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Novel multiply hydrogen-bonded heterodimers based on heterocyclic ureas. Folding and stability

Xiao-Qiang Li, Xi-Kui Jiang, Xiao-Zhong Wang and Zhan-Ting Li*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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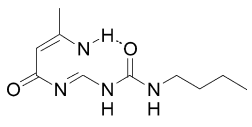
Abstract—A new series of multiply hydrogen-bonded heterodimers have been self-assembled in chloroform-*d*, with ureidopyrimidone derivatives **2** and **3** and 2,7-diamino-1,6-naphthyridine diamide **4** and ureas **5** and **6** as monomers. The self-associating behavior of the compounds and the binding modules of the new heterodimers have been investigated. New tri-center hydrogen bonds have been proposed to explain the stability of the new heterodimers. 2D-NOESY, COSY and temperature variable ^{1}H NMR studies revealed that all the new heterodimers are substantially more stable than the ureidopyrimidone-based quadruply hydrogen-bonded homodimers in chloroform-*d*. As a result, heterodimers **2·4** and **3·4** were assembled quantitatively, while heterodimers **2·5**, **3·5**, **2·6**, and **3·6** were formed in 80–85% yields. It is also revealed that intramolecular hydrogen bonds formed in monomers **5** and **6** reduce the stability of the corresponding heterodimers.

1. Introduction

Intermolecular interactions, particularly hydrogen bonds, are the base of many processes of supramolecular assembly and molecular recognition.[1,2] The strength of these interactions depends mainly on the number of the hydrogen bonds as well as the structural and geometric features of the monomers. With increasing number of the hydrogen bonds, molecular recognition usually becomes more specific and the corresponding supramolecular assemblies become more stable. Nevertheless, intramolecular hydrogen bonds,[3] secondary hydrogen-bonding interactions[4] and prototropic tautomerism[5] can also impose important influence on the binding stability. Systematic investigations of these discrete electronic and structural effects are crucial to control binding selectivity and future design of new binding motifs.

In recent years, quadruply hydrogen-bonded dimeric modules have attracted considerable attention because of their substantially increased stability and selectivity relative to doubly and triply hydrogen-bonded complexes.[3] Among others,[6] the ureidopyrimidone-based AADD (A: proton acceptor, D: proton donor) homodimeric binding motif **1·1**, reported initially by Meijer et al.,[3c] has extensive application in self-assembly of hydrogen bonded supramolecular polymers and oligomers with specific structures or functions[7] and used for regulating the self-assembly of a new series of highly stable donor–acceptor interaction-induced pseudo[2]rotaxanes.[8] We had been interested in developing new non-covalent approaches to dissociating this important homodimeric motif. We envisioned that study in this line would not only lead to the development of new hydrogen bonded assembling modules, but also provide potentially useful principles for regulating the structure and function of ureidopyrimidone-related supramolecular species. In this paper, we report that such kind of highly stable hydrogen-bonded homodimers can be fully or partially dissociated by readily available 2,7-diamino-1,6-naphthyridine amide and urea derivatives, to generate a new series of more robust heterodimers. ^{1}H NMR studies reveal that the stability of the novel heterodimers is remarkably affected by the structures of the 2,7-diamino-1,6-naphthyridine-derived monomers.



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2. Results and discussion

Five compounds **2-6** have been used as monomers to develop new multiply hydrogen-bonded heterodimers. Two new ureidopyrimidone derivatives **2** and **3** have been prepared conveniently in high yields from the reactions of commercially available **7** with the corresponding isocyantes **8a** or **8b** in hot pyridines, as shown in Scheme 1, according to the reported procedures for compounds with similar structures.[3c] Both molecules are substantially more soluble than **1** in organic solvents like chloroform and

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* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail address: ztli@mail.sioc.ac.cn

