ORGANIC LETTERS

2001
Vol. 3, No. 24
3887−3889

A Multiple Hydrogen-Bond Scaffold Based on Dipyrimidin-2-ylamine

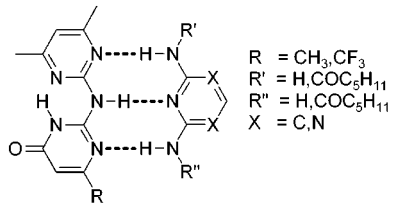
Serge H. M Sönjens,[†] Joris T. Meijer,[†] Huub Kooijman,[‡] Anthony L. Spek,[‡] Marcel H. P. van Genderen,[†] Rint P. Sijbesma,*[,†] and E. W. Meijer[†]

Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB, Eindhoven, The Netherlands, and Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Padualaan 8, 3584 CH, Utrecht, The Netherlands

r.p.sijbesma@tue.nl

Received September 13, 2001

ABSTRACT



A multiple hydrogen-bond array based on dipyrimidin-2-ylamine is presented, which is easily accessible. The influence of a preorganizing intramolecular hydrogen bond, tautomeric equilibria, and steric effects on the association behavior were investigated. X-ray diffraction shows that the molecules feature an ADA (acceptor−donor−acceptor) array of hydrogen-bonding sites in the solid state. The array persists in solution, and ^{1}H NMR titrations show that molecules with sterically nondemanding DAD arrays are selectively bound.

In supramolecular chemistry[1−3] one of the goals is to construct functional multimolecular aggregates in a selective and controlled way via reversible secondary interactions. To allow the construction of intricate supramolecular assemblies, these secondary interactions need to be strong enough to drive the equilibrium toward the associated product and weak enough to allow the system to reach equilibrium within a reasonable time frame. Selectivity is required to drive the equilibrium to a single product and to permit the use of different modes or motifs of association, allowing the construction of different building blocks for supramolecular systems that can be used in each other's presence. It has been shown that arrays of multiple hydrogen bonds display the required versatility and selectivity.[4−6] The strength of the hydrogen-bonding interaction can be tuned by varying the number and configuration of the hydrogen bonds in an array from as low as 10 M^{-1} up to about 1×10^9 M^{-1}. We have shown that very strong ($K_a > 10^7$ M^{-1}) complexation[7] is obtained in quadruple hydrogen-bonded dimers of ureidopyrimidinone derivatives, which feature a self-complementary AADD array.[8]

For the targeted construction of complex self-assembled aggregates, however, selective association of heterocomplexes is highly desirable. In particular, the self-assembly of microphase-separated architectures from reversibly associating end-functionalized polymers requires hetero-associating functionalities.[9] We report here the mode of association of dipyrimidin-2-ylamine derivatives **3**, which

[†] Eindhoven University of Technology.
[‡] Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry.

(1) Vögtle, F. *Supramolecular Chemistry*; Wiley: New York, 1991.
(2) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
(3) Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F. *Comprehensive Supramolecular Chemistry*; Pergamon: Oxford, 1996.
(4) Sijbesma, R. P.; Meijer, E. W. *Curr. Opin. Colloid Interface Sci.* **1999**, *4*, 24−32.
(5) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63−94.
(6) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2446−2492.
(7) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487−7493.
(8) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761−6769.
(9) Tanaka, F.; Ishida, M.; Matsuyama, A. *Macromolecules* **1991**, *24*, 5582−5589.

10.1021/ol016750a CCC: $20.00
Published on Web 11/09/2001

were designed to display either an ADA or an AADA array of hydrogen-bonding sites, depending on the tautomeric form of the pyrimidinone unit (Figure 1). We were particularly

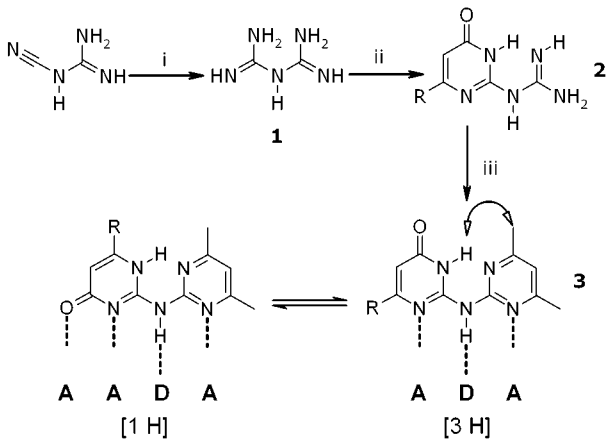


Figure 1. Synthesis of dipyrimidin-2-ylamines **3a** (R = CH_3) and **3b** (R = CF_3). (i) Ammonium chloride, phenol, 120 °C. (ii) Ethyl acetoacetate or ethyl 1,1,1-trifluoroacetylacetate, biguanidinium sulfate, NaOH, EtOH, reflux. (iii) 2,4-Pentanedione, HOAc, reflux. Two tautomeric forms of **3** are shown: 2-(4,6-dimethylpyrimidin-2-ylamino)-6-methyl-[1*H*]-pyrimidin-4-one, featuring an AADA array, and 6-methyl-[3*H*]-pyrimidin-4-one, featuring an ADA array. The observed NOE effect in the [3*H*] tautomer is indicated with a double-headed arrow.

interested in the possibility of biasing the tautomeric form of **3** by complexation with complementary DAD or DDAD arrays.

