## Self-Association without Regard to Prototropy. A Heterocycle That Forms Extremely Stable Quadruply Hydrogen-Bonded Dimers

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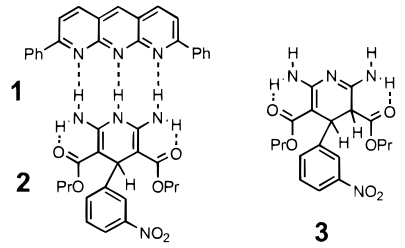
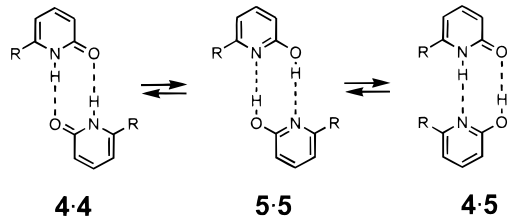
There is a continuing challenge to develop a diverse set of molecular subunits for supramolecular assembly.[1] Along these lines, we have a long-standing interest in heterocycles capable of forming robust hydrogen-bonded complexes in solution.[2,3] The use of heterocycles in this manner can, however, be complicated by prototropy.[4] Although undesirable protomers are often converted to the desired form by complexation, the observed association constants ($K_{assoc}$) are lowered, and the information content can be compromised. For example, complex **1·2**, containing an AAA·DDD (A, D = hydrogen-bond acceptor and donor) motif, is the strongest, neutral triply hydrogen-bonded complex known.[2,5] However, its stability is lowered because in addition to the desired 1,4-dihydro form (**2**), a significant portion of the dihydropyridine monomer exists as the noncomplementary 3,4-dihydro form (**3**) in chloroform-*d* ($CDCl_3$).[2a]

