used of -8 kJ mol^{-1} for each primary interaction and -2.9 kJ mol^{-1} and $+2.9$ kJ mol^{-1} for each attractive and repulsive secondary interaction, respectively, it was found that stabilities of a set of 58 different complexes, was predicted with an average difference between calculated and observed values of just 1.7 kJ mol^{-1}, corresponding to an average factor of 2 in K_a value. The six linear quadruple hydrogen bonded dimers (Fig. 1) have different

Rint P. Sijbesma is associate professor in supramolecular polymer chemistry at the Eindhoven University of Technology, The Netherlands. He received his Ph.D. in Organic Chemistry at the University of Nijmegen in 1993, where he studied synthetic receptor molecules with professor Roeland Nolte. From 1992 to 1993, he worked as a postdoctoral research fellow with professor Fred Wudl (University of California, Santa Barbara) on the synthesis of water-soluble C_{60} derivatives. In 1993 he moved to Eindhoven as assistant professor, where he became associate professor in 2002 . His research interests are focused on the application of supramolecular concepts in polymer chemistry.

E. W. 'Bert' Meijer is professor of Macromolecular and Organic Chemistry at the Eindhoven University of Technology, The Netherlands. He received his Ph.D. in Organic Chemistry at the University of Groningen with professor Hans Wijnberg. He was research scientist in the area of optoelectronic materials at Philips Research Laboratories from 1982 to 1989 and group leader of new polymeric materials at DSM Research from 1989 to 1992. Since 1992 he has been a full professor in Eindhoven and since 1995 he is also adjunct professor at the University of Nijmegen. His research interests are in dendrimers, supramolecular systems, and organic materials for electronics.

DOI: 10.1039/b205873c

numbers of attractive and repulsive secondary interactions, and their predicted complex stabilities are indicated. Apart from their strength, the possibility to achieve self-complementarity distinguishes linear quadruple hydrogen bonding units from units with three hydrogen bonding sites. While self-complementarity may limit the applicability in recognition, it offers distinct advantages in other fields of interest, such as the self assembly of supramolecular polymers,[12–14] where the use of complementary units has the drawback that very precise control over stoichiometry is required to obtain high degrees of polymerization.

Considering the large body of literature on the use of double and triple hydrogen bonding units in self assembly, there are surprisingly few reports on linear arrays of more than three hydrogen bonds. Although it would be hard to prove, it seems likely that many scientists in the field of self assembly have been reluctant to design quadruple hydrogen bonding units because the heterocyclic chemistry involved in their synthesis was considered to be more troublesome than the gain in binding strength and recognition capabilities would justify. In the present feature article we will discuss quadruple hydrogen bonding units, both from our own work and that of others, and we hope to convince the reader that, at least for quadruple hydrogen bonding units, the fear to venture beyond the triple hydrogen bond is unwarranted, both in the sense of the limited synthetic effort required for their preparation, as well as for the enormous gain in binding strength achieved.

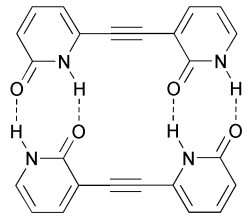
Bis-double hydrogen bonded arrays

A conceptually appealing way to arrive at linear quadruple hydrogen bonded arrays is to combine two double hydrogen bonded arrays in one molecule. One of the first examples of this approach emphasizes the informational content of a self complementary array consisting of two pyridone units. Ducharme and Wuest,[15] have synthesized dipyridone **1**, featuring a self complementary array of four hydrogen bonding sites and have compared its association properties with those of symmetric, non-self complementary dipyridone **2**. The dimerization constant of **1** was determined to be higher than 6×10^4 M^{-1} in $CHCl_3$, while the pyridone units of **2** are dimerized to the same extent as the model compound 2-pyridone, which has a dimerization constant of approximately 10^2 M^{-1}.[16] The crystal structures of **1** and **2** reflect the information encoded in the hydrogen bond arrays. Whereas dimers are found for **1**, compound **2** forms planar polymeric chains of molecules. Related molecule **3** has been used by Wash *et al.* to probe the strength of acid–amide hydrogen bonds.[17] It was shown that the stability constant of the dimer $\mathbf{3}_2$ exceeds 10^4 M^{-1} in $CDCl_3$.

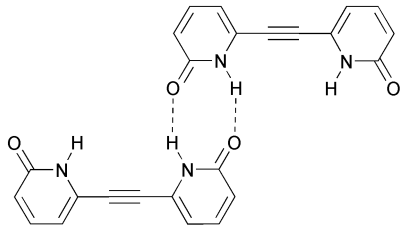
DADA arrays in pyridines, pyrimidines and triazines

Development of DADA arrays

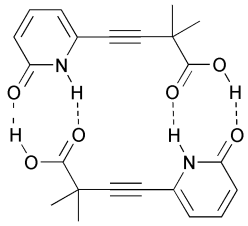
Our involvement in the development of novel hydrogen bonding units stems from our interest in supramolecular polymers,[12] reversible polymers in which the monomers are held together by non-covalent interactions. The construction of linear supramolecular polymers requires strong (but reversible) interactions that are highly directional. Multiple hydrogen bonding units are nearly ideal for this purpose, and we felt that development of building blocks which combine synthetic accessibility with strong complexation would be a prerequisite for success in the field. Our efforts had initially focused on synthetically highly accessible building blocks, *e.g.* triple hydrogen bonded complexes of melamine and imides,[18] which have a K_{dim} value of approximately 10^2 M^{-1}. Triple hydrogen bonding interactions between acylated diaminopyridines with thymines or uracil derivatives had been used in pioneering work by the group of Jean-Marie Lehn.[19] However, the association constant (K_a) of 800 M^{-1} in $CHCl_3$ of this combination is



1·1



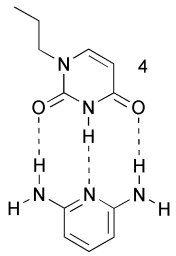
2·2



3·3

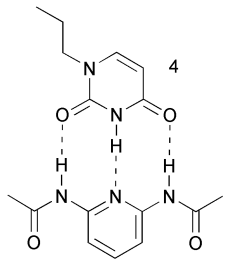
moderate at best, and only leads to polymers with a high degree of polymerization (DP) when the molecules are in the liquid crystalline state.

Remarkably, acylation of the diaminopyridine is a highly effective method to strengthen the interaction in the complexes with ADA arrays, as it increases the dimerization constant approximately tenfold from K_a = 84 M^{-1} for the complex of diaminopyridine **5** with *N*-propylthymine **4**, to K_a = 800 M^{-1} for the complex of **4** with diacetylaminopyridine **6**.[20] In an effort to increase the complexation strength of the triazine–thymine couple, we prepared diacylated triazine derivative **7**, expecting to find a binding constant in the order of 10^4 M^{-1}, as compared to a value of 890 M^{-1} for the complex of a non-acylated triazine with **4**.[20]



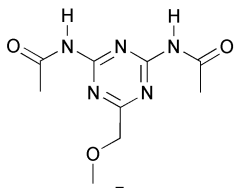
5

4·5 K_a= 84 M^{-1}



6

4·6 K_a= 800 M^{-1}

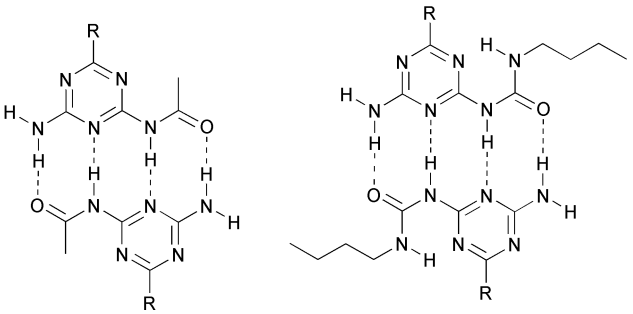


7

Much to our surprise, the complex of **7** with *N*-propylthymine turned out to have a K_a value not higher than 6 M^{-1}. Thus, instead of raising the complex stability, a dramatic drop in stability resulted from acylation of the triazine amino groups! However, the experiment turned out to be an instructive failure.

Because we had decided to routinely check for dimerization of the separate components in our study of DAD–ADA hydrogen bonded complexes, the weak, but significant dimerization of **7** (K_{dim} = 37 M^{-1}) had not escaped our notice. But why would dimerization of **7** be stronger than in diacylaminopyridine? It occurred to us that the key to understanding the dimerization might lie in the different conformational properties of amidopyridines and amidotriazines. Although *trans* amides are generally more stable than *cis* amides,[21] a *trans* conformation of the amide groups in **7**, would result in considerable electrostatic repulsion between the carbonyl groups and the nitrogen atoms in the triazine ring. When the amides are *cis*, however, an ADADA array of five hydrogen bonding sites is formed, of which four sites can be involved in dimerization *via* a DADA array (Scheme 1).

