Cooperative Dynamics in Duplexes of Stacked Hydrogen-Bonded Moieties

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Abstract: The self-assembly of two bis-2-ureido-4[1*H*]-pyrimidinones by eight intermolecular hydrogen bonds results in extremely stable dimers. These dimers exist both in solution and in the solid state as two different isomers. By single-crystal X-ray analyses the structures of both the syn-isomer and the anti-isomer have been determined. In addition, with ROESY experiments the structure of a third isomer is revealed. By a combination of NMR techniques the mutual rate of exchange has been determined. Interestingly, these values are significantly lower than the comparable processes of a single 2-ureido-4[1*H*]-pyrimidinone. These experiments allowed us to determine the cooperativity in conformational behavior and tautomerization of stable dimers.

Introduction

Supramolecular objects with predefined shapes are important targets of current research.[1] The directionality and specificity make hydrogen bonds useful tools for the design of such complexes.[2] Low molecular weight compounds can assemble into infinite linear polymer arrays when two hydrogen bond forming units are connected by a spacer.[3] The directionality of the hydrogen bond and the information content of multiple hydrogen bonds can be used to create selectively cyclic arrays instead of polymeric structures.[4] By a clever combination of self-complementarity and chirality, Lehn et al. designed bis-lactams that cannot form polymeric arrays due to the stereochemical arrangement of hydrogen-bonding sites.[5] When bowl-shaped building blocks such as glycoluril[6] or calixarenes[7] were provided with hydrogen-bonding functional groups at the rim, dimeric capsules were formed by self-assembly. The group of Whitesides has studied multicomponent self-assembled structures based on the cyanuric acid−melamine motif, the hydrogen-bonded motif that is studied most thoroughly. Trismelamine rosettes have provided important insights into the role of preorganization in self-assembly processes. It was shown that the complicated mixture of isomers that is formed in stacked rosettes can be analyzed using NMR; molecular dynamics simulations afforded the deviation from planarity as a measure for the stability of the complexes.[8] Further proof for the structure and the exchange processes in these aggregates has come from diastereoisomerism in complexes with optically active isocyanurates.[9] Subsequently, the group of Reinhoudt has used calix-4-arene as a scaffold to self-assemble double rosettes.[10] The exchange rates of dimerization of asymmetric tetraurea calix-[4]arenes could be determined by NOESY experiments.[11] Stable dimeric structures based on eight hydrogen bonds have been obtained by using preorganization of molecules.[12] Recently, Sessler et al. reported the extreme stability of dimeric structures based on guanine, even in solvents such as DMSO.[12d] The symmetry of the structure, however, hampered detailed dynamical studies to evaluate the cooperativity in supramolecular binding.

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(1) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
(2) For review articles, see: (a) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154. (c) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647. (d) de Mendoza, J. *Chem. Eur. J.* **1998**, *4*, 1373. (e) Sijbesma, R. P.; Meijer, E. W. *Curr. Opin. Colloid Interface Sci.* **1999**, *4*, 24.
(3) (a) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89. (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304. (c) Fouquey, C.; Lehn, J.-M.; Levelut, A.-M. *Adv. Mater.* **1990**, *2*, 254. (d) Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787. (e) Lillya, C. P.; Baker, R. J.; Hütte, S.; Winter, H. H.; Lin, Y.-G.; Shi, J.; Dickinson, L. C.; Chien, J. C. W. *Macromolecules* **1992**, *25*, 2076. (f) Bladon, F.; Griffin, A. C. *Macromolecules* **1993**, *26*, 6604.
(4) (a) Kolutchin, S. V.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9092. (b) Yang, W. S.; Chai, X. D.; Tian, Y. Q.; Chen, S. G.; Cao, Y. W.; Lu, R.; Jiang, Y. S.; Li, T. J. *Liq. Cryst.* **1997**, *22*, 579. (c) Marsh, A.; Silvestri, M.; Lehn, J.-M. *Chem. Commun.* **1996**, 1527. (d) Mascal, M.; Hext, N. M.; Warmuth, R.; Moore, M. H.; Turkenburg, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2204. (e) Zimmerman, S. C.; Duerr, B. F. *J. Org. Chem.* **1992**, *57*, 2215.
(5) Brienne, M. J.; Gabard, J.; Leclerq, M.; Lehn, J.-M.; Cheve, M. *Helv. Chim. Acta* **1997**, *80*, 856.
(6) (a) Wyler, R.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699. (b) Grotzfeld, R. M.; Branda, N.; Rebek, J., Jr. *Science* **1996**, *271*, 487.
(7) (a) Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 4282. (b) Hamann, B. C.; Shimizu, K. P.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326.
(8) Chin, D. N.; Simanek, E. E.; Li, X.; Wazeer, M. I. M.; Whitesides, G. M. *J. Org. Chem.* **1997**, *62*, 1891.
(9) Simanek, E. E.; Qiao, S.; Choi, I. S.; Whitesides, G. M. *J. Org. Chem.* **1997**, *62*, 2619.
(10) Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1215.
(11) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706.
(12) (a) Ghadiri, M. R.; Kobayashi, K.; Granja, J. R.; Chadha, R. K.; McRee, D. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 93. (b) Kobayashi, K.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 95. (c) Valdés, C.; Spitz, U. P.; Toledo, L. M.; Kubik, S. W.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 12733. (d) Sessler, J. L.; Wang, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1726.