Compounds **3a** and **3b** were synthesized by two successive cyclocondensation reactions of biguanide **1**, using ethyl acetoacetate followed by pentanedione,[10] and were obtained in yields of 69% and 50%, respectively. Pyrimidinones usually exist in the [3*H*] form, presumably because this tautomer has a smaller dipole moment than the [1*H*] tautomer.[11] We expected to observe the former tautomer in compound **3a**. The relative stability of the [1*H*] tautomer was anticipated to be higher in fluorinated derivative **3b**, since the dipole moment of the pyrimidinone moiety of this tautomer is partly compensated by the CF_3 group.

A single-crystal X-ray study[12] (see Supporting Information) confirms the presence of the [3*H*] tautomer of **3a** in the solid state (Figure 2). The asymmetric unit consists of two molecules, with slightly different conformations. Figure 2 shows the presence of an intramolecular hydrogen bond between the heterocyclic units. The N − N distance between the nitrogen atoms involved in the intramolecular hydrogen bond (average distance 2.67 Å) is larger than the C − C

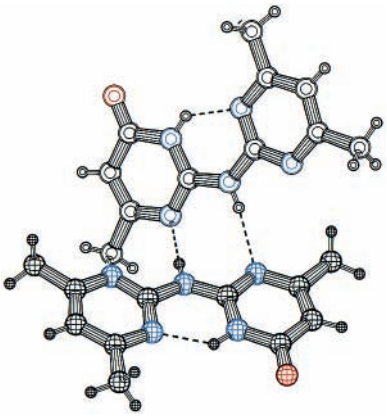


Figure 2. Pluton representation of single-crystal X-ray structure of compound **3a**. The dimer consists of both independent molecules.

distance between the atoms connected to the amino group (average distance 2.49 Å). This results in a nonlinear ADA array, with an N−N−N angle of 165.2° and 167.5° for the nonequivalent molecules in the unit cell. The molecule is also not fully planar; the planes of the rings are at an angle of 1.99(7)° and 4.69(7)° for the two independent molecules. These deviations from linearity may have a pronounced effect on the capability of **3a** to bind molecules with linear DAD arrays.

In the crystalline state two hydrogen bonds are observed between two distinct molecules of **3a**, indicating that interaction between molecules via hydrogen bonds is also likely in solution. Dimerization of **3a** and **3b** in $CDCl_3$ solution was determined with ^{1}H NMR dilution experiments, and both compounds were indeed found to self-associate (**3a** K_{dim} = 12 M^{-1}, **3b** K_{dim} = 9 M^{-1} in $CDCl_3$ at 298 K).

Nuclear Overhauser experiments using selective excitation[13] were performed to establish the tautomeric form of **3a** in $CDCl_3$ solution. No NOE effect was observed on the intramolecularly hydrogen-bonded proton when the pyrimidinone methyl group was excited, while a significant effect was observed upon excitation of the pyrimidine methyl groups. This indicates that the [3*H*] tautomer of **3a** is also favored in solution.

Complexation of **3a** and **3b** with compounds **4** and **5**, featuring DAD arrays of hydrogen-bonding sites, and with **6**, featuring a DDAD array, was investigated using ^{1}H NMR titration experiments. The results were compared with association constants of these compounds with *N*-1-propylthymine **7**, featuring a linear[14] ADA array (Figure 3).

The association constants are summarized in Table 1.

N-Propylthymine **7** binds to DAD molecules with little selectivity; K_a values range from 845 M^{-1} for the complex

(10) Curd, F. H. S.; Graham, W.; Rose, F. L. *J. Chem. Soc.* **1948**, 594−596.

(11) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. In *Advances in Heterocyclic Chemistry, the Tautomerism of Heterocycles*; Academic Press: New York, 1976.

(12) R_1 = 0.046, wR2 = 0.120, S = 1.04 for 337 parameters and 5297 reflections. The coordinates of the N−H hydrogen atoms have been refined.

(13) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302−324.

(14) Crystal structures of *N*-alkylthymines show a deviation from linearity of the array of 2−4°. (a) Kvick, A.; Koetzle, T. F.; Thomas, R. *J. Chem. Phys.* **1974**, *61*, 2711−2719. (b) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035−5036.