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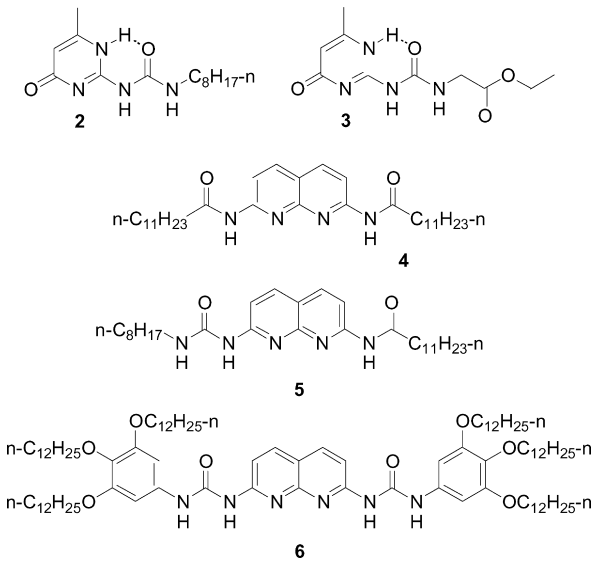
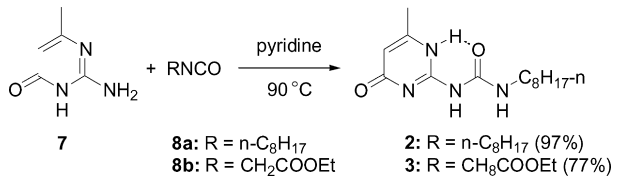
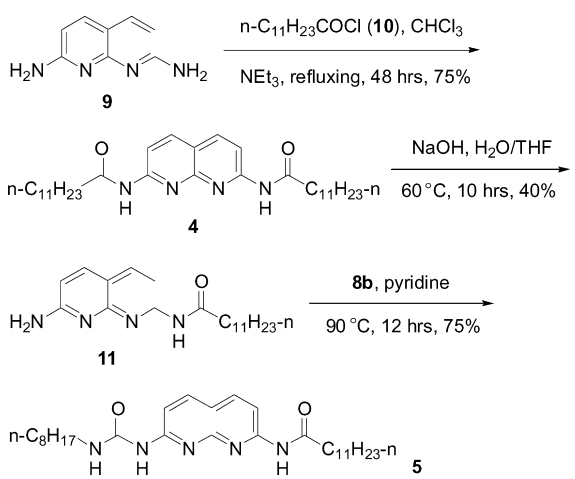


dichloromethane. The synthesis of compounds **4** and **5** is outlined in Scheme 2. Treatment of diamine **9**[3f,9] with excess of lauroyl chloride **10** in refluxing chloroform afforded **4** in good yield. Compound **4** was selectively hydrolyzed, with sodium hydroxide as base, to give amine **11** in 40% yield. The treatment of compound **11** with octyl isocyanate **8b** in hot pyridine led to the formation of compound **5** in 75% yield. Compound **11** could not be prepared directly from the reaction of **9** and **10**, possibly due to the fact that **11** was much more soluble than **9** in chloroform and consequently converted to **4** upon being generated. Compound **6** was prepared following the literature method.[3f] All the compounds have been characterized by ^{1}H NMR and mass spectroscopy and gave right elemental analysis.

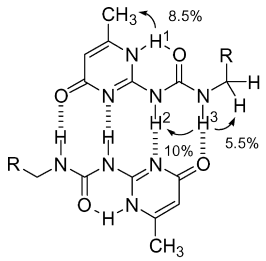


Scheme 1.

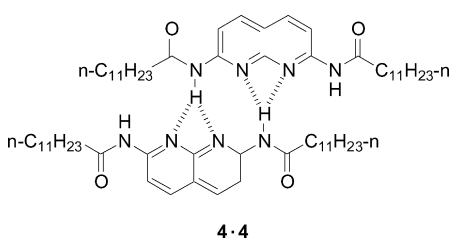


Scheme 2.

^{1}H NMR investigations revealed that compounds **2** and **3** exist exclusively as homodimers **2·2** and **3·3** in $CDCl_3$, respectively. The large downfield chemical shifts observed for NH protons (for **2**: 12.87 (H-1), 12.13 (H-2), 10.76 (H-3) ppm; for **3**: 12.82 (H-1), 12.13 (H-2), 10.72 (H-3) ppm) provided direct evidence for their involvement in strong hydrogen bonding. The assignment of the NH protons and the AADD hydrogen-bonding motif of the homodimers had been determined by the 2D-NOESY and COSY ^{1}H NMR spectra. No other binding modes were observed.[3c] Dilution of the solutions of the compounds in $CDCl_3$ to 1.0×10^{-5} M did not lead to observable dissociation, thus giving a lowest estimate of the binding constants of 1×10^7 M^{-1}. This result is in good agreement with the value obtained for a similar compound.[10] In order to check if the introduction of the ester group to **2** has important effect on the hydrogen bonding motif, quantitative binding studies in the mixed solvent of $CDCl_3$ and DMSO-d_6 (7%, v/v), a strong hydrogen bond acceptor solvent, were performed with the ^{1}H NMR dilution method,[11] which gave the K_{dim}'s to be ca. 780 and 850 M^{-1} for dimers **2·2** and **3·3**, respectively. These values are comparable within the experimental error of the ^{1}H NMR measurements.