The initial attempts to find stronger triple hydrogen bonded complexes had thus led to the accidental discovery of quadruple hydrogen bonds, but stronger complexes had not been found. Instead, the dimer of **7** had a disappointingly low stability, considering the number of hydrogen bonds involved. We were aware of the fact that the DADA dimer had been predicted to be the least stable of all quadruple hydrogen bonded complexes, based on Jorgensen's[10] concept of secondary interactions. Inspection of the structure of the dimer shows that in a ADADA dimer, two additional repulsive interactions are present, which we coined 'spectator repulsions', because the carbonyl groups causing the repulsion are not involved in hydrogen bonding. These spectator repulsions are readily eliminated, by removing one of the acyl groups, and we found that the K_{dim} value is indeed higher by a factor of 4 (K_{dim} = 530 M^{-1}) in monoacylated diaminotriazine **8a**.[22]



8a R = $Ar(OC_{12}H_{25})_3$
8b R = CH_3

8a·8a K_{dim}= 530 M^{-1}

9a R = $Ar(OC_{12}H_{25})_3$
9b R = CH_3

9a·9a K_{dim}= 2 x 10^4 M^{-1}

The crystal structure of the methyl derivative **8b** (Fig. 2(a)) confirmed the hypothesis that the dimers are held together by quadruple hydrogen bonds.

Incidentally, a search for similar structures in the crystallographic database revealed that we were not the first to find dimerization *via* linear arrays of four hydrogen bonding sites. Dimerization *via* such an array had been found in the crystal structure of acylated pyrimidine derivative **10** in 1992,[23] although the stability of the dimers in solution was not investigated.

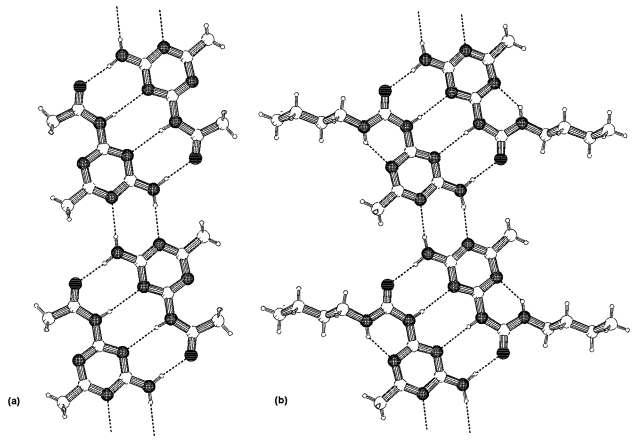
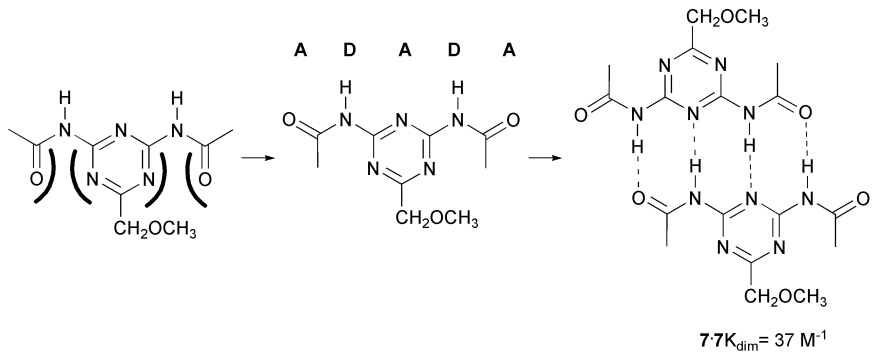


Fig. 2 PLUTON representation of the hydrogen bonding patterns in the crystal structures of: (a) 2-(acetylamino)-4-amino-6-methyl-*s*-triazine **8b**, (b) 2-butylureido-4-amino-6-methyl-*s*-triazine **9b**.

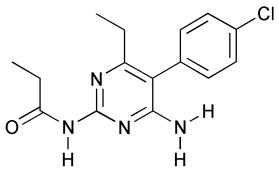
A further increase in complex stability was observed in preorganized ureidotriazine **9**. Here, an intramolecular hydrogen bond fixes the DADA array in a planar conformation as can be seen in the crystal structure of **9b** (Fig. 2(b)), resulting in a dimerization constant of 2×10^4 M^{-1}. Yet, this turned out not to be the limit of stability for DADA arrays in solution. A further dimerization study, which included amido and ureido pyrimidines **11**–**13**, showed dimerization constants ranging from 170 M^{-1} (for the dimer of **11**), to larger than 2×10^5 (for the dimer of **13**), corresponding to a 17.5 kJ mol^{-1} difference in stability of dimers that are held together by identical arrays, and consist of atoms with comparable donor and acceptor strength.

These large differences indicate the limitations of the additivity rules based on the concepts of secondary interactions.[11] In particular the stabilities of the dimers of **9** and **13** are in excess of the predicted values for DADA arrays by 10.3 and 16.0 kJ mol^{-1}, respectively. We have ascribed part of the difference to a high degree of preorganization in these compounds, but other factors, such as overall charge distribution may play a role as well.

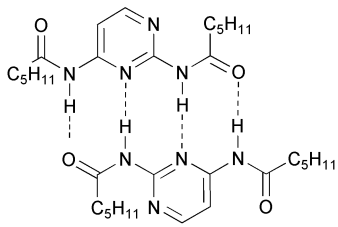
The ease of synthesis of diaminotriazines, and the sizable dimerization constant of the mono-ureido derivative encouraged us to employ this unit as a building block for self-assembly of highly organized supramolecular structures. In a number of investigations, ureidotriazine unit **9a**, provided with a trialkoxyphenyl group, has been used as an element that induces a high degree of order due to the strong anisotropy of its disk shaped dimer.[24]



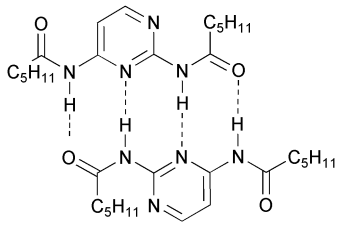
Scheme 1



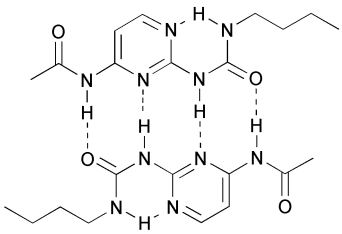
10



11·11 K_{dim}= 170 M^{-1}



12·12 K_{dim}= 890 M^{-1}



13·13 K_{dim}> 2 x 10^5 M^{-1}

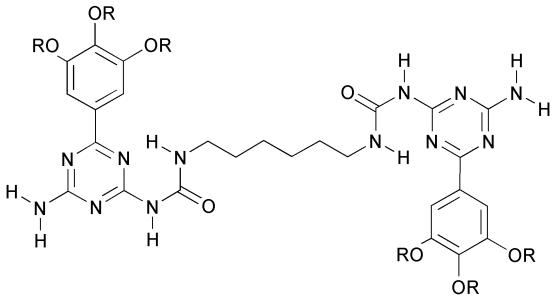
Compound **9a** is liquid crystalline over a large temperature range, and X-ray diffraction has shown that the molecules are organized in dimers, which stack in columns with hexagonal order. IR measurements indicate that the strength of the quadruple hydrogen bonds is such that upon isotropization at 183 °C, the molecules remain dimerized to a large extent.

DADA arrays in supramolecular polymers

The relatively strong dimerization, and the simple preparation of ureidotriazines are attractive features for the use of this unit in bifunctional compounds which can assemble into linear polymeric aggregates, termed 'supramolecular polymers'. We have recently shown that combining hydrogen bonding with solvophobic interactions in bifunctional trialkoxyphenyl derivatives of ureidotriazines results in a hierarchical aggregation process, which is solvent dependent.[25] While bifunctional molecules **14a** are present as monomers in DMSO, they self assemble into random coil polymers in $CDCl_3$.

In dodecane, solvophobic interactions induce stacking of dimerized ureidotriazine units in a similar fashion as was observed in the mesophase of the monofunctional analog. This process results in highly ordered polymers with a helical columnar architecture (Fig. 3).

Analogs **14b**, with chiral oligoethylene side chains instead of alkyl side chains were also studied.[25,26] The side chains render this compound water soluble. Amazingly, quadruple hydrogen bonding of this compound persists in this solvent because a



14a R = $OC_{12}H_{25}$

14b R =

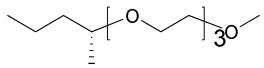
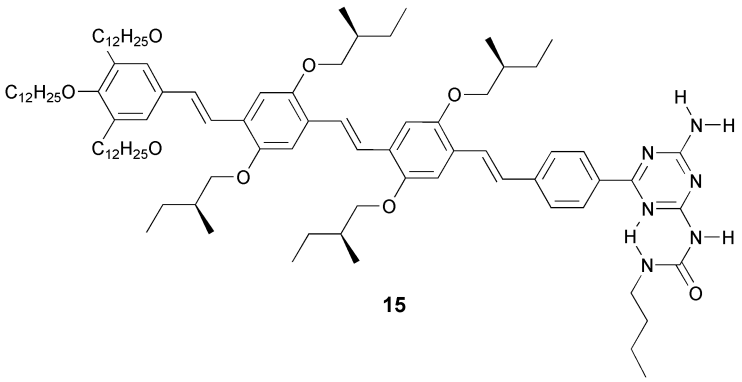


Fig. 3 Proposed mode of aggregation of molecules **14** in helical columns.