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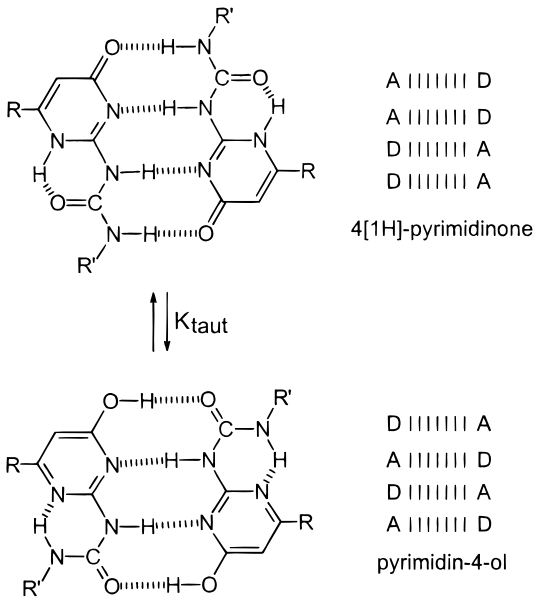


Figure 1. Two tautomeric forms of dimers of 2-ureido-4-pyrimidone, with corresponding arrays of donor and acceptor sites.[12]

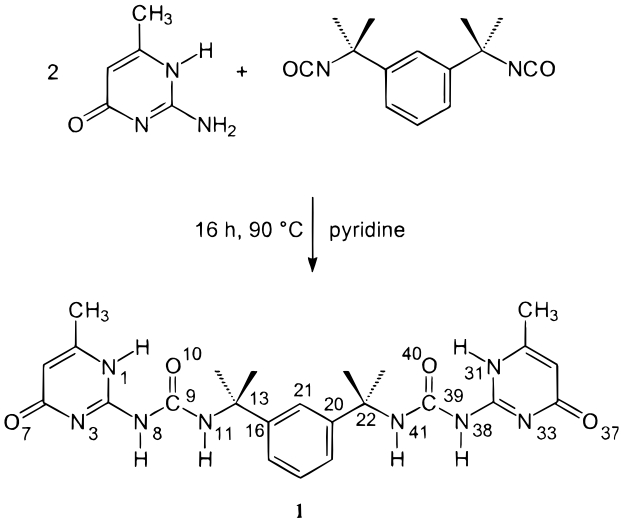
We have shown the potential of the donor−donor−acceptor−acceptor (DDAA) array of hydrogen-bonding sites of 2-ureido-4[1*H*]-pyrimidinones (Figure 1).[13] Due to its simple preparation and high dimerization constant ($K_{dim} \sim 10^8$ M^{-1}), the 2-ureido-4[1*H*]-pyrimidinone functionality is a useful building block for supramolecular chemistry. The 4-[1*H*]-pyrimidinone tautomer is in equilibrium with the pyrimidin-4-ol tautomer; this equilibrium is influenced by solvent and electronegativity of the substituent on the pyrimidinone ring. The very strong dimerizing ureidopyrimidinone units were used to obtain linear polymers and reversible networks.[14] De Mendoza et al. reported calixarene dimers formed by eight hydrogen bonds between 2-ureido-4[1*H*]-pyrimidinones bonded to calix[4]arene platforms.[15]

Here, we report on dimeric structures composed of two bisureidopyrimidinones **1** which are held together by eight hydrogen bonds. These dimers exist in solution and in the solid state as different but exceptional stable supramolecular isomers. Their exact structures have been assigned by single-crystal X-ray analysis and their mutual equilibrium constants have been determined by using NMR spectroscopy. The dynamics of this preformed dimer are used to discuss the cooperativity in these processes.

Results

Synthesis and Structure. We designed compound **1**, which contains two 2-ureido-4-pyrimidinone units connected by a *m*-xylylene spacer. Compound **1** was prepared in 85% yield by the reaction of 1,3-bis(1-isocyanato-1-methylethyl)benzene with 6-methylisocytosine, both commercially available compounds. The dimeric nature of **1** was confirmed with ESI-MS; next to a monomer peak at *m*/*z* 495, a sizable peak at *m*/*z* 989 is detected, even in chloroform acidified with formic acid (0.1% v/v). Vapor pressure osmometry at concentrations between 35 and 135 mM of **1** in chloroform revealed a molecular weight of 990 ± 90, proving the selective formation of dimeric structures. The NMR spectra are fully consistent with the proposed dimeric structure, and these dimeric structures are stable in the presence of hydrogen bond breaking solvents; even upon addition of 25% DMSO in $CDCl_3$ no monomeric structures were observed.

Scheme 1



Two types of crystals suitable for single-crystal X-ray analysis were obtained, from dimethylformamide (DMF) and from chloroform, respectively. In crystals **I** from DMF, melting point 220 °C, both 2-ureido-4-[1*H*]-pyrimidinone units of one molecule are located at the same side of the plane of the phenyl ring (syn) and both units exist as pyrimidinone tautomers (Figure 2). The asymmetric unit of **I** contains two independent molecules of compound **1** together with four solvent molecules. Dimers of **I** are formed by association of each of the independent molecules with the molecule generated by a crystallographic inversion center. The hydrogen-bonding geometry of the dimers is summarized in Table 1. In one of the dimers **IA** (Figure 2a) the two hydrogen bond arrays are not exactly on top of each other, but are shifted over approximately 1.4 Å. The pyrimidinone ring systems of one molecule are parallel; the angle between the least-squares planes through the ring systems amounts to 1.6°. The interplanar distance is 3.44 Å. In the other dimer **IB** (Figure 2b) the hydrogen bond arrays are located nearly on top of each other. The difference is reflected in a small change in conformation of the independent molecules, which are given in Table 2. The angle between the least-squares planes through the pyrimidinone rings is 3.2°, and the interplanar distances is 3.66 Å. Each dimer donates a weak hydrogen bond from an aromatic NH group to a solvent dimethylformamide molecule.