The self-association behaviors of compounds **4** and **5** were then investigated in $CDCl_3$ solutions, also by the ^{1}H NMR dilution method. Important upfield chemical shifts ($\Delta\delta_{max}\approx0.11$ ppm) were observed for the NH signal of **4** upon dilution from 0.1 M to 0.4 mM. By fitting the data to a 1:1 binding isotherm, a K_{dim} of ca. 10 M^{-1} was observed for dimer **4·4** with the proposed binding motif.[12]



More complicated changes of chemical shifts of the NH and aromatic proton signals were observed from the ^{1}H NMR dilution experiments of **5**. Representative data are presented in Figure 1. The signals had been assigned based on the 2D-COSY and NOESY experiments (see Scheme 3). All the NH signals were substantially downfield (>9.97 ppm), indicating that these protons were involved in strong hydrogen bonding. Upon dilution from 0.1 M to 0.4 mM, the signals of both NH-1 ($\Delta\delta_{max}\approx1.58$ ppm) and NH-2 ($\Delta\delta_{max}\approx2.74$ ppm) shifted upfield remarkably, indicating

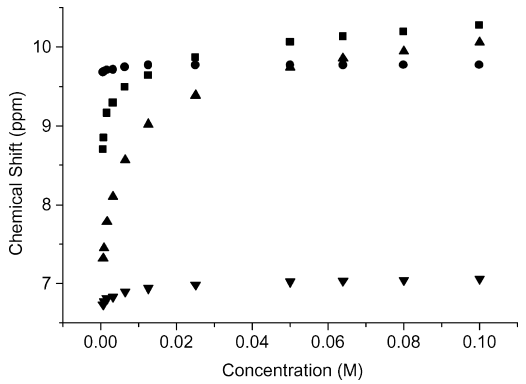
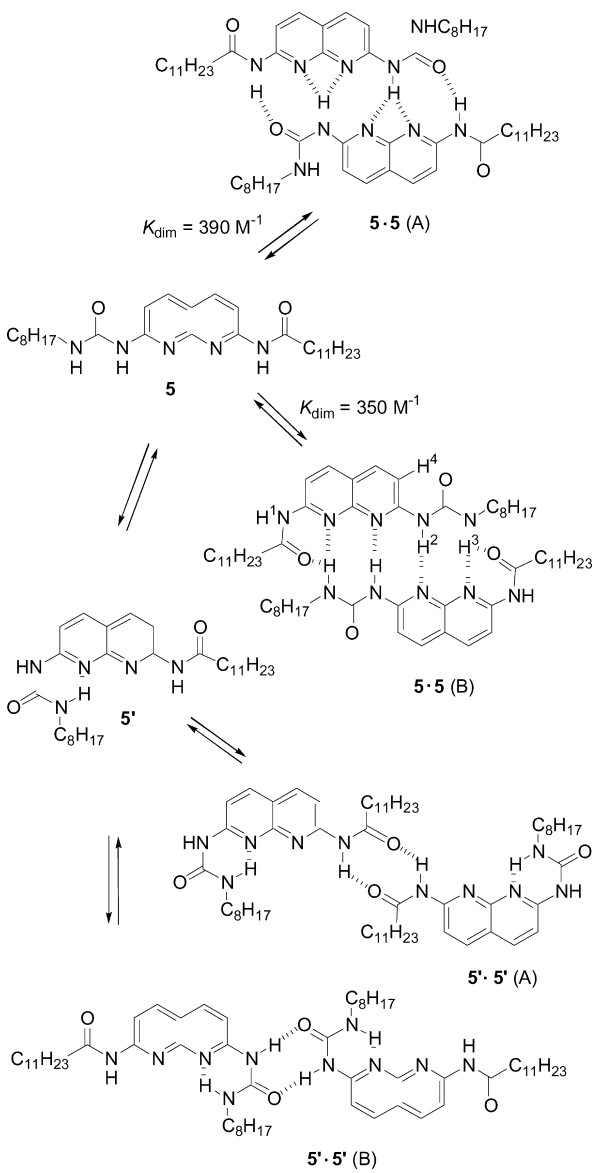


Figure 1. Chemical shift summaries of the dilution study of **5** in $CDCl_3$ from 0.1 M to 0.4 mM at 25 °C: NH-1 (■), NH-2 (▲), NH-3 (●), and H-4 (▼).



Scheme 3.

the formation of intramolecular hydrogen bonds. A fit of the data for NH-1 and NH-2 to a 1:1 binding isotherm gave a comparable K_{dim} of 390 (±40) M^{-1} and 350 (±30) M^{-1}, respectively. Both values are 20 times more than that of doubly hydrogen bonded dimer **4·4** and that of a pyridine-derived urea dimer (K_{dim}=16 M^{-1}),[3f] respectively. Therefore, obviously these binding constants could not be attributed to homodimers **5′·5′** (A) or **5′·5′** (B) (Scheme 3). We propose the formation of two tri-center multiply hydrogen bonded dimers **5·5** (A) and **5·5** (B) (Scheme 3) for the binding constants. Further evidence to support dimer **5·5** came from the fact that H-4 signal of the naphthyridine unit shifted upfield remarkably ($\Delta\delta_{max}$≈0.34 ppm, Figure 1) upon dilution, whereas the signals of other aromatic protons did not exhibit similar concentration dependence ($\Delta\delta_{max}$<0.04 ppm). This observation was consistent with the formation of dimer **5·5** since, in this dimer, H-4 was forced into the anisotropic deshielding area of the urea carbonyl group. The signal of the NH-3 proton was nearly concentration-independent ($\Delta\delta_{max}$≈0.09 ppm), implying that strong hydrogen bonding was always formed for this proton within the concentration range investigated, which could be reasonably attributed to an equilibrium between dimers **5·5** (A) and **5·5** (B) and folded monomer **5′**, which possesses an intramolecular hydrogen bond. Upon dilution, the dimers dissociated gradually into monomer **5′**, leading to upfield chemical shifting of the signals of both NH-1 and NH-2 but not that of NH-3.