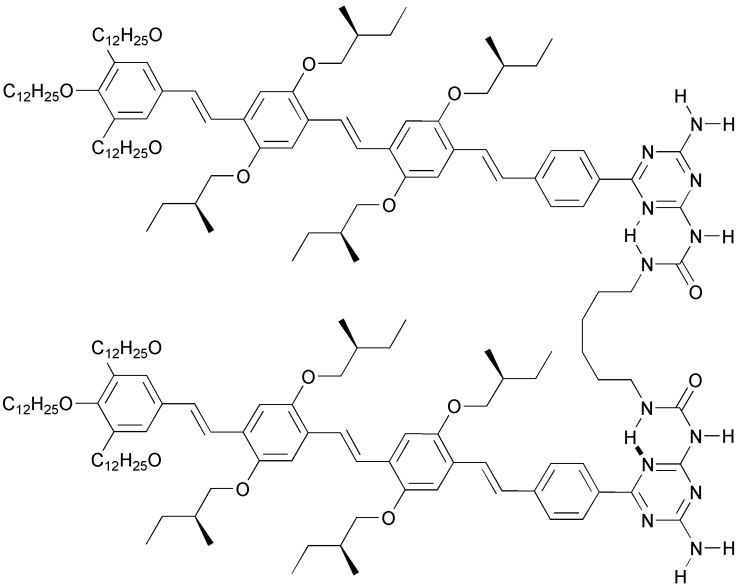
hydrophobic microenvironment is created by stacking of the planar trialkoxyphenyltriazine moieties, in which disruption of the hydrogen bonds by water molecules is prevented.

Dimerization of oligo(*p*-phenylenevinylene)-functionalized ureidotriazine **15**, (K_{dim} = $2.1 \pm 0.3 \times 10^4$ M^{-1} in $CDCl_3$) is the first step in a hierarchical self assembly process that leads to chiral π-conjugated stacks of dimers in dodecane. These supramolecular architectures are our building blocks for supramolecular electronics. Bifunctional compound **16** forms random coil polymers in chloroform, while in dodecane, aggregates are less organized than those of **15**, presumably because the hexyl spacers frustrate the formation of well-ordered helical stacks.

Self-complementary DADA hydrogen bonding in diacetamidopyridine has been used to prepare supramolecular tapes as well as cyclic tetramers in solution.[27] The association constant of porphyrin **17** with one diacetamidopyridyl group was determined to be 160 M^{-1} in $CDCl_3$ using NMR dilution experiments. Bifunctional compound **18** is preorganized to form tetrameric cycles, while by combining monofunctional compound **17** with bifunctional derivative **19**, oligomers with different average degrees of polymerization were obtained. The proposed structure of the dimer of **17**, with a DADA quadruple hydrogen bonding array was later questioned by Ercolani,[28] based on the known preference of amides for an *trans* conformation.[29] With the acetamido groups in the *cis* conformation, the most probable mode of association would be *via* double hydrogen bonds. It was also pointed out by Ercolani, that although the average degree of polymerization can be adjusted by adding monofunctional **17** to **19**, there is no independent control over the polydispersity, because a statistical mixture of oligomers is still formed. In fact, the effects of adding **17** on both the degree of polymerization and the polydispersity are



15



16

indistinguishable from the effects of diluting a solution of pure **19**.

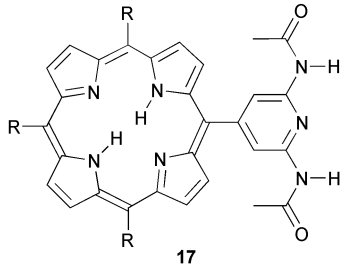
DDAA arrays in ureidopyrimidinones

Development of ureidopyrimidinone hydrogen bonding units

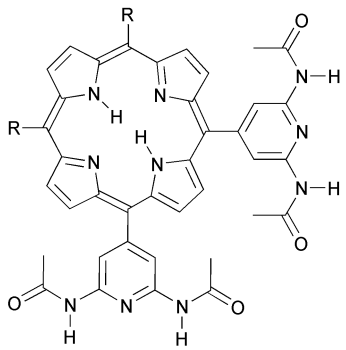
With the DADA arrays based on ureidotriazines, our group had developed easily accessible and versatile hydrogen bonding units, but for the purpose of obtaining linear supramolecular polymers with a higher degree of polymerization, a unit with a substantially higher association constant would be attractive. The limits of stability of DADA dimers had probably been reached with pyrimidine **13** ($K_a = 2 \times 10^5$ M^{-1}), and its preparation requires chromatographic separation and a relatively expensive starting material, diaminopyrimidine. We therefore set out to find molecules which would dimerize *via* a self complementary DDAA array and which would be simple to prepare. Ureidopyrimidinones (UPy's) **20** seemed to be good candidates, because they are easily synthesized in two steps by reaction of β-keto esters with guanidine[30] followed by acylation of the resulting isocytosine with an isocyanate.

We noted that the synthesis of several ureidopyrimidinones had been published,[31] but dimerization *via* quadruple hydrogen bonds had not been reported, possibly because dimerization in this fashion requires the molecules to be present in the non-standard [1H] tautomeric form. Fortunately, synthesis of **20a**, from commercially available compounds methyl isocytosine and butylisocyanate led to a highly soluble product, which could be crystallized to afford crystals for X-ray diffraction.[32] The results of crystal structure determination (Fig. 4) justified the assumptions of the design, as it shows dimers of **20a**, which are held together by quadruple hydrogen bonds *via* a DDAA array.

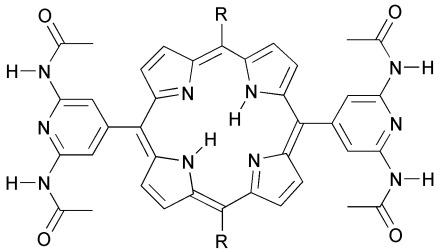
The molecules are preorganized by an intramolecular hydrogen bond from the urea NH group to one of the nitrogen atoms in the pyrimidine ring. The NMR spectrum of **20a** in $CDCl_3$ is relatively simple, and the position of the NH signals indicates extensive hydrogen bonding. The most encouraging feature of the spectrum was the complete lack of chemical shift changes upon dilution down to 10^{-4} M, indicating that dimerization of **20a** persists at low concentrations, and that the K_{dim} value should be very high. Because the dimerization constant in chloroform was beyond the range that could be determined by ^{1}H NMR dilution experiments, measurements were performed in more polar solvent mixtures ($CDCl_3$–DMSO). Extrapolation of these values to pure chloroform gave a lower limit for K_{dim} of 10^6 M^{-1}. In later work,[33] thermodynamic parameters of dimerization were studied by using the excimer fluorescence in dimers of pyrene labeled derivative **21**, and the K_{dim} value was determined to be approximately 2×10^7 M^{-1} in chloroform, and 10^8 M^{-1} in toluene at 298 K. Statistical mixtures of homo and heterodimers of UPy derivatives **22** and **23** have been used to determine the exchange rate, and hence the pre-exchange lifetime of the dimers by NMR. In $CDCl_3$ the lifetime of the dimer is approximately 0.1 s. at 298 K, while in toluene, the kinetic stability of the dimer is increased to give a lifetime of 1.7 s at room temperature. Ikegami and Arai showed that anthracenyl labeled UPy derivative **24** and *N*,*N*-dimethylaniline labeled UPy derivative **25**, give exciplex emission at concentrations as low as 10^{-5} M in chloroform, completely in line with the K_{dim} value determined with compound **21**.