In crystals **II** obtained from chloroform, also with a melting point of 220 °C, the two pyrimidinone units of one molecule are on opposite sides of the plane of the phenyl ring (anti) (Figure 3). The asymmetric unit of **II** contains one molecule of compound **1** and four chloroform molecule sites, two of which are only partly occupied. A dimer of **II** is located on a crystallographic 2-fold rotation axis. The hydrogen bond geometry is summarized in Table 1; the conformation-defining torsion angles are given in Table 2. The hydrogen bond arrays are positioned on top of each other and are rotated approximately 42° with respect to each other. The dihedral angle between the least-squares planes through the pyrimidinone angles located

(13) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761. For other quadruple hydrogen-bonded units: (a) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710. (b) Gong, B.; Yan, Y.; Zeng, H.; Skrzypczak-Jankunn, E.; Kim, Y. W.; Zhu, J.; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607.

(14) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997,** *278***,** 1601.

(15) González, J. J.; Prados, P.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 525.

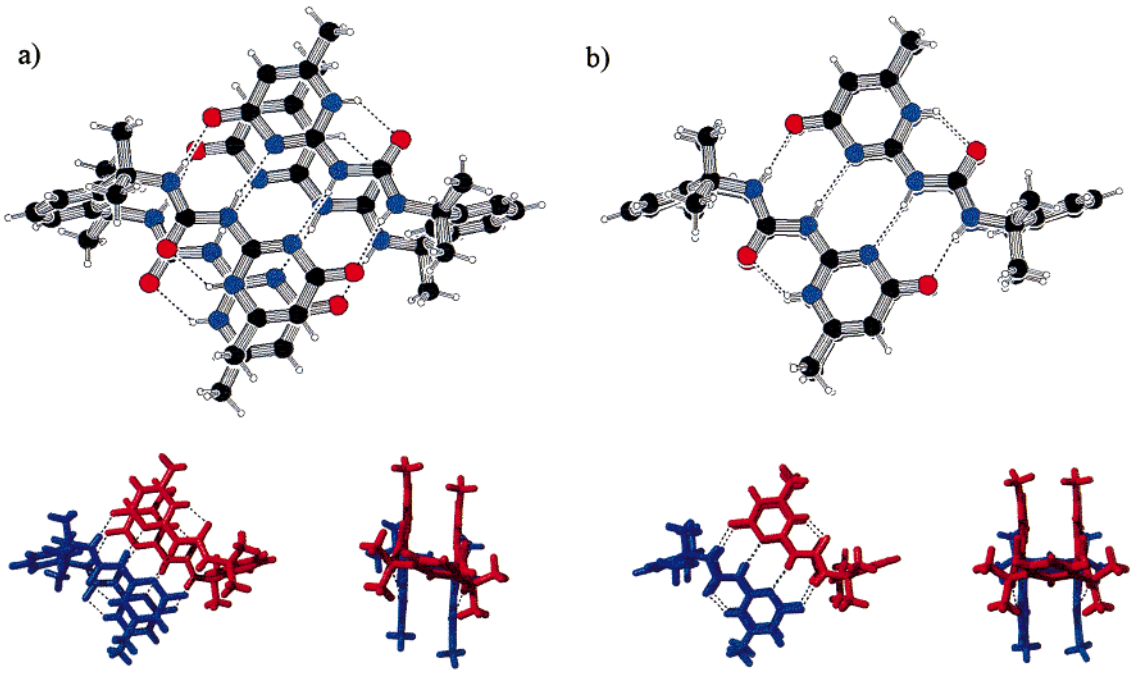


Figure 2. PLUTON representation of the dimer geometry of **I** in crystals from DMF: (a) **IA** and (b) **IB**. Both crystal structures are viewed perpendicular to the plane of hydrogen bonds.

Table 1. Hydrogen Bond Geometry (Å, deg) of Dimers **I** and **II**[a]

	H···A	D···A	D−H···A
	dimer **IA**		
N1−H1···O10[b]	1.94(3)	2.565(3)	131(3)
N8−H3···N33	2.09(3)	2.994(4)	163.3(6)
N11−H4···O37	1.94(3)	2.755(4)	163.7(7)
N31−H24···O40[b]	1.97(3)	2.616(3)	132(2)
N38−H26···N3	2.17(3)	3.005(4)	169.9(7)
N41−H27···O7	2.07(3)	2.789(4)	147.7(11)
	dimer **IB**		
N1−H1···O10[b]	1.95(3)	2.587(3)	130(2)
N8−H3···N33	2.14(3)	2.979(4)	164.2(7)
N11−H4···O37	2.02(3)	2.743(4)	150.3(8)
N31−H24···O40[b]	1.94(3)	2.594(3)	131(2)
N38−H26···N3	2.10(3)	3.001(4)	167.7(7)
N41−H27···O7	1.94(3)	2.772(4)	163.8(11)
	dimer **II**		
N1−H1···O10[b]	1.92(3)	2.582(4)	131(2)
N8−H8···N3	2.13(3)	2.993(4)	166.1(10)
N11−H11···O7	1.94(3)	2.801(4)	167.1(10)
N31−H31···O40[b]	1.91(3)	2.573(4)	131(2)
N38−H38···N33	2.11(3)	2.969(4)	165.9(10)
N41−H41···O37	1.93(3)	2.774(4)	160.3(10)

[a] Estimated standard deviations in parentheses. [b] Intramolecular hydrogen bond.

