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A New Quadruple Hydrogen-Bonding Module with a DDAA Array: Formation of a Stable Homodimer without Competition from Undesired Hydrogen-Bonded Dimers

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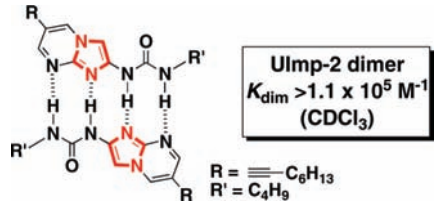
ABSTRACT



A new DDAA hydrogen-bonding module (Ulmp-2), based on a ureidoimidazo[1,2-a]pyrimidine structure, forms a highly stable homodimer (K_{dim} > 1.1 × 10^5 M^{-1} in $CDCl_3$) without competition from undesired hydrogen-bonded dimers.

Hydrogen bonding, which exhibits directionality, specificity, cooperativity, and reversibility, is one of the most useful interactions in the construction of well-defined supramolecular architectures.[1] Among these, the supramolecules obtained by quadruple hydrogen-bonding modules, such as supramolecular polymers, have become an important research topic in supramolecular chemistry.[2] Meijer and co-workers have developed ureidopyrimidinone derivatives (**UPy**) as well-known DDAA (D = hydrogen-bond donor, A = hydrogen-bond acceptor) modules (Figure 1A).[3] The linear quadruple hydrogen-bonding array of **UPy** is preorganized by intramolecular hydrogen bonding. Due to its high dimerization constant ($K_{dim} = 6 \times 10^7$ M^{-1} in $CHCl_3$) and synthetic accessibility, **UPy** has attracted considerable attention as a building block for various supramolecular architectures and materials.[2−4] However, the self-assembly of **UPy** is sometimes complicated due to the presence of three different tautomers. Two of these tautomers (keto and enol tautomers)

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can form the homodimers with different recognition systems and different dimerization constants, respectively.[3,5] On the other hand, deazapterin (**DeAP**), reported by Zimmerman and co-workers, is able to form stable homodimers in $CDCl_3$ ($K_{dim} > 10^7$ M^{-1}) via a DDAA array regardless of its tautomers (Figure 1B). This system consists of three major DDAA•AADD dimers including two homodimers and one heterodimer. In addition, unfortunately, a small amount (6%) of DADA•ADAD homodimer is also detected in $CDCl_3$.[6]

To address this tautomeric problem, Gong and co-workers reported a DDAA module that consisted of an oligoamide (K_{dim} = ~6.5×10^4 M^{-1} in $CDCl_3$).[7] More recently, to reduce the possible number of unfavorable tautomers, Sanjayan and co-workers reported a ureido pyrimidinedione derivative (K_{dim} = 1.2×10^4 M^{-1} in $CDCl_3$).[8] Although these modules are free from the problem of tautomers, K_{dim} values are only moderate.[9]

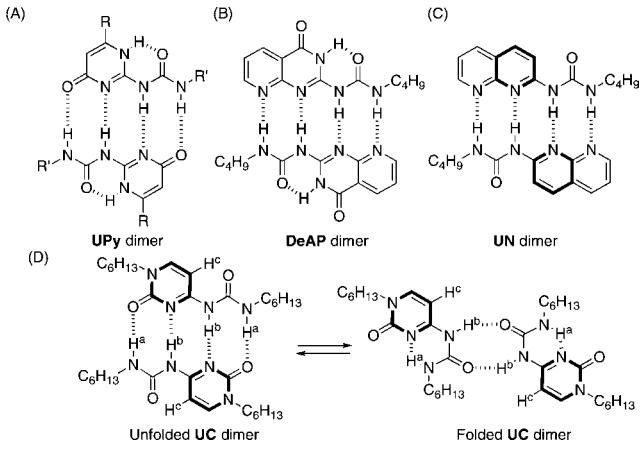

Figure 1. Homodimer structures of modules with a DDAA array: (A) **UPy**, (B) **DeAP**, (C) **UN**, and (D) **UC**.