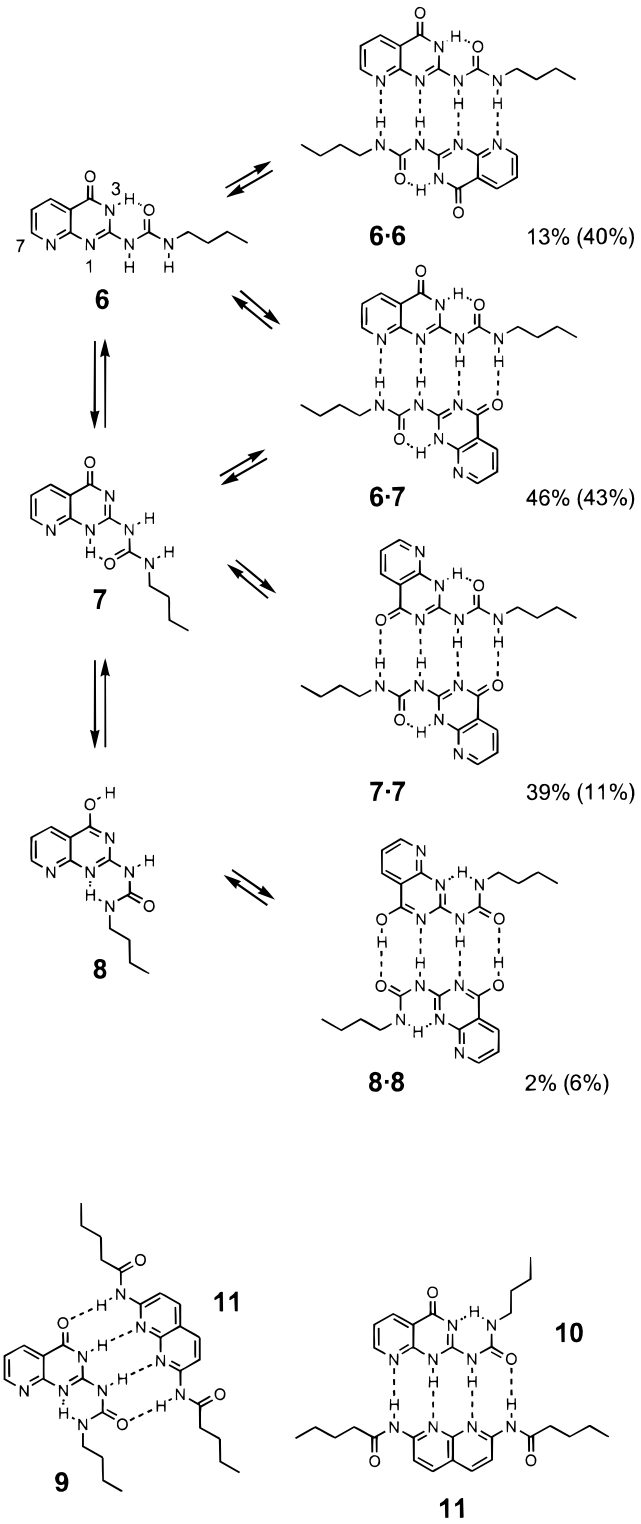



Interestingly, prototropy does not compromise the ability of all heterocycles to self-associate. For example, 2-pyridone can dimerize in its lactam (**4**) or lactim (**5**) form,[6] and form heterodimer **4·5**.[7] The spatial disposition of the R groups is similar in both homodimers, but a different arrangement is seen in **4·5**.




Herein we describe a new heterocycle (**6**) designed to contain a self-complementary AADD hydrogen-bonding array irrespective of its protomeric form and to maintain a similar spatial arrangement of an alkyl substituent in both homo- and heterodimers (i.e., Scheme 1).[8] Urea **6** was prepared by heating 2-amino-3*H*-pyrido(2,3-*d*)pyrimidin-4-one, available in two steps from commercially available 2,4-diamino-6-hydroxypyrimidine,[9,10] with butylisocyanate. Contrary to its precursors, **6** was soluble in nonpolar organic solvents, which suggested that the polar hydrogen-bonding groups were protected by dimerization.

**Scheme 1**




$^1$H NMR spectra in toluene-$d_8$ were consistent with the formation of **6·6**, **7·7**, and **6·7**. All NH signals were downfield and

(1) (a) Lehn, J.-M *Pure Appl. Chem.* **1994**, *66*, 1961−1966. (b) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229−2260. (c) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37−44. (d) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668.

(2) (a) Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *57*, 4010−4011. (b) Zimmerman, S. C.; Murray, T. J. *Philos. Trans. R. Soc. London, Ser. A* **1993**, *345:1674*, 49−56.

(3) For selected examples of robust host−guest complexes with four or more hydrogen bonds see: (a) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 5033−5035. (b) Chang, S.-K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318−1319. (c) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673−3674. (d) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055−8057. (e) Ghadiri, M. R.; Kobayashi, K.; Granja, J. R.; Chadha, R. K.; McRee, D. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 93−95.

(4) Prototropy, the most common type of tautomerism, involves a proton shift.

(5) For a charged DDD·AAA complex see: Bell, D. W.; Anslyn, E. V. *Tetrahedron* **1995**, *51*, 7161−7172.

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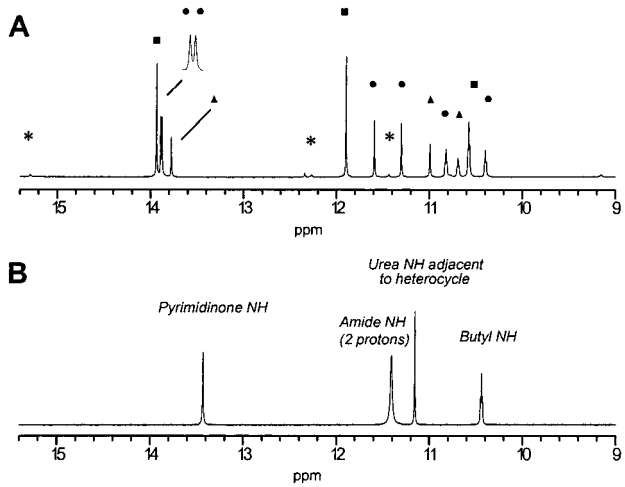


**Figure 1.** $^1$H NMR (NH region) spectrum of (A) **6**(**7**) in toluene-$d_8$ at −30 °C: ▲, **6·6**; ■, **7·7**; ●, **6·7**; ∗, **8·8**. (B) Complex **9**(**10**)**·11** in toluene-$d_8$ at 25 °C.