Table 2. Monomer Conformation for Structures **I** and **II**[a]

	IA	**IB**	**II**
C9−N11−C13−C16	−62.5(4)	−61.9(3)	−70.1(4)
N11−C13−C16−C21	−22.6(4)	−32.3(4)	−5.1(4)
C21−C20−C22−N41	32.3(4)	34.7(4)	−8.8(4)
C20−C22−N41−C39	70.8(4)	63.6(4)	−70.9(4)

[a] Torsion angles in deg; estimated standard deviations in parentheses.

on top of each other amounts to 6.2°, with an interplanar distance of 3.66 Å.

Characterization of the Isomers with NMR Spectroscopy. NMR spectroscopy of solutions of crystals out of DMF as well as crystals out of $CHCl_3$ in $CDCl_3$ resulted in the same proton NMR spectrum (Figure 4). The signals of the two different structures (**I** and **II**) were observed in the spectra, which leads to the conclusion that at room temperature, in chloroform, the isomers exchange within a few minutes. Using ROESY NMR we could assign most of the signals in ^{1}HNMR; the assignments are given in Table 3 using the labeling designated in Scheme 2. Interestingly, when amorphous powder of compound **1** is dissolved in chloroform or when a solution of the crystals in chloroform has been stored for a few hours at room temperature, signals of a new isomer are observed in the proton NMR spectrum (Figure 5). Signals of **III** occur in pairs with equal intensity, indicating asymmetry of this isomer. Careful analysis of the spectrum in Figure 4 shows already small resonances of **III**. The ratio between the isomers is solvent dependent; isomer **III** is highly favored in aromatic solvents such as 1,2-dichlorobenzene and toluene.

A 2D-ROESY experiment is used to reveal the structure of **III**. Nuclear Overhauser effects between the hydrogen between the two substituents and the *o*-phenyl protons clearly show the asymmetric substitution around the phenyl ring (Scheme 2). The ortho protons exhibit different chemical shifts, but equal NOE to the central proton. The asymmetrical substitution could be further proved by the NOE's between the alkylidene protons of the hydrogen bond unit and the protons of the attached methyl group; a short-range NOE to the methyl protons of the same unit as well as a long-range NOE to the different methyl protons of the other unit are observed. The positions of the methyl protons and the alkylidene proton, which resonate downfield of the corresponding protons of a 4-[1*H*]-pyrimidinone unit, indicated that these protons are attached to a pyrimidin-4-ol unit. This is in agreement with the chemical shifts of aminocarbonyl-6-phenylpyrimidin-4-ol, which were published before.[13] Thus dimer **III** consists of two identical asymmetric molecules in which one-half is the 4[1*H*]-pyrimidinone tautomer and the other half is the pyrimidin-4-ol tautomer (Scheme 2; **2**). A dimer is formed by self-complementary quadruple hydrogen bonding between the two pyrimidinone units and between the two pyrimidinol units, respectively. The assignment of ^{1}H NMR signals is given in Table 3.

Dynamics of Equilibration. The interconversion of **I** and **II**, as well as **III**, has been studied in solution, and the results

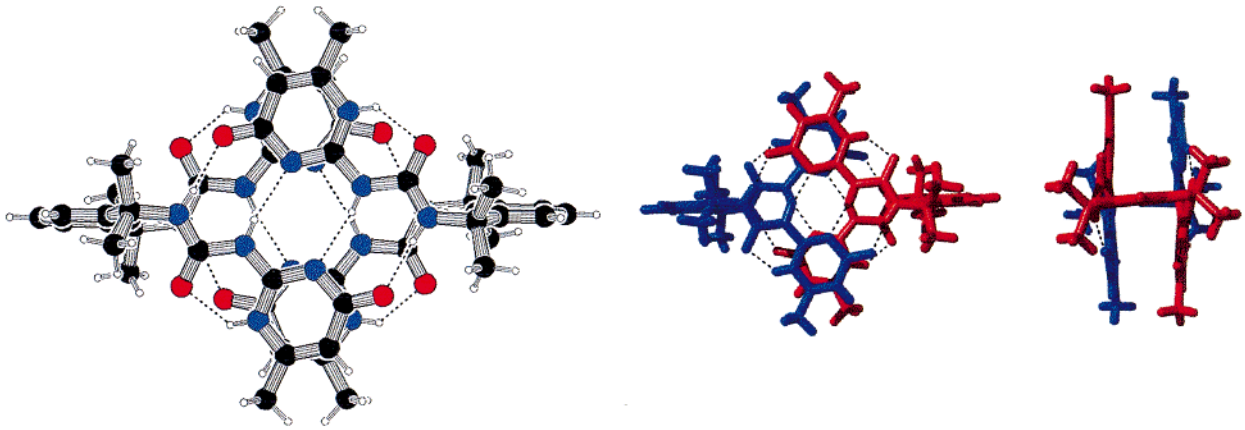


Figure 3. PLUTON representation of the dimer geometry of **II** in crystals from chloroform. The crystal structure is viewed perpendicular to the plane of hydrogen bonds.