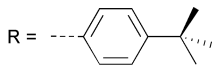
17

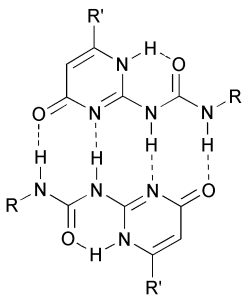


18



19





20a R = *n*Bu; R'= Me
20b R = *n*Bu ; R' = $C_{13}H_{27}$

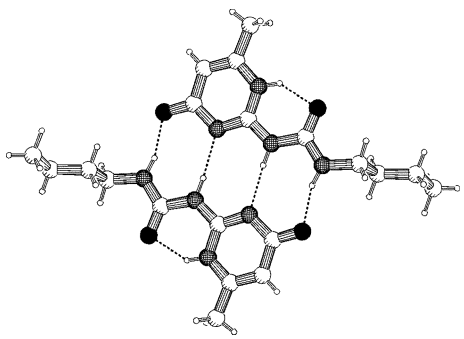
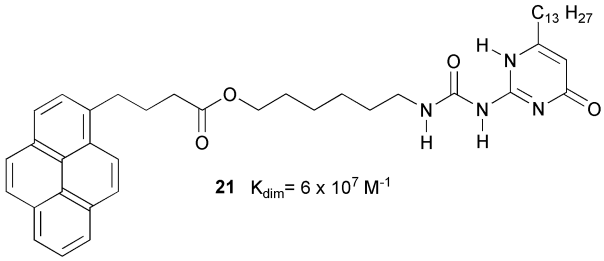
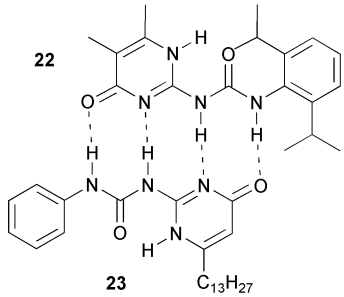


Fig. 4 Crystal structure of **20a**, in which the molecules are dimerized *via* DDAA arrays of hydrogen bonding sites.

The thermal stability of the ureidopyrimidinone group is important for applications, because chemical degradation of this group at high temperatures may limit its use in supramolecular polymers. Armstrong and Buggy[34] studied the stability of **20a** as a model compound. Above 225 °C, the melting point of this compound, it underwent thermal degradation in three stages. Degradation was proposed to start with cleavage of the butane isocyanate.

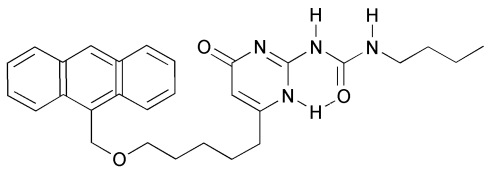


21 K_{dim}= 6 x 10^7 M^{-1}

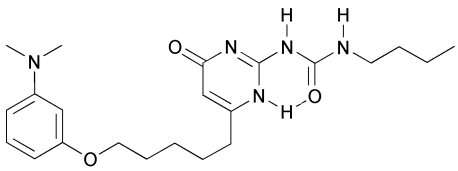


22

23



24

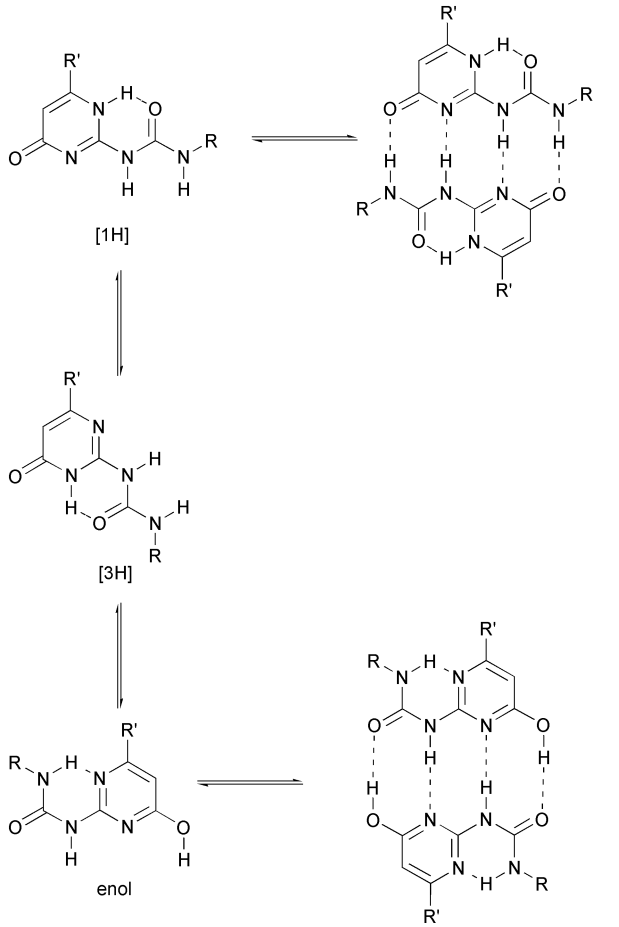


25

An important aspect of the ureidopyrimidinone unit as a building block in self-assembly is the presence of different tautomeric forms (Scheme 2). Three different forms have been observed in solution. In DMSO, a solvent which strongly competes for hydrogen bonding, the molecules are in the monomeric [3*H*] tautomeric form. In $CDCl_3$, the molecules are present as a mixture of [1*H*] and pyrimidinol tautomers. Both tautomers are dimeric.

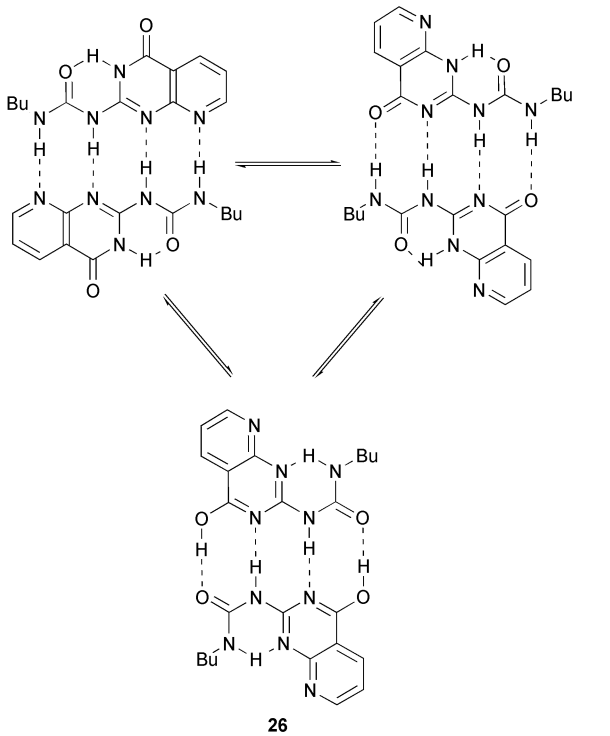
Substituents on the 6-position of the heterocycle were found to have a strong effect on the position of the equilibrium between these tautomers; electron withdrawing substituents such as CF_3 and *p*-nitrophenyl groups strongly favor the pyrimidinol form. The pyrimidinol tautomer dimerizes *via* a DADA array, and is expected to form weaker complexes due to a higher number of secondary repulsions in DADA dimers. Although the presence of the pyrimidinol tautomer does not compromise the ability of the unit to form very strongly associated dimers, as determined by excimer fluorescence studies (see above), the stability of the ureidopyrimidinone dimers might be even higher when the molecules could be fixed in their [1*H*] tautomeric form.

In an inventive approach to heterocyclic quadruple hydrogen bonding units that do not suffer from weakening effects of tautomerism, Corbin and Zimmerman have prepared **26**, a molecule that is able to dimerize regardless of the tautomeric



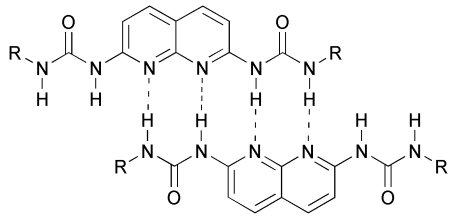
Scheme 2 Equilibria between monomers and dimers of the three tautomeric forms of ureidopyrimidinones (UPy's).

form it is in[35] (Scheme 3) Moreover, the relative spatial arrangement of the substituents does not change upon tautomerization, an important feature for the reliability of the self-



Scheme 3 Equilibria of **26**, which forms dimers regardless of tautomeric form.

assembly processes. Recently, the same authors[36] reported the dimerization of **27**, with a K_a value of 259 M^{-1}. This low value is due to a number of factors. The molecules need to unfold for dimerization *via* four hydrogen bonds, and repulsive spectator interactions further reduce the stability of the complex.



Ureidopyrimidinones in self-assembly and in supramolecular polymers

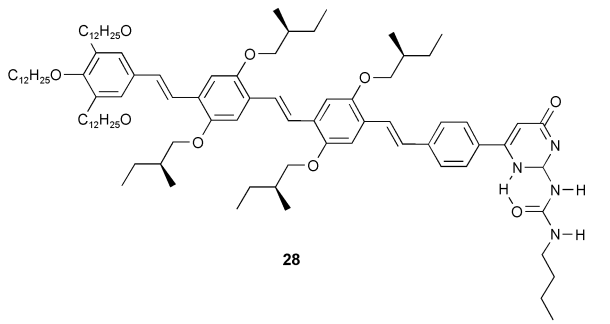
Oligo(*p*-phenylene vinylene) derivatives **28**, provided with a UPy group were shown to form strong dimers. These compounds open new possibilities for the design of electronic materials.[37] Strong dimerization of UPy groups of **29** in combination with threading of protonated amines in the crown ether ring of this compound has been used recently to self assemble four molecules into an organized complex.[38]

The UPy group has also been used to organize fullerenes in supramolecular dimers.[39,40] Two independent studies report the functionalization of C_{60} with UPy. Photophysical measurements on dimers of **30** showed strong electronic coupling through the hydrogen bond edge. However, cyclic voltammetry of **30** in toluene–acetonitrile showed that there is very little interaction between C_{60} units in the dimers. The C_{60} reduction waves in **31** were also affected very little compared to a model compound without the UPy unit attached. It was shown that a statistical mixture of dimers was formed when equimolar amounts of **31** and **20a** were mixed in $CDCl_3$.