in the region expected for hydrogen-bonded dimers.[11] A minor set of peaks has been tentatively attributed to a small amount (ca. 2%) of **8·8**.[12] Most interestingly, at room temperature there were 12 major NH signals with concentration independent (20 mM to 48 $\mu$M) chemical shifts. These signals were fully resolved at −30 °C (Figure 1A), and three signals were attributed to each homodimer and six to heterodimer **6·7**. Tentative assignments of the dimers were made with difference NOE's. For studies carried out on a 20 mM solution of **6** in toluene-$d_8$ (room temperature), irradiation of the $\beta$-methylene protons led to an enhancement (ca. 2%) of the H-7 signal of **6** corresponding to the minor homodimer. Thus, the ratios of dimers in toluene-$d_8$ are tentatively given in Scheme 1, and those in $CDCl_3$ are given parenthetically.

Because hydrogen-bonded complexes have been traditionally studied in chloroform, dimerization was probed in $CDCl_3$. In fact, $CDCl_3$ spectra were similar to those obtained in toluene. The downfield NH chemical shifts were again indicative of dimerization, although the peaks were not as well resolved. There was no apparent change in protomeric ratio or chemical shifts across a broad concentration range (40 mM to 12 $\mu$M) in dilution studies performed on a 750 MHz spectrometer. Because the chemical shifts did not change and no new peaks appeared, only a lower limit to the dimerization constant, $K_{dimer} > 10^7$ M$^{-1}$, could be estimated. This is among the largest stability constants reported to date for a neutral, hydrogen-bonded species.[2,3,8]

To further assess dimer strength, a $CDCl_3$ solution of **6** (5 mM) was titrated with DMSO-$d_6$. This study along with qualitative dilution studies suggested that **6** and **7** dimerize in polar solvent mixtures containing up to ∼50% (v/v) DMSO-$d_6$. Quantitative binding studies were carried out in 5% (v/v) DMSO-$d_6$/$CDCl_3$. Contrary to spectra obtained in more nonpolar solvents, there were only two sets of NH signals (six peaks) at room temperature in 5% DMSO-$d_6$/$CDCl_3$. Upon cooling these signals could be resolved into three sets of peaks corresponding to **6·6**, **7·7**, and **6·7** which suggested that the signals for **6** in **6·6** and **6·7**, as well as for **7** in **7·7** and **6·7**, were averaged at room temperature. Protomerization, however, remained slow on the NMR time scale at ambient temperature. Upon dilution (20 mM to 80 $\mu$M, 25 °C) the NH signals moved upfield, and the protomeric ratio shifted from approximately 5:2 to 9:2 (**6**:**7**). The chemical shift data for the major protomer fit reasonably well to a 1:1 binding isotherm[13] ($K_{dimer}$ = 1100 M$^{-1}$) and indicated that the $K_{dimer}$ values for the major homodimer, **6·6**, and heterodimer, **6·7**, are similar. Moreover, the change in protomeric ratio observed upon dilution implied that the $K_{dimer}$ for **7·7** is slightly larger.[14]

Protomers **6** and **7** may also exist as noncomplementary conformers **9** and **10**.[15] To examine this potential equilibrium, **11** was synthesized because its DAAD hydrogen-bonding motif is complementary to the ADDA array in **9** and **10**.[10,16] Addition of a small excess of **11** to a toluene-$d_8$ or $CDCl_3$ solution of the dimers of **6** and **7** caused the robust dimers to fully dissociate, and a complex with **11** was observed (Figure 1B).[17] Enhancements (NOE) of the amide and heterocyclic urea NH signals were observed when irradiating the pyrimidinone NH and are indicative of the hydrogen-bond pattern in **9**(**10**)**·11**. In addition, a titration study carried out under conditions where dimerization of **6**(**7**) and **11** were minimal gave $K_{assoc}$ = 3033 M$^{-1}$ (5% DMSO-$d_6$/$CDCl_3$). That complex **9**(**10**)**·11** is as robust as the aforementioned dimers is unexpected when solely considering secondary hydrogen-bond interactions.[2,18] This finding could indicate a preference for conformers **9** and **10** or that there are inherently stronger primary interactions in **9·11** and **10·11**. Preliminary computational studies support the latter.