Addition of 1 equiv. of **4** to a solution of **2** or **3** in $CDCl_3$ caused the highly stable homodimers **2·2** and **3·3** to fully dissociate and exclusively led to the formation of new complexes **2′·4** and **3′·4**, respectively, as evidenced by ^{1}H NMR spectra.[13] Partial ^{1}H NMR spectra of **2**, **4** and 1:1 mixture solution of **2** and **4** in $CDCl_3$ are presented in Figure 2. The amide proton signal of **4** shifted downfield ($\Delta\delta$ 3.05 ppm) substantially as a result of strong binding to **2**. The self-complementary 4[1*H*]-pyrimidinone conformer **2** isomerized completely to a non-complementary 4[3*H*]-pyrimidinone conformer **2′**. The latter possesses an ADDA quadruple hydrogen bond assay, which is complementary to the ADDA array in compound **4**.[14] The structure of the 4[3*H*]-pyrimidinone skeleton in **2′** was determined by 2D-NOESY technique, which revealed important enhancement of the heterocycle-linked methyl proton signal when irradiating the octyl-linked NH-3 proton. Pronounced intermolecular NOEs were also observed between NH-1 and NH-2 in **2′** and NH in **4**, supporting the complementary binding motif in heterodimer **2′·4**. Upon cooling or heating, all the NH signals moved noticeably, but no further splitting was observed, indicating that no new form of isomeric dimers were generated.

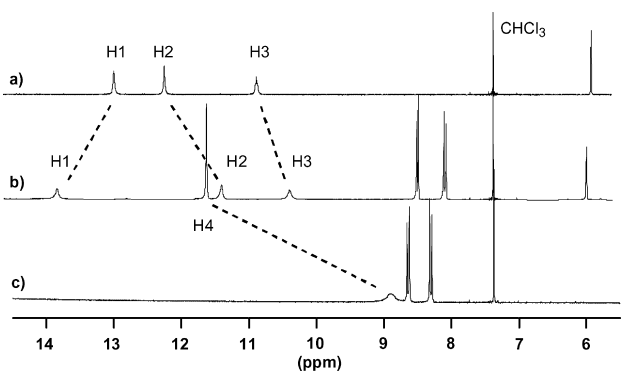
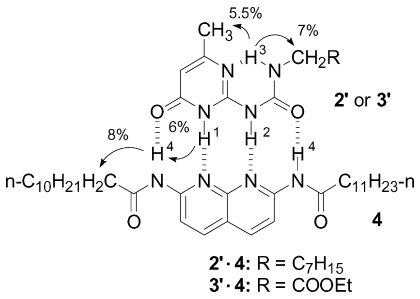


Figure 2. Partial ^{1}H NMR (300 MHz, 10 mM) of (a) **2**, (b) **2**+**4** (1:1), and (c) **4** in $CDCl_3$ at 25 °C.



Obviously it was impossible to determine the binding constant of **2′·4** in pure $CDCl_3$ with the ^1H NMR method, a quantitative binding study was performed in $CDCl_3$/DMSO-d_6 (7%, v/v). Upon dilution of the 1:1 mixture solution of **2** and **4** from 0.1 M to 0.2 mM, the NH signal of **4** moved upfield substantially (Fig. 3). The chemical shift data fit well to a 1:1 binding isotherm, giving a K_{dim}=1.3 (±0.17)×10^4 M^{-1}, which is substantially larger than that of homodimers **2·2** or **3·3**. By using the same principle, K_{dim} for **3′·4** in $CDCl_3$/DMSO-d_6 (7%, v/v) was also obtained to be 1.5 (±0.17)×10^4 M^{-1}, which is comparable to that of **2′·4**.