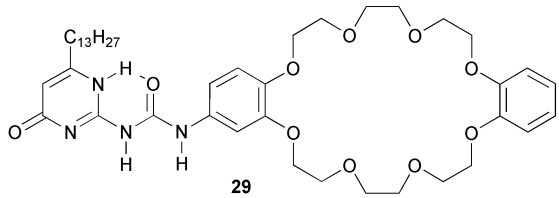
Hummelen's group has also reported the synthesis of C_{60} derivative **32** with two UPy groups, which was shown to form supramolecular polymers at 100 mM in $CDCl_3$, while complex ^1H NMR spectra were formed at low concentration, due to the formation of cyclic species. The polymers hold promise as well-organized materials for organic photovoltaic devices with increased efficiency.[41]

Combining two hydrogen bonding units in highly preorganized scaffolds is a simple and effective way to obtain dimers with very high stability. This approach, when applied to double or triple hydrogen bonding arrays[42,43] leads to dimers that can be considered as artificial dinucleotides, and which are stable in DMSO–$CDCl_3$ mixtures. We have shown that dimers of **33**, in which two UPy units are connected by a tetramethyl xylylene spacer, also have a high kinetic stability.[44]

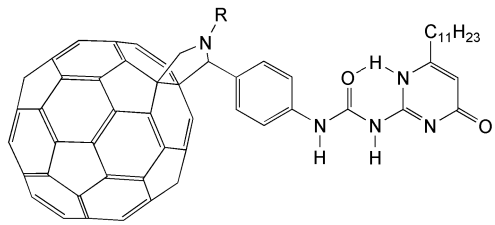
Different isomers of this dimer exist in the solid state (Fig. 5), differing in the relative arrangement of the dimerized UPy groups, or in the tautomeric form in which these groups exist. In solution, the symmetric dimers are found, in which all UPy groups are the [1*H*] tautomer, as well as an asymmetric isomer in which half of the UPy groups is the enol tautomer (Scheme 4) It was shown that in $CDCl_3$, isomerization of the dimer, a process which is expected to proceed as least as fast as complete dissociation, proceeds with a time constant of approximately 44 min. Thus, an exceedingly stable 8-H bonding unit is formed by the simple combination of the UPy unit with a preorganized spacer. Similar preorganization is responsible for the strong dimerization of calixarene **34** reported by de Mendoza and coworkers.[45] The stability of this dimer in $CDCl_3$ is too high to allow observation of dissociation using NMR. Therefore, the extent of dissociation in DMSO–$CDCl_3$ solvent mixtures was investigated, and K_a values of 2500 M^{-1} and 572 M^{-1} were calculated in solutions containing 64% and 73% of DMSO,

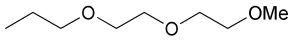


28

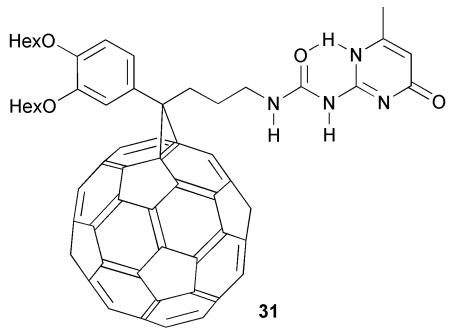


29

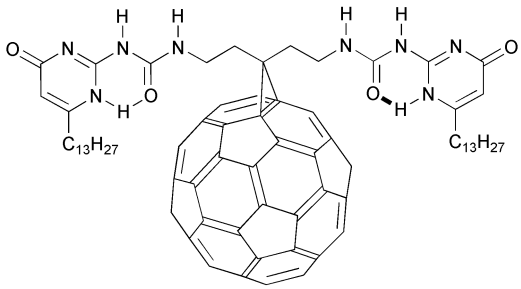


30a R = 

30b R = CH_3



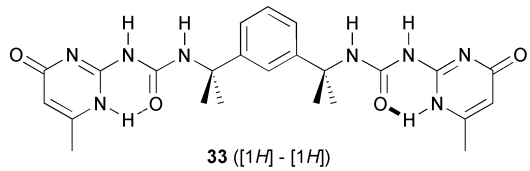
31



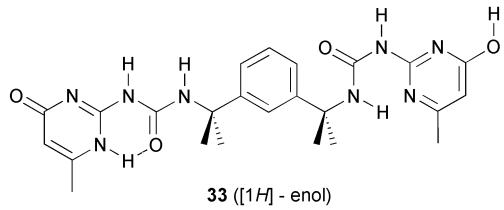
32

respectively. It was also demonstrated that addition of a triflate salt leads to dissociation of the dimer, presumably due to complexation of the triflate anion to the urea part of the UPy units.

It can be calculated that with a dimerization constant of 6×10^7 of the ureidopyrimidinone group, bifunctional derivatives that are not preorganized to form cycles, may reach high degrees of polymerization. We decided to investigate the possibilities of obtaining supramolecular polymers by connecting two UPy units by a C_6-spacer (compound **35a**). This bifunctional compound forms viscous solutions in chloroform, and the pure



33 ([1*H*] - [1*H*])



33 ([1*H*] - enol)

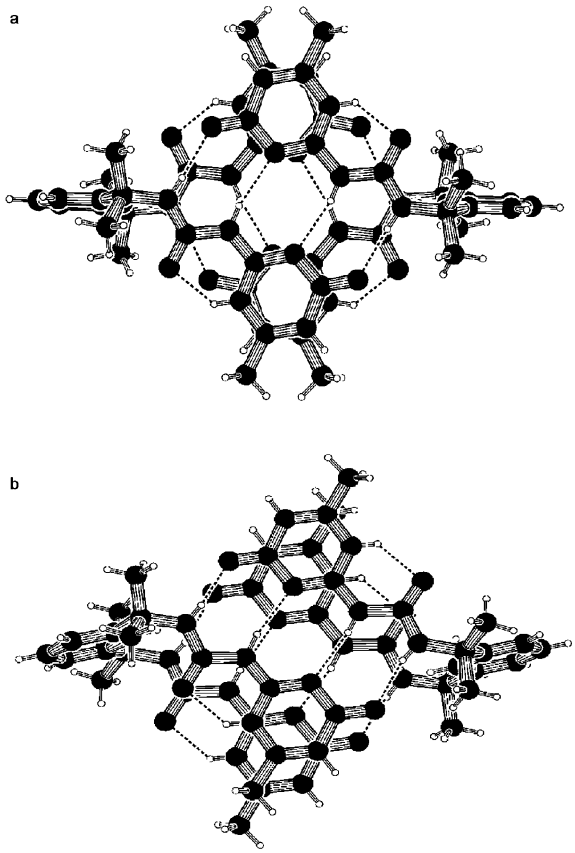
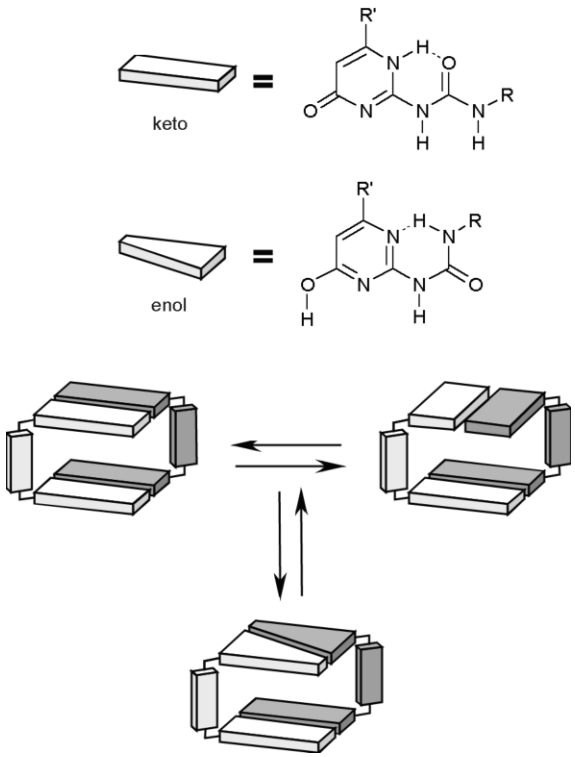


Fig. 5 *Anti*-[1H]–[1H] (a), and *syn*-[1H]–[1H] (b) forms of dimers of **33** found in different crystal modifications.

material is a rubber like solid, which crystallizes upon standing.[46]

Addition of monofunctional UPy derivative **20b** to solutions of **35a** has a dramatic effect on the viscosity (Fig. 6). Like in conventional condensation polymerization, monofunctional molecules act as 'chain stoppers', and reduce the average degree of polymerization. In solutions of **35**, the reduction of viscosity takes place immediately, showing that the polymer chains are continuously breaking and recombining, and quickly establish a new equilibrium degree of polymerization. Analysis of the effect of varying amounts of chain stoppers on solution viscosity allowed us to estimate the degree of polymerization in 40 mM solutions of pure **35a** to be in the order of 700 monomer units.