An alternative approach to the tautomeric problem is removal of the intramolecular hydrogen-bonding site in the aromatic ring. However, the dimerization constant of the ureidonaphthyridine (**UN**) dimer (Figure 1C) (K_{dim} = 1.1 × 10^2 M^{-1} in $CDCl_3$) is much lower than the expected value[10] since modules that include pyridin-2-yl urea structures prefer a folded conformer, which is stabilized by intramolecular hydrogen bonding, rather than an unfolded conformer.[10,11] As another DDAA module that does not have an intramolecular hydrogen-bonding site, Hailes and co-workers developed ureidocytosine **UC** (Figure 1D).[12] Although **UC** can form a highly stable unfolded dimer in $CDCl_3$ ($K_{dim} > 2.5 \times 10^5$ M^{-1}), a small amount (5%) of the folded **UC** dimer is also present. Therefore, despite considerable progress in this field, the development of a DDAA module that forms a highly stable homodimer without competition from undesired dimers has been still difficult.

Recently, we found that the difference between six- and five-membered heteroaromatic rings was a predominant factor in the equilibrium between the unfolded and folded conformers of heterocyclic ureas with a DDA array.[13] We proposed that the six-membered heterocyclic ureas including pyridin-2-yl urea structures would be destabilized as an effect of steric repulsion due to the closer distance between H-3 on the pyridine ring and the oxygen on the urea carbonyl substitute. Thus, their conformational equilibria were biased toward the folded conformer stabilized by the intramolecular hydrogen bonding.[10,11] In contrast, some five-membered heterocyclic ureas, such as oxazol-4-yl urea derivatives, were capable of forming unfolded conformers, since the five-membered heterocyclic ureas decreased such unfavorable interactions (Figure 2A). We anticipated that quadruple hydrogen-bonding modules based on the five-membered heterocyclic urea structures should overcome both problems of a folded dimer and unfavorable tautomers.

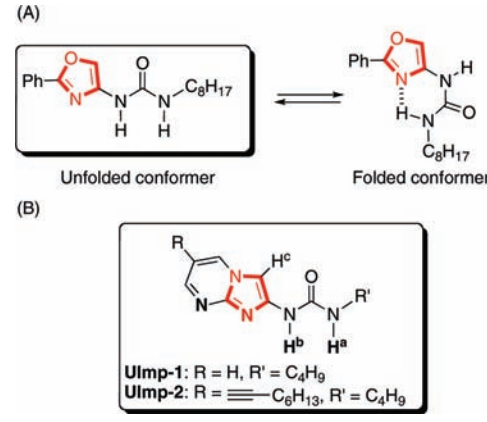

Figure 2. (A) Equilibrium between the unfolded and folded conformers in the oxazol-4-yl urea derivative and (B) structures of **UImp** with a DDAA array.

We report here a new DDAA module based on a ureidoimidazo[1,2-a]pyrimidine (**UImp**) structure (Figure 2B). To the best of our knowledge, this is the first example of a DDAA module forming a highly stable unfolded dimer

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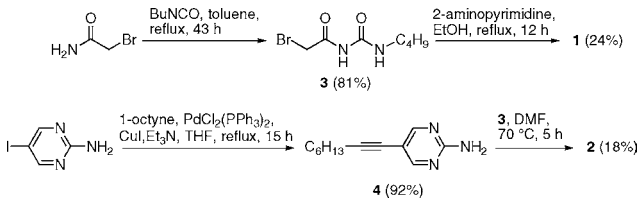
($K_{dim} > 1.1 \times 10^5$ M^{-1} in $CDCl_3$) without competition from undesired hydrogen-bonded dimers.