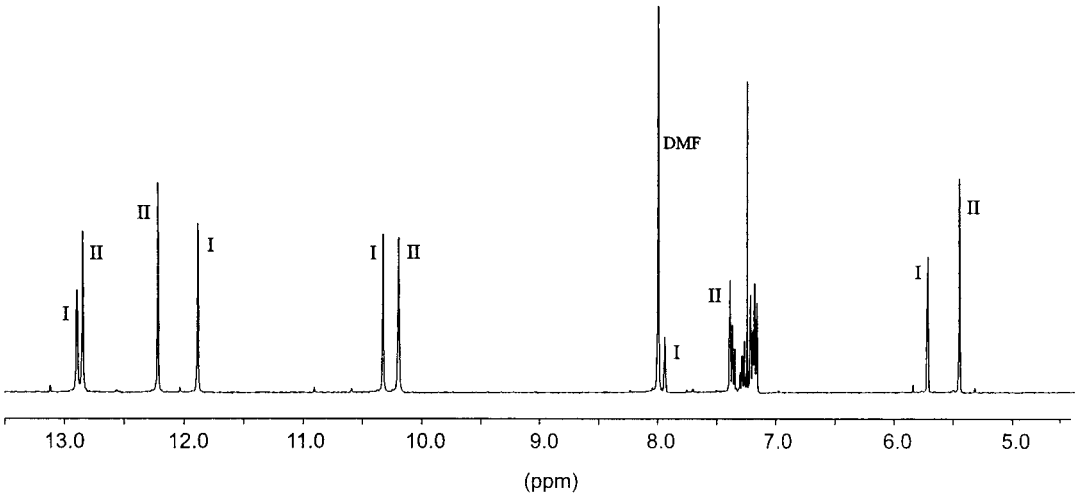


Figure 4. Part of the ^{1}H NMR spectrum of **I** in $CDCl_3$. Signals of syn-isomer **I** and anti-isomer **II** are assigned.[15] See also Table 4.

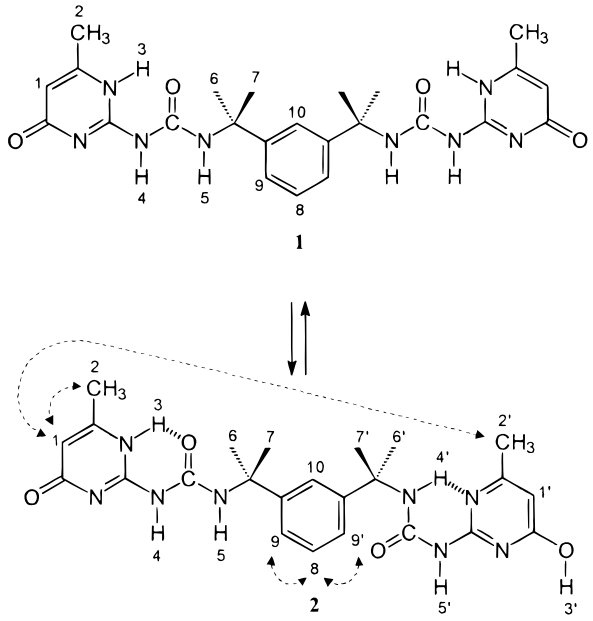
Table 3. Assignment of ^{1}H NMR Signals of Isomers **I**, **II**, and **III** in $CDCl_3$[a]

	δ (ppm)				δ (ppm)		
	I	**II**	**III**		**I**	**II**	**III**
1	5.71	5.46	5.34	6	1.90	1.89	1.88
1′			5.86	6′			1.91
2	2.08	1.99	2.06	7	1.54	1.55	1.51
2′			2.32	7′			1.52
3	12.86	12.84	12.59	8	7.96	7.45	7.74
3′			13.08	9	7.23	7.18	7.20
4	11.88	12.20	10.91	9′			7.26
4′			12.00	10	7.30	7.37	7.34
5	10.33	10.15	10.19				
5′			10.57				

[a] Proton ration = 0.2 (**I**), 0.4 (**II**), and 0.4 (**III**).

are presented in Figure 6. A fast equilibration between isomer **I** and **II** is observed with NOE difference and 2D-ROESY experiments, while equilibration from **I** and **II** into isomer **III** is very slow. The rate constant for the chemical exchange between isomers **I** and **II** could be determined by means of 2D-exchange spectroscopy, using the equations given by Jeener et al.[17] and taking into account the difference in mole fractions of both isomers.[18] Assuming a first-order process for the exchange between the different isomers, at room temperature in chloroform, the rate constant for the chemical exchange is 1.25 s^{-1}, indicating a lifetime of 800 ms of isomers **I** and **II**.

Scheme 2



(16) Although only a representative part of the spectrum is shown in Figure 1, the signals of the different isomers are clearly visible throughout the whole spectrum.

(17) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546.

(18) Perrin, C. L.; Dwyer, T. J. *Chem. Rev.* **1990**, *90*, 935.

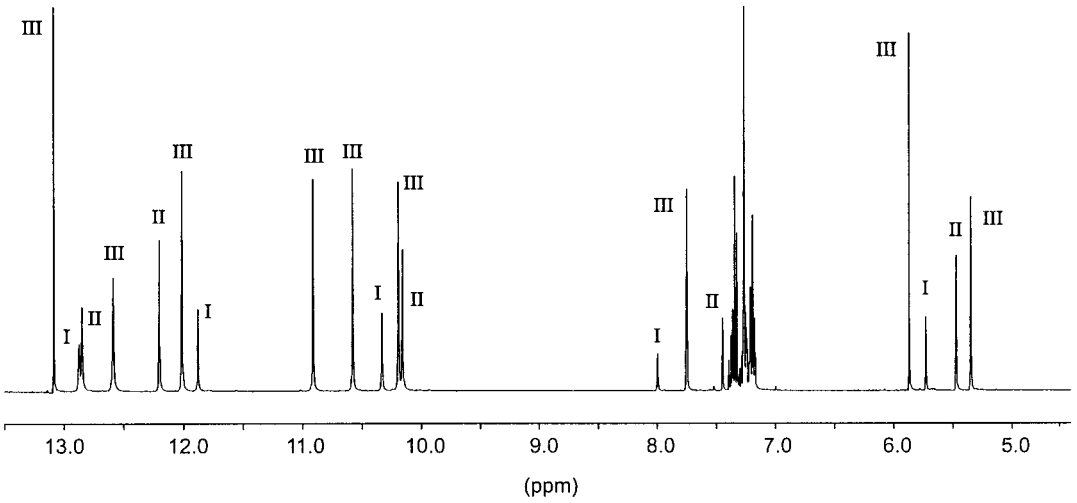


Figure 5. Partial proton NMR spectrum of **1** in $CDCl_3$. Signals of structures **I**, **II**, and **III** are assigned.[15]