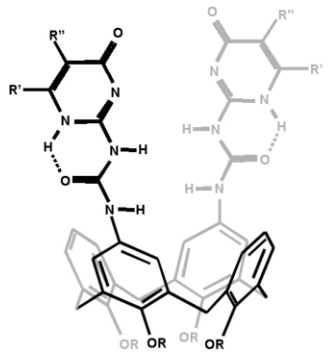
A protected monofunctional UPy derivative with a photo-cleavable *o*-nitrobenzyl group has been used as a stopper molecule that can be activated by light. When a viscous solution of **35a**, containing small amounts of the *o*-nitrobenzyl protected



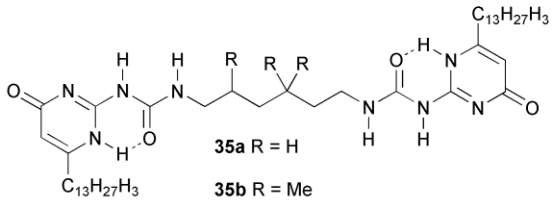
Scheme 4 Equilibrium between isomers of dimeric **33**.

derivative **36** was irradiated with UV light, the stopper molecules were activated, and the DP of the polymer dropped, resulting in a large decrease in viscosity[47] (Fig. 7)

Bifunctional UPy derivatives have been prepared with a range of oligomeric or polymeric spacers, such as polysiloxanes,[48] poly(ethylene/butylenes), polyethers, polyesters and polycarbonates.[49] Introduction of UPy end groups results in dramatic changes of the mechanical properties of the polymers, and materials were obtained that combine many of the mechanical properties of conventional macromolecules with the low melt viscosity of organic compounds.



34 R = $CH_2CH_2OCH_2CH_3$



35a R = H

35b R = Me

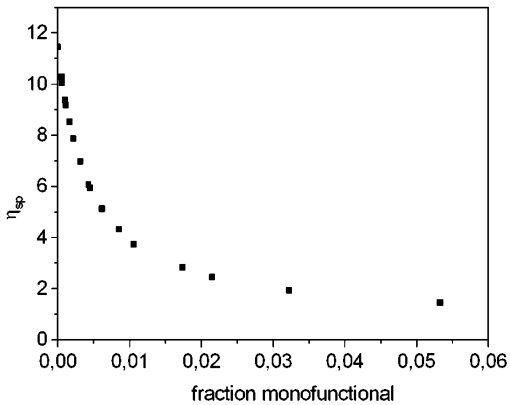


Fig. 6 Specific viscosity of a 40 mM chloroform solution of bifunctional UPy derivative **35a** as a function of the fraction of added monofunctional molecules **20b**.

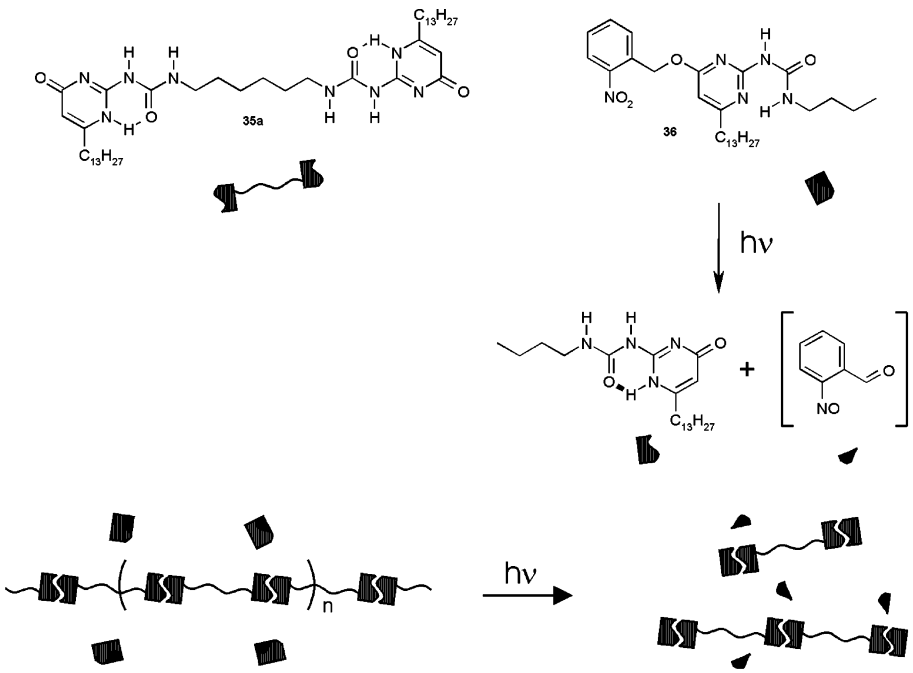
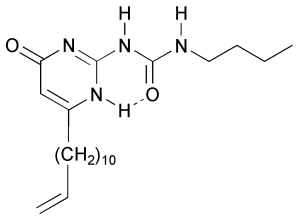


Fig. 7 Photodeproctection of **36**, leading to a decrease in the average DP of a solution of **35a**.

Further control over the topology of supramolecular polymers is attained when trifunctional monomers are used, which lead to the formation of reversible networks.[50]

Recently, Coates and co-workers have incorporated vinyl-substituted unit **37** in poly(1-hexene), using a nickel-based polymerization catalyst which is tolerant to functional Lewis basic groups. With small amounts of UPy-units incorporated, the polyolefins show thermoplastic elastomeric properties.[51]

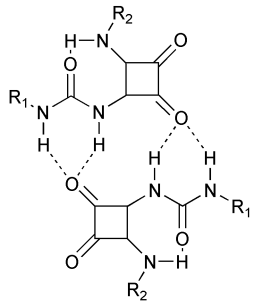


37

Supramolecular polymers based on UPy, are in dynamic equilibrium with cyclic species. In equimolar mixtures of compounds **35a** and **38** in chloroform, the preferential formation of cyclic heterodimer **35a·38** can be observed due to the distinct signals of this medium-sized ring in the ^{1}H NMR spectrum. When the concentration of this species is plotted as a function of the total solute concentration, the presence of a critical concentration is evident, below which little polymer is present, and above which the concentration of cycles remains constant. This phenomenon, which is predicted by theory, has been observed for polycondensations under equilibrating conditions, but it is generally difficult to observe in truly reversible systems.[52] Entropy driven ring-opening polymerization is another remarkable phenomenon that has been observed in UPy-based supramolecular polymers. In solutions of **35b**, the equilibrium between cycles and polymers shifts to favor polymerization when the temperature is increased. As a result, the viscosity of the solutions increases upon increasing the temperature.[53]

Squaramide dimers

Recently, *N*-carbamoyl squaramides **39** were introduced as readily available units which dimerize *via* four hydrogen bonds.[54] In contrast to the units based on triazine, isocytosine, or Zimmerman's pyrimidopyrimidinone unit, the dimers are held together by two bifurcated instead of four separate hydrogen bonds, as is evident from the crystal structure of this compound.. Nevertheless, no signs of dissociation of the dimers is observed by NMR spectroscopy in $CDCl_3$ down to concentrations of 0.5 mM, suggesting strong dimerization. Dilution studies in a 95:5 solvent mixture $CDCl_3$–CD_3CN allowed determination of K_{dim}, which has values of up to 9800 M^{-1} for **39b** in this solvent.