First, **UImp-1** (**1**) was synthesized in two steps from commercially available reagents (Scheme 1). Compound **3**, which was obtained by the reaction of 2-bromoacetamide with butylisocyanate, was condensed with 2-aminopyrimidine to give **1** in 24% yield.[14] However, we were unable to study the self-assembly of **1** in $CHCl_3$ because of poor solubility. To increase the solubility of **1** in $CHCl_3$, compound **4**, which was prepared from 2-amino-5-iodopyrimidine by a Sonogashira coupling, was condensed with **3** to give **UImp-2** (**2**) in 18% yield.[15]

Scheme 1. Synthesis of **UImp-1** and **-2**



The dimerization of **2** was investigated by ^{1}H NMR measurements. In the ^{1}H NMR spectrum of **2** (6.0 mM) in $CDCl_3$ at 25 °C (Figure 3A), the NH^a and NH^b proton signals were observed downfield at 7.13 and 12.24 ppm, and these protons gradually shifted upfield when the $CDCl_3$ solution of **2** was heated to 50 °C (Table 1). The NH^a and NH^b proton signals of **2** in a competitive hydrogen-bonding solvent such as DMSO-d_6 were observed at 6.54 and 9.11 ppm, which were more upfield than those in $CDCl_3$.[16] In the 2D-NOESY spectrum, the observation of the NOE correlation between the NH^a and NH^b protons of **2** in $CDCl_3$ suggested a linear arrangement of them. In addition, the ESI mass spectrum showed molecular ion peaks of **2•2** (*m*/*z*: 683.4 $[2M + H]^+$ and 705.5 $[2 M+ Na]^+$). These results indicate the formation of the unfolded dimer **2•2** in $CDCl_3$ by intermolecular hydrogen bonds involving both the NH^a and NH^b protons (Figure 4).[17] The formation of the unfolded **2a** (R = H, R′ = C_2H_5) dimer was also supported by the DFT calculation by the B3LYP method with a 6-31+G** basis set. The distance of NH^a···N (2.3 Å) was longer than that of NH^b···N (1.9 Å), which suggested that the NH^a···N hydrogen bond was weaker than the NH^b···N hydrogen bond. This calculation result corresponds to the large change in the chemical shift of the NH^b proton ($\Delta\delta$ = 3.13 ppm) between $CDCl_3$ and DMSO-d_6 at 25 °C (Table 1) relative to the small change of the NH^a proton ($\Delta\delta$ = 0.59 ppm).

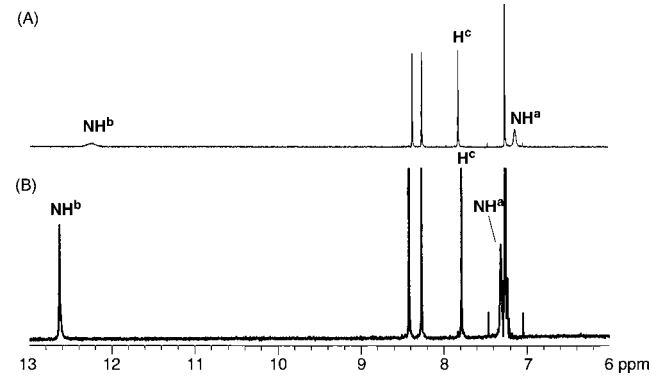


Figure 3. Partial ^{1}H NMR spectra (500 MHz) of **UImp-2** in $CDCl_3$: (A) at 25 °C and (B) at −50 °C.

Table 1. ^{1}H NMR Chemical Shift Data for **UImp-2**

solvent	temp (°C)	NH^a (ppm)	NH^b (ppm)
$CDCl_3$	50	7.07	11.93
$CDCl_3$	25	7.13	12.24
$CDCl_3$	−50	7.32	12.64
DMSO-d_6	25	6.54	9.11

When a $CDCl_3$ solution of **2** was diluted from 8.0 to 0.40 mM, no changes were observed in chemical shift values of NH^a and NH^b.[18] This shows that the dimerization of **2** persists at a low concentration and that the K_{dim} value should be high. Assuming that at this concentration there is less than 10% dissociation that is not detected by ^{1}H NMR,[3b] the K_{dim} of **2** was estimated to be a lower limit of 1.1×10^5 M^{-1}. The K_{dim} value of **2** is 1000-fold greater than that of **UN**[10] by replacement of the naphthyridine ring with the imidazo[1,2-a]pyrimidine ring.