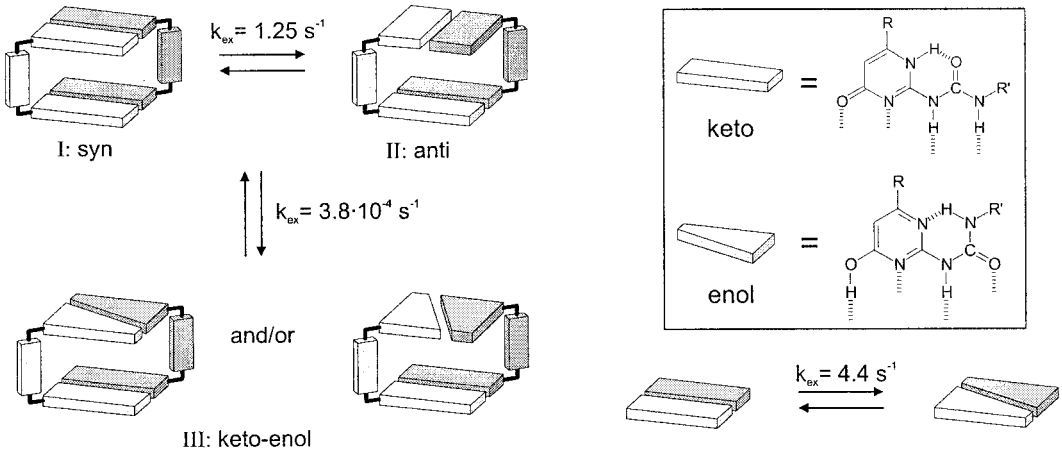


Figure 6. Schematical representation of the interconversion of isomers **I**, **II**, and **III**.

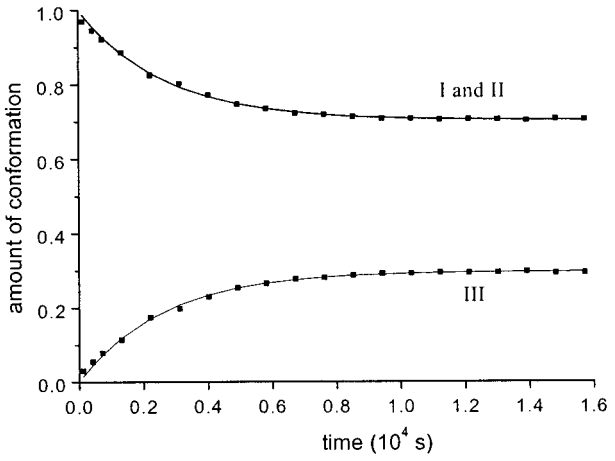


Figure 7. Relative amount of structures **I**, **II**, and **III** versus time, after dissolving a crystal of structure **I** in chloroform, and the least-squares curve fitting.

The rate constant for the exchange of **I** and **II** into **III** could not be determined with this method, but could be obtained by dissolving crystals of isomer **I** in $CDCl_3$ and determination of the increase in intensity of the signals of **III** and the concomitant decrease in intensity of the sum of the signals of **I** and **II** versus time (Figure 7). In this manner, a plot obeying a first-order relationship is obtained; from least-squares curve fitting the rate constant of exchange is calculated to be 3.8×10^{-4} s^{-1}, which corresponds to a pre-tautomerization lifetime of 44 min for isomer **III**.

Discussion

The easily accessible bis-2-ureido-4[1*H*]-pyrimidinone (**1**) self-assembles in dimeric structures as is confirmed by ESI-MS, VPO, NMR, and X-ray analysis. At least three different isomers of this dimer are formed. By single-crystal X-ray analyses two isomers are characterized. The first isomer is a syn-conformer, with both 2-ureido-4-[1*H*]-pyrimidinone units located at the same side of the plane of the phenyl ring. This isomer is achiral. The second isomer is characterized as an anti conformer with the two 4-[1*H*]-pyrimidinone units located on opposite sides of the plane of the phenyl ring. Due to this orientation this isomer is axial chiral. But despite the chirality of one dimer, the crystal is achiral due to the existence of both M,M and P,P dimers in alternating fashion in the crystal lattice. P,M dimers are not formed, because P,M dimers will form polymer structures, which is in this case entropically unfavorable. The different isomers can be compared to a slightly modified "coupe du roi".[19]

Comparison of the hydrogen bond geometry of dimers **I** and **II** with the geometry of monofunctional 2-ureido-4[1*H*]-pyrimidinone reported by Beijer et al. shows similar lengths of the N−H···N and N−H···O bonds.[13] However, there is a

(19) Mislow, K. *Bull. Soc. Chim. Fr.* **1994**, *131*, 534.

pronounced difference in the bond angles in these structures. While the bond angle of the N−H···N of the monofunctional 2-ureido-4[1*H*]-pyrimidinone is approximately 175°, the corresponding bond in dimers **I** and **II** is between 163.3° and 169.9°. A related difference is observed in the N−H···O bond angle; in monofunctional 2-ureido-4[1*H*]-pyrimidinone a value of about 163° is found, while values between 130° and 167.1° are found in dimers **I** and **II**. These differences are rationalized by taking the reduced flexibility of the hydrogen-bonded units in **1**, due to the spacer that connects the two units, into account. Furthermore, the two hydrogen-bonding planes are stacked with a distance of 3.4−3.66 Å, very close to the stacking of base pairs[20] and discotic liquid crystals.[21]