The binding behavior of **5** to **2** and **3** was then investigated. Adding 1 equiv. of **5** to **2** could also induce homodimer **2·2** to dissociate and generate the new heterodimer **2·5**. However, the dissociation of **2·2** was not exclusive and ca. 15% of **2** still existed as homodimer, as revealed by the ^1H NMR spectrum (Fig. 4(b)). The ratio of the dimers had been determined based on the integrating intensity of NH signals in the two tautomers of **2**. The DAAD tautomer of **2** in the new complex had been referred according to the NOESY experiment and also by comparing it with that of heterodimer **2′·4**. The signals of homodimer **2·2** could be assigned by changing the relative ratio of the two molecules. Very broad signals were exhibited for all the NH protons of **5**, which we attributed to the formation of two isomeric heterodimers **2′·5** (A) and **2′·5** (B) as a result of the unsymmetric structural feature of the two monomers. The fact that homodimer **2·2** exhibited sharp peaks for its NH's indicates that the protomeric isomerization between **2** and **2′** is slow on the NMR time scale. The existence of two isomeric heterodimers A and B had been proved by temperature variable ^1H NMR experiments. For example,

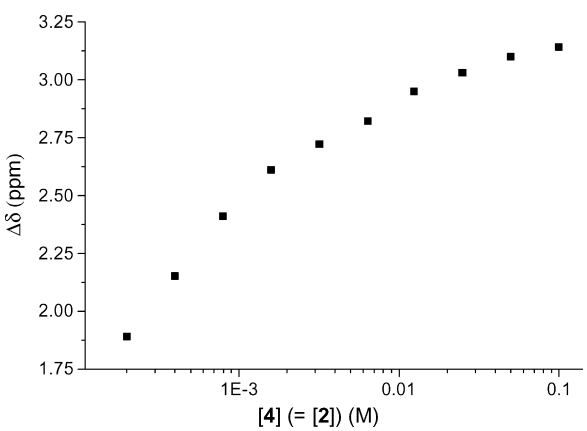


Figure 3. Plot of Δδ of NH signal of **4** upon dilution of the 1:1 mixture solution of **2** and **4** (0.1 M to 0.2 mM) in $CDCl_3$/DMSO-d_6 (7%, v/v) at 25 °C.

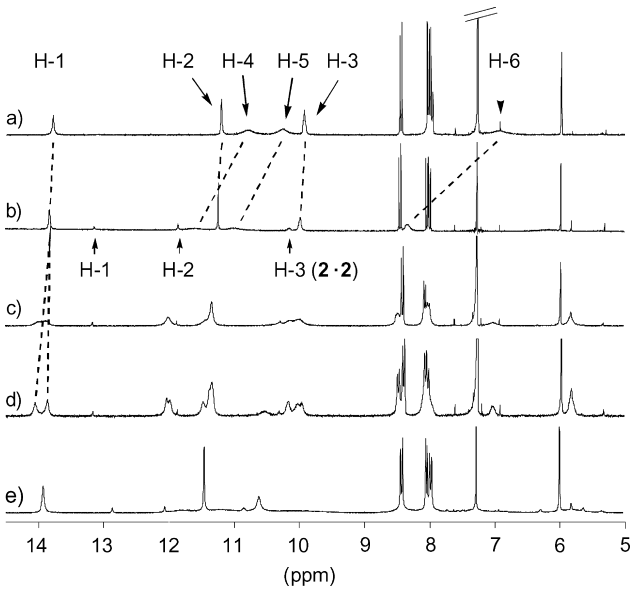
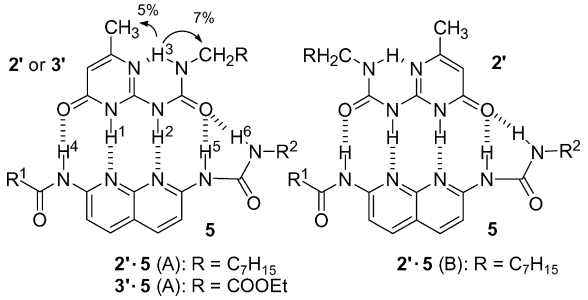


Figure 4. Partial ^1H NMR spectra (300 MHz) of a solution of **3** and **5** (1:1, 4.0 mM) in $CDCl_3$ at 50 °C (a), 25 °C (b), −30 °C (c) and −40 °C (d) and a solution of **3** and **5** (1:1, 4.0 mM) at 25 °C.

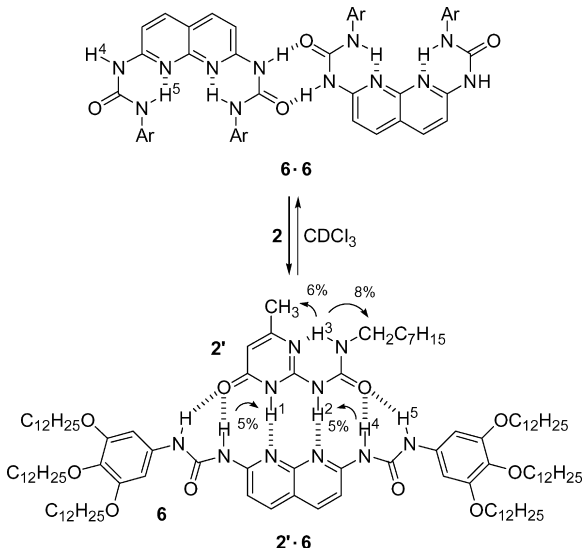
increasing the solution temperature to 50 °C led to pronouncedly sharpening of the NH signals (Fig. 4(a)), suggesting an increased exchange process between dimers A and B, whereas reducing the solution temperature to −40 °C induced the NH-1 to split (Fig. 4(d)), clearly indicating that the two isomers transformed into each other very slowly on the NMR time scale. The value of the corresponding free energy of exchange Δ*G* was determined to be ca. 9.5 kJ/mol based on the coalescence method.[15] Reducing temperature also facilitated the formation of heterodimers. Thus, at −40 °C, ca. 92% (based on the integrating intensity of NH-1) of compound **2** existed in the form of heterodimers (Fig. 4(d)).