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(15) Leonard, N. J.; Cruickshank, K. A. *J. Org. Chem.* **1985**, *50*, 2480.

(16) **UImp-1** and **-2** should exist mainly as monomers in DMSO-d_6 since concentration-dependent changes in the chemical shifts were not observed at each concentration range. **UImp-1** and **-2** were saturated at ~9.3 and ~1.8 mM in DMSO-d_6, respectively.

(17) Despite numerous attempts, crystals of **UImp-1** and **-2** suitable for X-ray analysis could not be obtained.

(18) The NH^b proton signal was not observed at concentrations below 0.4 mM due to broadening.

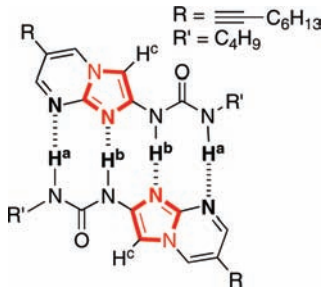

Figure 4. Structure of the unfolded dimer **2**·**2**.

To evaluate the existence of the folded dimer, **UImp-2** was examined by variable-temperature ^{1}H NMR measurement.[19] When the $CDCl_3$ solution of **2** (6.0 mM) was cooled to −50 °C, a splitting of proton signals or new peaks indicating the folded dimer were not observed (Figure 3B). A similar result was obtained with a dilute concentration of **2** (0.68 mM) at −50 °C.[20] In addition, the H^c proton signal of **2** in $CDCl_3$ (Figure 3A) was sharp as well as other aromatic protons on the imidazo[1,2-a]pyrimidine ring. If there was equilibrium between the unfolded and the folded dimers, the H^c proton signal would be broadened on the time scale of the NMR experiment.[10−12] Furthermore, a cross-peak between NH^b and H^c of **2** was not observed in the 2D-NOESY spectrum. These results suggest minimal contribution from the folded conformer in the $CDCl_3$ solution of **UImp-2**.

Hailes and co-workers reported that **UC** (Figure 1D) exists as a folded monomer in DMSO.[12] The NH^a proton signal of the folded **UC** monomer is observed at 8.96 ppm due to intramolecular hydrogen bonding. On the other hand, the NH^a of monomer **2**[16] in DMSO-d_6 was observed at 6.54 ppm, which was 2.42 ppm upfield compared to the corresponding NH^a of **UC**. In addition, the linear arrangement of NH^a and NH^b proton signals of **2** in DMSO-d_6 was suggested based on the 2D-NOESY spectrum. Therefore, the major conformer of the **UImp-2** monomer in DMSO-d_6 would be the unfolded one. The interesting difference in the major conformer between **UImp-2** and **UC** in DMSO-d_6 can be explained by the difference in six-membered and five-membered heterocyclic urea structures.[13]

In conclusion, we have described a new DDAA module, ureidoimidazo[1,2-a]pyrimidine (**UImp-2**), which forms a highly stable unfolded dimer via a DDAA array ($K_{dim} > 1.1 \times 10^5$ M^{-1} in $CDCl_3$) without competition from undesired dimers. This result shows the usefulness of quadruple hydrogen-bonding modules based on the five-membered heterocyclic urea structures. We are currently studying the application of **UImp** as a building block for the construction of supramolecular architectures.

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Supporting Information Available: Details of the synthesis and characterization for all new compounds, the complexation studies by NMR measurements, ESI-MS measurement, and DFT calculation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) At room temperature, both ^{1}H and ^{13}C NMR (500 and 125 MHz, respectively) spectra of **2** in $CDCl_3$ show a single set of well-resolved signals.

(20) Upon dilution of the concentration of **2** from 8.0 to 0.40 mM, the proton signal of H^c broadened. This might suggest the presence of a small amount of monomer **2** which can form both the folded and unfolded conformers.