In conclusion, urea **6**(**7**) was designed to contain a self-complimentary hydrogen-bonding array irrespective of its protomeric form. Indeed, **6** and **7** associate forming exceedingly robust quadruply hydrogen-bonded hetero- and homodimers where the alkyl substituents maintain similar spatial arrangements. By inducing a conformational switch, **11** forms an even more stable complex with **9**(**10**). In comparison, we previously found that **1·2** had a $K_{assoc} \geq 10^5$ M$^{-1}$ in $CDCl_3$ and a $K_{assoc}$ of 201 M$^{-1}$ in 5% DMSO-$d_6$/$CDCl_3$. In both cases, the observed association constants ($K_{obs}$) were lower than the actual $K_{assoc}$ values because of a required protomeric shift prior to complexation.[2] The exceptional strength of the hydrogen-bonded complexes reported herein and the ready availability of both **6** and **11** make them ideal building blocks for the preparation of supramolecular oligomers and polymers. Efforts in this area will be reported in due course.

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(7) Almlöf, J.; Kvick, A.; Olovsson, I. *Acta Crystallogr., Sect. B* **1971**, *27*, 1201−1208.

(8) During the course of this study a related hydrogen-bonded dimer was reported: 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*, 1601−1604.

(9) Pfleiderer, M.; Pfleiderer, W. *Heterocycles* **1992**, *33*, 905−929.

(10) All compounds described herein gave correct elemental analyses and had spectral properties consistent with the assigned structures.

(11) Several nonassociating aryl and alkyl ureas were examined which possessed non-hydrogen-bonded NH signals in a region from ca. 3.5 to 7.5 ppm in chloroform-*d* and toluene-$d_8$.

(12) Establishing the protomeric forms is difficult because the standard approach of comparing with *O*- and *N*-methylated analogues cannot be used due to the internal hydrogen bond in **6**(**7**). $^1$H NMR, NOE, and IR data, as well as molecular mechanics (OPLS*) and semiempirical (AM1) calculations, are all consistent with **6** and **7** being the major protomers/conformers in the dimers. That the keto forms **6** and **7** dominate over hydroxy form **8** is consistent with studies of 2-pyridone (ref 5), isocytosine (Vranken, H.; Smets, J.; Maes, G.; Lapinski, L.; Nowak, M. J.; Adamowicz, L. *Spectrochim. Acta* **1994**, *50A*, 875−889 and references therein), and deazaguanine (Murray, T. J.; Zimmerman, S. C. Unpublished results).

(13) Wilcox, C. S. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Durr, H., Eds.; VCH: New York, 1991; pp 123−143.

(14) The $K_{dimer}$ for the minor homodimer is estimated to be approximately 3000 M$^{-1}$. The $K_{assoc}$ for the protomeric dimers in tetrahydrofuran-$d_8$ is ∼$10^4$ M$^{-1}$.

(15) For studies of hydrogen-bonded "foldamers" see: Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. Nowick, J. S.; Smith, E. M.; Pairish, M. *Chem. Soc. Rev.* **1996**, *25*, 401−415.

(16) Naphthyridine **11** was prepared by aminolysis of 2,7-dichloro-1,8-naphthyridine (Newkome, G. R.; Garbis, S. J.; Majestic, V. K.; Fronczek, F. R.; Chiari, G. *J. Org. Chem.* **1981**, *46*, 833−839) and subsequent reaction with valeric anhydride.

(17) The single set of peaks for **9**(**10**)**·11** observed in the $^1$H NMR spectrum indicate a strong preference for one of the complexes or rapid interconversion of the complexes on the NMR time scale. The slow protomerization observed for **6**(**7**), and variable-temperature $^1$H NMR (only five NH peaks at −70 °C), computational, and NOE studies of **9**(**10**)**·11** support selective formation of one of the complexes, possibly **9·11**.

(18) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810−2819.