39a R^1= Bu, R^2= cyclohexyl

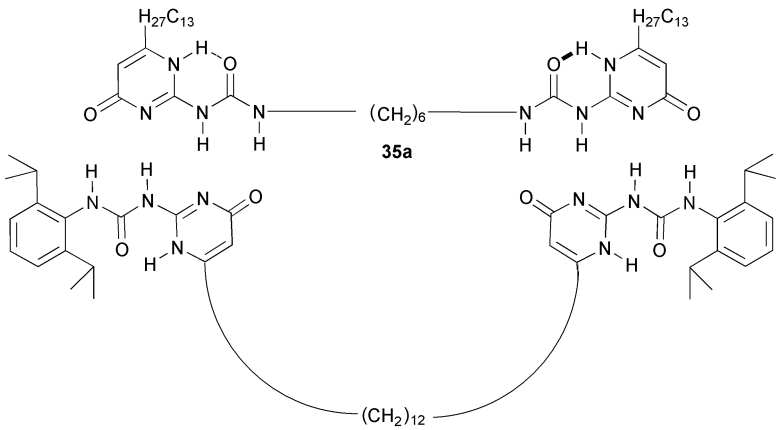
39b R^1= 2,6 difluorophenyl, R^2= Bu

Complementary arrays

The possibilities of complementary quadruple hydrogen bond arrays remains largely unexplored. Of the four different types of quadruple hydrogen bonded complexes that are possible, only the binding properties of the DAAD–ADDA couple have been reported.[35,55] Two of the tautomeric forms of **26** contain a ADDA array, and its complexation with the complementary DAAD array of 2,7-bis(acylamino)-1,8-naphthyridine **40** has been studied in solution.[35] Addition of a small excess of **40a** led to the dissociation of dimers of **26**, and the formation of a complex with **40a**. The complex **26·40** is consequently even more stable than the dimer **26·26** (K_a = > 3 × 10^7). In a related approach to DAAD–ADDA dimers, Lüning and Kuhl chose to study the combination of a 2,7-bis(acylamino)-1,8-naphthyridine with dipyridyl ureas.[55]

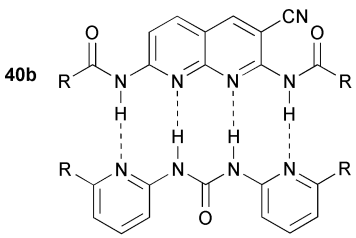
The formation of heterocomplexes was studied with ^{1}H NMR titrations. In contrast to the complex reported by Corbin and Zimmerman, binding constants are relatively low (2000 and 160 M^{-1}, for the complexes of **40b** with **41a** and **41b**, respectively), possibly due to steric interactions between R substituents on both components. An additional aspect that may negatively influence the complex stability of dimers involving pyridyl ureas is the presence of an intramolecular hydrogen bond in the monomer which must be disrupted in order to form a ADDA array. Similar effects destabilize the complex of **42** with **43** which is held together by six hydrogen bonds.[36] Here the intramolecular hydrogen bond in monomeric **42** is observed not only in solution but also in the solid state. As a result, the K_a value of this complex is 5 × 10^5 M^{-1}, at least two orders of magnitude lower than predicted for a six-fold hydrogen bonded complex.

In an attempt to create a pair of hydrogen bonding units which dimerize *via* complementary ADAA and DADD arrays, our group prepared dipyrimidinylamines **44** with the aim to form stable complexes with pyridylureas **45**.[56] However, X-ray crystal structure determination of **44a** showed that the compound exists in the [3*H*] tautomeric form, which displays a



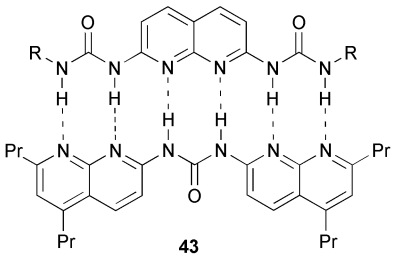
35a

38



40b

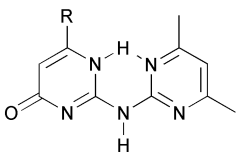
41a R = H
41b R = CH_3



42

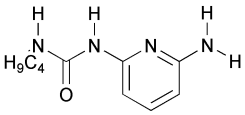
43

ADA, instead of a ADAA array of hydrogen bonding sites. This tautomeric form persists in solution, as was shown with NOE experiments. As a result of the tautomerization, no binding of pyridylureas was observed.

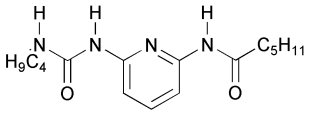


44a R = CH_3

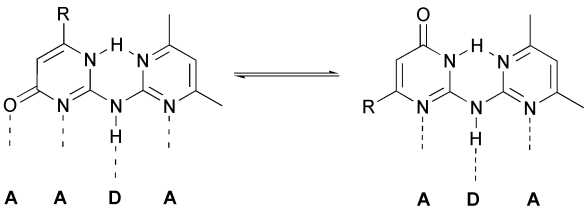
44b R = CF_3



45a



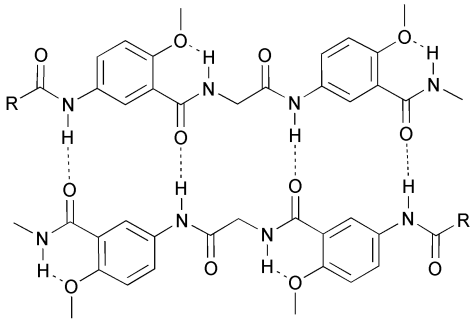
45b



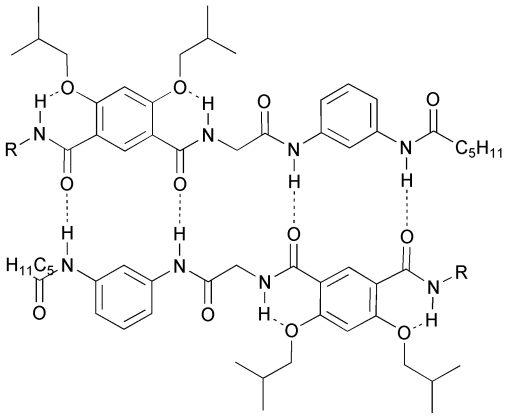
Recently, Bing Gong and coworkers have introduced a new type of recognition unit featuring linear arrays of hydrogen bonding sites.[57] These units are based on combining residues from 3-aminobenzoic acid, isophthalic acid and 1,3-diaminobenzene in oligoamides which are held in a planar arrangement by intramolecular hydrogen bonding of amide N–H groups to ether oxygen atoms.

The validity of the concept was demonstrated by the stability of complexes **46·46** and **47·47**, in $CHCl_3$ solution (K_a values are 4×10^4 M^{-1} and 6.5×10^4 M^{-1}, respectively). The proposed mode of complexation was confirmed by the crystal structure determination of the dimers.

In later work,[58] Bing Gong has demonstrated that this concept can be extended to six-hydrogen bonded molecular duplexes with K_a values of the order of 10^9 M^{-1}. Comparison of two closely related duplexes, with single mismatched binding sites indicate that the mismatch leads to a significant (approximately 40-fold) reduction in binding constant, but that the remaining five hydrogen bonds are sufficiently strong to keep the components together in solution.[59]



46·46 K_{dim}= 4 x 10^4 M^{-1}



47·47 K_{dim}= 6 x 10^4 M^{-1}

Outlook

The development of a range of linear quadruple hydrogen bonding units in the past five years, has shown that these units may combine synthetic accessibility with high association constants. These properties make the hydrogen bonding units ideal building blocks for self assembly, or 'non-covalent synthesis'[1] of functional materials and supramolecular polymers. Although even stronger binding is desirable in some cases, the slower kinetics of the strongest complexes may limit their reversibility. Recent development of molecules with complementary quadruple hydrogen bonding arrays fills a distinct need for such recognition units. These arrays, as well as compounds with non-linear arrays, which have been developed as hydrogen bonding receptors,[60] allow further control in self-assembly and recognition processes, such as the directed formation of switchable supramolecular block-copolymers,[61] or the selective sequestration of tagged species (catalysts or synthetic targets) on a solid phase.[62] At present, supramolecular polymers based on quadruple hydrogen bonds are used in thermoplastic elastomers and π-conjugated materials, and technological applications of supramolecular polymers processed out of solution are foreseen in the near future.

Notes and references

1 L. J. Prins, D. N. Reinhoudt and P. Timmerman, *Angew. Chem., Int. Ed.*, 2001, **40**, 2382–2426.
2 G. A. Jeffrey, *An introduction to hydrogen bonding*, Oxford University Press, Oxford, 1997.
3 S. C. Zimmerman and P. S. Corbin, *Struct. Bonding (Berlin)*, 2000, **96**, 63–94.
4 The number of different arrays with n sites is $\frac{1}{2}(2^n + 2^{1/2n})$ (n = even) or $\frac{1}{2}(2^n + 2^{1/2(n-1)})$ (n = odd).
5 T. W. Bell and Z. Hou, *Angew. Chem., Int. Ed.*, 1997, **36**, 1536–1538.
6 S. K. Chang, D. Van Engen, E. Fan and A. D. Hamilton, *J. Am. Chem. Soc.*, 1991, **113**, 7640–7645.
7 J. Rebek, *Chem. Soc. Rev.*, 1996, **25**, 255–264.