Similar ^1H NMR spectral pattern was exhibited for the solution of **3** and **5** in $CDCl_3$ (1:1, Fig. 4(e)), suggesting the formation of heterodimer **3·5** (in ca. 80% yield based on integrating intensity of **3** and **3′**) with the same DAAD-ADDA binding module as that of **2·5**. Adding DMSO-d_6 to the solution of the 1:1 mixtures of **3** and **5** in $CDCl_3$ also promoted the formation of heterodimers (ca. 90% of **3·5** formed in $CDCl_3$/DMSO-d_6 (7%, v/v)). Since the formations of both heterodimers **2·5** and **3·5** were not quantitative and the resolution of the NH signals of compound **5** was very low, the binding constants of these heterodimers in $CDCl_3$/DMSO-d_6 (7%, v/v) could not be determined by ^1H NMR titration or dilution method. Nevertheless, the comparison of the binding behavior of **4** and **5** to **2** or **3** in

$CDCl_3$ reveals that heterodimers **2·4** and **3·4** are obviously more stable than dimers **2·5** and **3·5**. This result can be reasonably ascribed to the larger self-binding ability of **5** relative to **4**.

Previously, Zimmerman et al. had reported that compound **6** folded completely and self-associated through a doubly hydrogen bonded motif with a K_{dim}=95 M^{-1} in $CDCl_3$, as shown in Scheme 4.[3f] To explore if this highly stable folding conformation could be broken to form new heterodimers, ^1H NMR spectroscopic studies were carried out for the solutions of the mixtures of **6** with **2** and **3** in $CDCl_3$. Representative spectra are provided in Figure 5. It was found that ca. 80% of folded **6** were unfolded (based on the integrating intensity of NH-1 of **6** or pyrimidone proton of **2**), to afford the six hydrogen bond-driven heterodimer **2′·6**. This result implies that the stability of dimer **2′·6** is comparable to that of dimer **2′·5** or **3′·5**. Assignments of the peaks and the ADDA binding motif of **2** were achieved



Scheme 4.

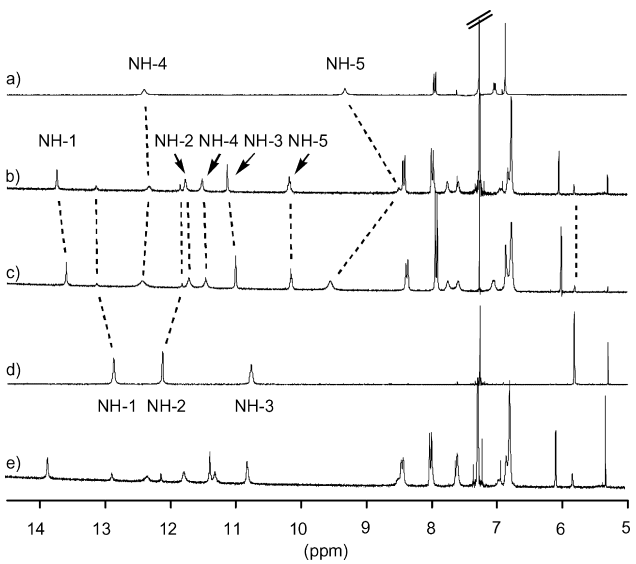


Figure 5. Partial ^1H NMR spectra (300 MHz) in $CDCl_3$ at 25 °C: (a) **6** (4.0 mM), (b) **2**+**6** (1:1, 4.0 mM), (c) **2** (4.0 mM)+**6** (8.0 mM), (d) **2** (4.0 mM), and (e) **3**+**6** (1:1, 4.0 mM).

by 2D-COSY and NOESY techniques (Scheme 4), together with changing the ratio of the monomers (Fig. 5(c)). As observed for the system of **2** and **5**, the remaining homodimer **2·2** also exhibited sharp NH peaks, suggesting that the transformation between the two tautomers of **2** in the two different dimers was slow on the NMR time scale. There are two points that support the formation of the intermolecular hydrogen bonds of NH-5 of **6** with the carbonyl oxygen of **2** in the complex (Scheme 4). First, this peak shifted downfield substantially ($\Delta\delta\approx$0.86 ppm) compared to that in pure **6** at the same concentration. Second, the formation of heterodimer **2′·6** required that the two intramolecular hydrogen bonds in folded **6** were broken, while formation of **2′·5** needed breaking of only one intramolecular hydrogen bond in folded **5**. Nevertheless, dimers **2′·6** and **2′·5** exhibited comparable stability, implying that additional hydrogen bonds, that is, those between NH-5 of **6** and the carbonyl oxygen of **2** were formed. Temperature variable ^1H NMR experiments for the 1:1 solution of **2** and **6** in $CDCl_3$ (4.0 mM, 50 to −40 °C) revealed no new peaks, implying that no new kind of dimers were formed.