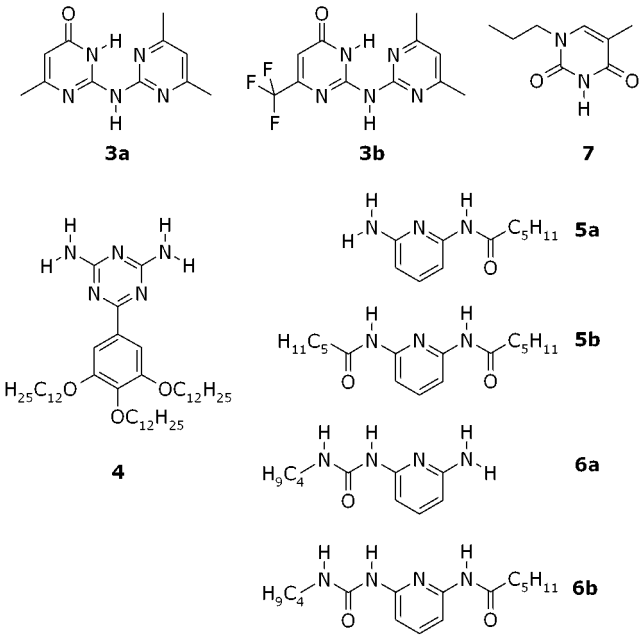


Figure 3. Compounds used in the DAD·ADA binding study, the upper three (**3a**, **3b**, and **7**) as ADA and the lower four (**4**, **5a**, **5b**, and **6**) as DAD hydrogen-bonding arrays.

with **4** to 460 M^{-1} for the complex with **5b**. Dipyridylamines **3a** and **3b**, on the other hand, show a remarkable selectivity for the complexation of triazine **4** (K_a = 230 and 225 M^{-1}, respectively) relative to the ureidopyridines **5a** and **5b**, which bind with a K_a less than 10 M^{-1}. Molecular models show that the formation of triply hydrogen bonded complexes of **3** with **5a** and **5b** is severely hampered by steric interactions of the (trifluoro)methyl groups in **3** with the substituents adjacent to the DAD arrays in **5**.

Complexation of **4** with **3a** is accompanied by a significant shift of the intramolecularly hydrogen bonded proton signal (CIS = 0.5 ppm), indicating that a significant adjustment of the structure of the dipyridylamine takes place upon binding of **4**.

Table 1. Association Constants in M^{-1} for Complexes of **3a**, **3b**, and **7** with **4**, **5**, and **6** Determined in $CDCl_3$ at 298 K

	7	**3a**	**3b**
4	845	230	225
5a	230[a]	<10	<10
5b	460[a]	<10	<10
6a	57	<10	<10
6b	110	<10	<10

[a] Data from ref 17.

Binding of **3** to DDAD arrays of pyridylureas **6** was investigated to establish whether complexation-induced tautomerization of **3** to the [1*H*] form with a complementary AADA array would occur. It has been reported that in the uncomplexed form pyridylureas have an intramolecular hydrogen bond,[15] which can, however, be broken upon complexation with a complementary guest.[16] The fact that the energetic penalty for disruption of the intramolecular hydrogen bond is relatively low is confirmed by the binding of **7** to **6b** with a K_a value of 110 M^{-1}, which is only a factor 4 lower than in the corresponding complex of **7** with **5b**. ^1H NMR titrations of **3a** and **3b** with pyridylureas **6** demonstrate, however, that binding between these molecules is weak (K_a < 10 M^{-1}), while a small complexation-induced shift of the intramolecularly hydrogen bonded proton signal indicates that **6** is not unfolded during complexation. We conclude that complexation of **3** in its [3*H*] tautomer is prevented by steric hindrance, while the penalty for tautomerization of both **3a** and **3b** to their [1*H*] forms is too high to allow significant binding as an AADA·DDAD complex.

In conclusion, we have shown that the dipyrimidin-2-ylamines **3**, which are easily accessible by two consecutive condensation reactions of biguanide,[10] display an ADA hydrogen-bonding array which is preorganized by a strong intramolecular hydrogen bond. Compounds **3** show high selectivity for the complexation of sterically unhindered complementary DAD arrays, based on the steric effect of substituents adjacent to the ADA array. Complexation-induced tautomerization to form an AADA array in the [1*H*] form of **3** was not observed. We continue to investigate the possibilities to bias the tautomeric equilibrium in derivatives of **3** in order to form a quadruple hydrogen-bonding AADA array.

Acknowledgment. Part of this investigation was supported by The Netherlands Foundation for Chemical Sciences (CW), with financial support from The Netherlands Organization for Scientific Research (NWO).

Supporting Information Available: Detailed synthetic procedures for compounds **3a**, **3b**, **5b** and **6** and crystallographic data (cif format) for compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016750A

(15) Sudha, L. V.; Sathyanarayana, D. N. *J. Mol. Struct.* **1984**, *125*, 89−96.
(16) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2000**, *122*, 3779−3780.
(17) Beijer, F. H. Cooperative Multiple Hydrogen Bonding in Supramolecular Chemistry. Thesis, Eindhoven University of Technology, 1998.