8 D. T. Bong, T. D. Clark, J. R. Granja and M. R. Ghadiri, *Angew. Chem., Int. Ed.*, 2001, **40**, 988–1011.
9 D. C. Sherrington and K. A. Taskinen, *Chem. Soc. Rev.*, 2001, **30**, 83–93.
10 W. L. Jorgensen and J. Pranata, *J. Am. Chem. Soc.*, 1990, **112**, 2008; J. Pranata, S. G. Wierschke and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1991, **113**, 2810.
11 J. Sartorius and H.-J. Schneider, *Chem. Eur. J.*, 1996, **2**, 1446–1453.
12 L. Brunsveld, B. J. B. Folmer, E. W. Meijer and R. P. Sijbesma, *Chem. Rev.*, 2001, **101**, 4071–4098.
13 *Supramolecular Polymers*, ed. A. Ciferri, Marcel Dekker inc., New York, 2000.
14 N. Zimmerman, J. S. Moore and S. C. Zimmerman, *Chem. Ind. (London)*, 1998, 604–610.
15 Y. Ducharme and J. D. Wuest, *J. Org. Chem.*, 1988, **53**, 5787–5789.
16 M. H. Krackov and C. M. Lee, *J. Am. Chem. Soc.*, 1965, **87**, 892–896.
17 P. L. Wash, E. Maverick, E. Chiefari and D. A. Lightner, *J. Am. Chem. Soc.*, 1997, **119**, 3806.
18 R. F. M. Lange and E. W. Meijer, *Macromolecules*, 1995, **28**, 782–783; R. F. M. Lange and E. W. Meijer, *Macromol. Symp.*, 1996, **102**, 301–308.
19 C. Fouquey, J.-M. Lehn and A.-M. Levelut, *Adv. Mater.*, 1990, **2**, 254–257; J.-M. Lehn, *Macromol. Chem., Macromol. Symp.*, 1993, **69**, 1–17; T. Gulik–Krzywicki, C. Fouquey and J.-M. Lehn, *Proc. Natl. Acad. Sci.USA*, 1993, **90**, 167; M. Kotera, J.-M. Lehn and J.-P. Vigneron, *J. Chem. Soc., Chem. Commun.*, 1994, 197–200; M. Kotera, J.-M. Lehn and J.-P. Vigneron, *Tetrahedron*, 1995, **51**, 1953–72.
20 F. H. Beijer, R. P. Sijbesma, J. A. J. M. Vekemans, E. W. Meijer, H. Kooijman and A. L. Spek, *J. Org. Chem.*, 1996, **61**, 6371–6380.
21 A. R. Katritzky and I. Ghiviriga, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1653.
22 F. H. Beijer, H. Kooijman, A. L. Spek, R. P. Sijbesma and E. W. Meijer, *Angew. Chem., Int. Ed.*, 1998, **37**, 75–78.
23 R. J. Griffin and P. R. Lowe, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1811–1819.
24 F. H. Beijer, PhD Thesis, Technische Universiteit Eindhoven, 1998.
25 J. H. K. K. Hirschberg, L. Brunsveld, A. Ramzi, J. A. J. M. Vekemans, R. P. Sijbesma and E. W. Meijer, *Nature*, 2000, **407**, 167–170.
26 L. Brunsveld, J. A. J. M. Vekemans, J. H. K. K. Hirschberg, R. P. Sijbesma and E. W. Meijer, *Proc. Natl. Acad. Sci.*, 2002, **99**, 4977–4982.
27 C. M. Drain, X. Shi, T. Milic and F. Nifiatis, *Chem. Commun.*, 2001, 287–288.
28 G. Ercolani, *Chem. Commun.*, 2001, 1416–1417.
29 F. H. Beijer, R. P. Sijbesma, J. A. J. M. Vekemans, E. W. Meijer, H. Kooijman and A. L. Spek, *J. Org. Chem.*, 1996, **61**, 6371–6380.
30 D. J. Brown, R. F. Evans, W. B. Cowden and M. D. Fenn, *The pyrimidines*, Wiley, New York, 1994, p. 193–196.
31 A. Kreutzberger and H. Schimmelpfennig, *Arch. Pharm.*, 1981, **314**, 34–41; J. Krepelka; A. Cerny, R. Kotva, J. Vachek and M. Melka, *Collect. Czech. Chem. Commun.*, 1986, **51**, 1140–1149; G. Vasilev, *Dokl. Bolg. Akad. Nauk.*, 1990, **43**, 57–60 (*Chem. Abstr.*, **115**, 49603); J. Fan and C. C. Cheng, *J.Heterocycl. Chem.*, 1993, **30**, 1273–1276.
32 F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek and E. W. Meijer, *J. Am. Chem. Soc.*, 1998, **120**, 6761–6769.
33 S. H. M. Söntjens, R. P. Sijbesma, M. H. P. van Genderen and E. W. Meijer, *J. Am. Chem. Soc.*, 2000, **122**, 7487–7493.
34 G. Armstrong and M. Buggy, *Mater. Sci. Eng., C: Biomimetic Supramol. Syst.*, 2001, **18**, 45–49.
35 P. S. Corbin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 1998, **120**, 9710–9711.
36 P. S. Corbin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 2000, **122**, 3779–3780.
37 A. El–ghayoury, E. Peeters, A. P. H. J. Schenning and E. W. Meijer, *Chem. Commun.*, 2000, 1969–1970.
38 Y. Tokunaga and T. Seo, *Chem. Commun.*, 2002, 970–971.
39 J. J. Gonzalez, J. de Mendoza, S. Gonzalez, E. M. Priego, N. Martin, C. Luo and D. M. Guldi, *Chem. Commun.*, 2001, 163–164.
40 M. T. Rispens, L. Sanchez, J. Knol and J. C. Hummelen, *Chem. Commun.*, 2001, 161–162.
41 L. Sanchez, M. T. Rispens and J. C. Hummelen, *Angew. Chem., Int. Ed.*, 2002, **41**, 838–840.
42 J. L. Sessler and R. Wang, *J. Org. Chem.*, 1998, **63**, 4079–4091.
43 H. Kagechika, I. Azamuya, A. Tanati, K. Yamaguchi and K. Shudo, *Tetrahedron Lett.*, 1999, **40**, 3423–3426.
44 B. J. B. Folmer, R. P. Sijbesma, H. Kooijman, A. L. Spek and E. W. Meijer, *J. Am. Chem. Soc.*, 1999, **121**, 2001–2007.
45 J. J. Gonzalez, P. Prados and J. de Mendoza, *Angew. Chem., Int. Ed.*, 1999, **38**, 525–528.
46 R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe and E. W. Meijer, *Science*, 1997, **278**, 1601–1604.
47 B. J. B. Folmer, E. Cavini, R. P. Sijbesma and E. W. Meijer, *Chem. Commun.*, 1998, 1847–1848.
48 J. H. K. K. Hirschberg, F. H. Beijer, H. A. van Aert, P. C. M. M. Magusin, R. P. Sijbesma and E. W. Meijer, *Macromolecules*, 1999, **32**, 2696–2705.
49 B. J. B. Folmer, R. P. Sijbesma, R. M. Versteegen, J. A. J. van der Rijt and E. W. Meijer, *Adv. Mater.*, 2000, **12**, 874–878.
50 R. F. M. Lange, M. van Gurp and E. W. Meijer, *J. Pol. Sci. A, Pol. Chem.*, 1999, **37**, 3657–3670.
51 L. R. Rieth, R. F. Eaton and G. W. Coates, *Angew. Chem., Int. Ed.*, 2001, **40**, 2153–2156.
52 S. H. M. Söntjens, R. P. Sijbesma, M. H. P. van Genderen and E. W. Meijer, *Macromolecules*, 2001, **34**, 3815–3818.
53 B. J. B. Folmer, R. P. Sijbesma and E. W. Meijer, *J. Am. Chem. Soc.*, 2001, **123**, 2093–2094.
54 A. P. Davis, S. M. Draper, G. Dunne and P. Ashton, *Chem. Commun.*, 1999, **2266**, 2265–2266.
55 U. Luning and C. Kuhl, *Tetrahedron Lett.*, 1998, **39**, 5735–5738.
56 S. H. M. Söntjens, J. T. Meijer, H. Kooijman, A. L. Spek, M. H. P. van Genderen, R. P. Sijbesma and E. W. Meijer, *Org. Lett.*, 2001, **3**, 3887–3889.
57 B. Gong, Y. Yan, H. Zeng, E. Skrzypczak–Jankunn, Y. W. Kim, J. Zhu and H. Ickes, *J. Am. Chem. Soc.*, 1999, **121**, 5607–5609.
58 H. Zeng, R. S. Miller, R. A. Flowers and B. Gong, *J. Am. Chem. Soc.*, 2000, **122**, 2635–2644.
59 H. Zeng, H. Ickes, R. A. F. Ii and B. Gong, *J. Org. Chem.*, 2001, **66**, 3574–3583.
60 J. H. Hartley, T. D. James and C. J. Ward, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3155–3184.
61 J. Ruokolainen, R. Makinen, M. Torkkeli, T. Makela, R. Serimaa, G. ten Brinke and O. Ikkala, *Science*, 1998, **280**, 557–560.
62 S.-Q. Zhang, K. Fukase, M. Izumi, Y. Fukase and S. Kusumoto, *Synlett*, 2001, 590–596.