When crystals of **I** are dissolved in chloroform, immediately signals of both **I** and **II** are detected in proton NMR. The relatively fast equilibration between **I** and **II** hampers the assignment of the different sets of signals to the two structures. Nevertheless, the more downfield position of the signal of the alkylidene proton of **I** (Figure 4) indicates that in structure **I** the hydrogen-bonded units are on top of each other, while in structure **II** the hydrogen-bonded units are shifted relative toward each other. The two hydrogen-bonded units of **IB** (Figure 2b) are on top of each other; however, in this orientation there is an unfavorable dipolar interaction between the two units present. In structure **IA** (Figure 2a) the two hydrogen-bonded units are not exactly on top of each other, but underwent a translation of about 1.4 Å to circumvent unfavorable dipolar interactions. It is reasonable to assume that the mean structure of **I** in solution would be a structure like **IA**. In structure **II** the two hydrogen-bonded units are positioned on top of each other with concomitant rotation; in this orientation no unfavorable dipolar interactions between the units are present. This leads to the conclusion that **II** gives rise to the set of signals designated as **II** in Figure 3, and **I** corresponds to the set of signals designated as **I**.

The syn and anti isomer exchange slowly on the NMR time scale, which resulted in separate set of signals for a mixture of the two isomers in solution. 2D exchange spectroscopy revealed a rate of exchange for these isomers of 1.25 s^{-1} (lifetime 800 ms). The lifetimes of the isomers can be rationalized by considering the mechanism of the chemical exchange. The transition of isomer **I** into **II** is only possible when one of the two hydrogen bond arrays is completely open, followed by a syn−anti isomerization from the units on the spacer and subsequent closing of the hydrogen-bonded unit. Due to the high dimerization constant of the 2-ureido-4[1*H*]-pyrimidinone unit, this transition is a slow process resulting in separate signals of both isomers in proton NMR. Recently, the lifetime of monofunctional 2-ureido-4[1*H*]-pyrimidinone was determined at 80 ms.[22] The difference of more than an order of magnitude (80 versus 2 × 800 ms[23]) between these two values is caused by the preorganization in dimers **I** and **II**. Hence, the two processes of hydrogen bond association and stacking of the planes act cooperatively. The X-ray analysis strongly supports the attractive stacking (3.4−3.66 Å distance between the hydrogen-bonding planes). The strength of the association is increased through the stacking, while the latter is increased in the case of stronger association. This cooperativity of two different secondary interactions is often used in explaining the tertiary structure of biomolecules. The simple features of our molecules make them interesting models.

In solution a third isomer is detected. ROESY experiments revealed the asymmetry in structure **2**; dimers consist of two identical asymmetric molecules in which one-half is the 4[1*H*]-pyrimidinone tautomer and the other half is the pyrimidin-4-ol tautomer. ^{1}H NMR of **2** in chloroform shows only one asymmetric dimer, although both the anti and the syn conformation should be envisaged. There are two plausible explanations; the first explanation is the existence of a fast transition between the anti and the syn conformation resulting in an averaged set of signals in proton NMR. The second plausible explanation holds a difference in stability between the anti and the syn conformation of **2**, responsible for a preference for one conformation. Examination of the CPK model of the syn conformer of asymmetric dimer **2** shows a significant reduction in flexibility of the dimer in comparison with that of the anti conformer. Consequently, the asymmetric dimer **2** only exists in the anti conformation. Measuring proton NMR at both higher temperatures, until 100 °C, and lower temperatures, until −50 °C, did not result in the occurrence of a new set of signals.

The transition of isomers **I** and **II** into structure **III** is a relatively slow process. The rate of exchange is determined by measuring the increase of the amount of structure **III** in time after dissolving crystals of isomer **I** in chloroform at room temperature. A rate constant of exchange as low as 3.8 × 10^{-4} s^{-1}, corresponding to a lifetime of 44 min, was determined. To determine the tautomerization of a single unit, the rate constant of the exchange of *N-tert*-butylaminocarbonyl-6-phenyl-4[1*H*]-pyrimidinone into the corresponding pyrimidin-4-ol tautomer was determined by means of 2D exchange spectroscopy. The rate constant of the chemical exchange is 4.4 s^{-1}, which corresponds to a lifetime of 225 ms. The large difference in rate shows that the tautomerization of one of the hydrogen bond units in the dimer is slow compared to the tautomerization of the single unit. It is plausible, that also in this tautomerization an important role is played by cooperativity. Since the difference here is 3 orders of magnitude larger than the difference in exchange between **I** and **II**, it is possible that the transition from a bis-4[1*H*]-pyrimidinone dimer to a pyrimidinone−pyrimidinol dimer can only take place provided both hydrogen bond arrays are open. However, tautomerization is a complex chemical event with significant rearrangement, involving a sequence of steps, not requiring complete dissociation of the duplex. Stacking of the planes increases the stability of the hydrogen bonding (see above) and as a result the concentration of half-open duplex is low. This low concentration is proposed to be responsible for the slow process of tautomerization in the duplex.

Conclusion

Due to the high association constant of the 2-ureido-4-pyrimidone unit, different supramolecular isomers of compound **1** were characterized in the solid state and in solution. The rate constants of the chemical exchange of the dimeric structures are determined. The exchange rates between the different isomers strongly suggest a cooperative action between separate secondary interactions similar to those found in biomolecules. The distance of 3.4−3.66 Å between the planes in the duplex supports the attractive interactions of the hydrogen-bonded planes. These results will contribute to the understanding of multiple hydrogen-bonded systems; the 2-ureido-4[1*H*]-pyri-

(20) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984.