Similar ^1H NMR spectral pattern was observed for the system of 1:1 mixtures solution of **3** and **6** (Fig. 5(e)) in $CDCl_3$. The result suggested that the heterodimer **3·6** with the structure similar to that of **2′·6** was also formed (in ca. 82% yield based on ^1H NMR integrating intensity). Attempt to determine the binding constants of both heterodimers in $CDCl_3$/DMSO-d_6 (7%, v/v) with the ^1H NMR dilution method was proved impossible due to rapidly reduced resolution at lowered concentrations.

3. Conclusion

We have reported the self-assembly and characterizations of a new series of multiply hydrogen-bonded heterodimers based on readily available ureidopyrimidones and 2,7-diamino-1,6-naphthyridine amides and ureas. New tri-center hydrogen bonds and exchanging processes between geometrically isomeric dimers have been revealed in the new heterodimers. All the new heterodimers are substantially more stable than the AADD quadruply hydrogen-bonded homodimers reported by Meijer et al. The result demonstrates that the stability of the heterodimers from self-associated heterocyclic monomers is remarkably affected by the number of intermolecular hydrogen bonds formed and the number of intramolecular hydrogen bonds formed in the monomers. Careful consideration of a balance between increasing intermolecular and intramolecular hydrogen bonds are important for future design of new stable hydrogen bonded assemblies.

4. Experimental

4.1. General methods

Melting points are uncorrected. All reactions were carried out under an atmosphere of nitrogen. The ^1H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts

per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use following standard procedures.

4.1.1. 1-(6-Methyl-4-oxo-1,4-dihydro-pyrimidin-2-yl)-3-octyl-urea (2). A suspension of 2-amino-4-hydroxy-6-methylpyrimidine **7** (0.50 g, 0.40 mmol) and octyl isocyanate **8a** (0.62 g, 0.40 mmol) in THF (120 mL) was heated at 90 °C for 48 h. After work-up, the crude product was purified by column chromatography (dichloromethane/methanol 10:1) to afford compound **2** (1.08 g, 97%) as a white solid. Mp 171–173 °C. ^{1}H NMR: δ 0.86 (t, J=6.6 Hz, 3H), 1.25–1.30 (m, 10H), 1.54–1.61 (m, 2H), 2.22 (s, 3H), 3.20–3.26 (m, 2H), 5.81 (s, 1H), 10.13 (s, 1H, NH), 11.85 (s, 1H, NH), 13.14 (s, 1H, NH). MS (EI) *m/z*: 280 [M$^+$]. Anal. calcd for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.84; H, 8.60; N, 19.97.

4.1.2. [3-(6-Methyl-4-oxo-1,4-dihydro-pyrimidin-2-yl)-ureido]-acetic acid ethyl ester (3). A mixture of compound **7** (0.50 g, 4.00 mmol) and ethyl 2-isocyanoglycinate **8b**[16] (0.50 g, 3.91 mmol) in dried pyridine (20 mL) was stirred at 90 °C for 12 h. Then, the solvent was removed under reduced pressure. The resulting residue was washed with ether thoroughly to give a white solid, which was subjected to flash chromatography (dichloromethane/methanol, 10:1) to give compound **3** as a white solid (0.77 g, 78%). Mp 197–199 °C. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J=7.6 Hz, 3H), 2.22 (s, 3H), 3.99 (d, J=7.6 Hz, 2H), 4.12–4.25 (m, 2H), 5.82 (s, 1H), 10.76 (s, 1H), 12.13 (s, 1H), 12.87 (s, 1H). MS (EI) *m/z*: 254 [M$^+$]. Anal. calcd for $C_{10}H_{14}N_4O_4$: C 47.24, H 5.55, N 22.03. Found: C 47.17, H 5.50, N 22.26.