(21) Chandrasekhar, S. *Handbook of Liquid Crystals*; Demus, D., Goodby, J., Gray, G. W., Spiess, H.-W., Vill, V., Eds.; Wiley-VCH: Weinheim, 1998; pp 749−780.

(22) This value has been determined by EXSY measurements of heterodimers of different substituted 2-ureido-4[1*H*]-pyrimidinones in $CDCl_3$ at 303 K; S. H. M. Söntjens, manuscript in preparation.

(23) A lifetime of 800 ms for the duplex corresponds to a lifetime of 1600 ms for each individual unit in the duplex.

midinones are not only interesting as model systems for biomolecules, but due to their simple synthesis can be used to construct functional systems as well. Incorporation of this eight-hydrogen-bonded unit in supramolecular polymers will presumably lead to reversible polymers with a long lifetime and a very high molecular weight.

Experimental Section

General Methods. 6-Methylisocytosine and 1,3-bis(1-isocyanato-1-methylethyl)benzene were purchased from respectively Acros Chimica and Aldrich. Pyridine was freshly distilled from $LiAlH_4$. Deuteriochloroform was used as received.

Instrumentation. NMR spectra were recorded on a Bruker AC400 spectrometer. The ROESY spectrum was recorded on a Varian Unity Inova 750 NB spectrometer. VPO measurements were performed on a Knauer A0280 osmometer with triphenylphosphine for calibration.

X-ray Crystal Structure Analysis. Pertinent data for the structure determinations are collected in the Supporting Information. Data for crystal structure **I** were collected on an Euraf-Nonius CAD4T diffractometer on a rotating anode. Data for structure determination **II** were collected on a Nonius κ-CCD diffractometer on a rotating anode. Both sets were measured at 150 K, using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The unit-cell parameters were checked for the presence of higher lattice symmetry.[24] Structures were solved with direct methods using SHELXS86[25] for structure **I** and SHELXS97[26] for structure **II**. Refinement on F^2 was performed with SHELXL97.[27] No observance criterion was applied during refinement on F^2. The hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. The non-hydrogen atoms of all structures were refined with anisotropic thermal parameters. The hydrogen atoms were refined with a fixed isotropic displacement parameter related to the value of the equivalent isotropic displacement parameter of their carrier atoms. For structure **II**, two of the four initially found chloroform solvent molecules turned out to be partly occupied as well as disordered. The associated contributions to the structure factors was taken into account using the SQUEEZE procedure[28] as incorporated in Platon.[29] The ratio chloroform:**1** in the unit cell was found to be approximately 3.5. Neutral atom scattering factors and anomalous dispersion corrections were taken from the *International Tables for Crystallography*.[30] Geometrical calculations and illustrations were performed with Platon;[29] all calculations were performed on a DEC Alpha 255 station.

Synthesis of 1. 1,3-Bis(1-isocyanato-1-methylethyl)benzene (4.3 mL, 19 mmol) was added to a stirring mixture of 6-methylisocytosine (4.9 g, 39 mmol) in pyridine (50 mL) under argon atmosphere. After being heated at 90 °C overnight, the solvent was removed under reduced pressure. The residue was purified by column chromatography with 5% methanol in chloroform. Subsequent crystallization from ethyl acetate/chloroform (1:1 v/v) gave pure **1** as white crystals (7.8 g, 85%). Mp 220 °C. ^{1}H NMR ($CDCl_3$) δ 13.10, 12.85, 12.60, 12.21, 12.00, 11.89, 10.92, 10.57, 10.36, 10.21, 10.18, 8.02, 7.75, 7.45−7.17 (multiple signals), 5.86, 5.70, 5.46, 5.34, 2.31, 2.07−2.04 (multiple signals), 1.98, 1.90−1.88 (multiple signals), 1.55−1.52 (multiple signals). ^{13}C NMR ($CDCl_3$) δ 172.2, 171.0, 166.7, 157.2−154.6 (multiple signals), 148.6−146.2 (multiple signals), 129.0−127.6 (multiple signals), 122.9−119.9 (multiple signals), 107.1−106.2 (multiple signals), 100.2, 60.4, 56.9, 56.3, 55.8, 55.4, 34.4, 33.9, 33.8, 33.6, 27.2, 26.7, 25.6, 23.5, 18.9, 18.8, 14.2. IR (KBr) ν 3444, 3226, 3052, 2976, 1703, 1665, 1616, 1578, 1458, 1327, 1251 cm^{-1}. Anal. Calcd for $C_{49}H_{61}N_{16}O_8Cl_3$ (dimer + $CHCl_3$): C, 53.09; H, 5.54; N, 20.02. Found: C, 53.11; H, 5.59; N, 19.99.

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Supporting Information Available: Further details of the structure determinations of **I** and **II**, including atomic coordinates and thermal parameters as an X-ray crystallographic file (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Spek, A. L. *J. Appl. Crystallogr.* **1988**, *21*, 578.
(25) Sheldrick, G. M. SHELXS86 program for crystal structure determination; University of Göttingen, Germany, 1986.
(26) Sheldrick, G. M. SHELXS97 program for crystal structure determination; University of Göttingen, Germany, 1997.
(27) Sheldrick, G. M. SHELXL97 program for crystal structure refinement; University of Göttingen, Germany, 1997.
(28) Sluis, P. van der; Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, 194.
(29) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C-34.
(30) Wilson, A. J. C., Ed. *International Tables for Crystallography*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Vol. C.