4.1.3. Dodecanoic acid (7-dodecanoylamino-[1,8]naphthyridin-2-yl)-amide (4). To a stirred suspension of 2,7-diamino-1,8-naphthyridine **9** (1.60 g, 10.0 mmol) in chloroform (200 mL) were added triethylamine (5 mL), *N*,*N*′-dimethyl-4-aminopyridine (DMAP, 61 mg, 5%), and lauroyl chloride **10** (5.48 g, 25.0 mmol), respectively. The mixture was heated under reflux for 72 h. Upon cooling to room temperature, the solid was filtrated off and washed with chloroform (50 mL). The combined organic phase was washed with dilute aqueous hydrochloride solution (1 N, 2×50 mL), aqueous sodium carbonate solution (1 N, 2×50 mL), water (30 mL), brine (50 mL), and dried over magnesium sulfate. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (dichloromethane/ethyl acetate 5:1). The title compound was obtained as a colorless solid in 75% yield. Mp 130–132 °C; ^{1}H NMR ($CDCl_3$): δ 0.89 (m, 3H), 1.42–1.20 (m, 16H), 1.75 (m, 4H), 2.43 (t, J=6.8 Hz, 4H), 8.15 (d, J=6.1 Hz, 2H), 8.17 (s, 2H), 8.42 (d, J=6.1 Hz, 2H). MS (FAB) *m/z*: 525 [M$^+$ +H]. Anal. calcd for $C_{32}H_{52}N_4O_2$: C 73.24, H 9.99, N 10.68. Found: C 73.15, H 10.07, N 10.75.

4.1.4. Dodecanoic acid (7-amino-[1,8]naphthyridin-2-yl)-amide (11). To a stirred solution of compound **4** (0.80 g, 1.60 mmol) in tetrahydrofuran (80 mL) was added sodium hydroxide (64.0 mg, 1.60 mmol). The mixture was heated under reflux for 6 h. Then, the solvent was removed under reduced pressure. The resulting residue was triturated with dichloromethane (400 mL) and the organic phase was washed with water (50 mL×2), saturated brine solution (50 mL), and dried over sodium sulfate. After the solvent was removed in vacuo, the crude product was purified by column chromatography (dichloromethane/ethyl acetate 5:1), to afford compound **11** (0.23 g, 40%) as a white solid and un-reacted compound **4** (0.32 g, 40%). Compound **11**. Mp 140–141 °C. ^{1}H NMR: δ 0.87 (t, J=6.3 Hz, 3H), 1.25–1.37 (m, 10H), 1.68–1.77 (m, 2H), 2.45 (t, J=7.5 Hz, 2H), 5.33 (s, 2H, NH_2), 6.66 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 8.20 (d, J=8.7 Hz, 1H), 8.28 (s, 1H, NH). MS (EI) *m/z*: 342 [M$^+$]. Anal. calcd for $C_{20}H_{30}N_4O$: C, 70.14; H, 8.82; N, 16.36. Found: C, 69.95; H, 8.91; N, 16.15.

4.1.5. Dodecanoic acid [7-(3-octyl-ureido)-[1,8]naphthyridin-2-yl]-amide (5). A suspension of compounds **11** (0.14 g, 0.40 mmol) and **8a** (0.12 g, 0.80 mmol) in tetrahydrofuran (50 mL) was heated under reflux for 6 h. The solvent was then removed under reduced pressure. The resulting residue was washed with ether thoroughly and then purified by column chromatography (dichloromethane/ethyl acetate 5:1), to afford compound **5** (0.20 g, 98%) as a white solid. Mp 166–167 °C. ^{1}H NMR: δ 0.83–0.89 (m, 6H), 1.24–1.35 (m, 24H), 1.60–1.76 (m, 6H), 2.45 (t, J=7.8 Hz, 2H), 3.35–3.40 (m, 2H), 6.96 (d, J=8.7 Hz, 1H), 7.93 (d, J=8.7 Hz, 1H), 8.04 (d, J=8.7 Hz, 1H), 8.38 (d, J=8.7 Hz, 1H), 8.77(s, 1H, NH), 9.12 (s, 1H, NH), 9.75 (s, 1H, NH). MS (EI) *m/z*: 497 [M$^+$]. Anal. calcd for $C_{29}H_{47}N_5O_2$: C, 69.98; H, 9.52; N, 14.07. Found: C, 70.02; H, 9.63; N, 14.01.

4.1.6. 1-(3,4,5-Tris-dodecyloxy-phenyl)-3-{7-[3-(3,4,5-tris-dodecyloxy-phenyl)-ureido]-[1,8]naphthyridin-2-yl}-urea (6). A solution of 3,4,5-tris-dodecyloxy-benzoyl azide[3f,17] (1.0 g, 1.33 mmol) in 20 mL of toluene was heated at 100 °C for 5 h. The solution was cooled and the solvent was removed under reduced pressure to afford the corresponding isocyanate, which was used in the next step without further purification. The above isocyanate (0.50 g, 0.75 mmol), naphthyridine **9** (47 mg, 0.35 mmol), and triethylamine (1 mL) were added to DMF (5 mL) with stirring at room temperature. The mixture was heated at 90 °C for 12 h. The solvent was then distilled under reduced pressure and the residue was triturated with chloroform (100 mL). After work-up, the crude product was purified by column chromatography (dichloromethane/methanol 20:1) to afford compound **6** (0.21 g, 40%) as a yellow powder. Mp >225 °C [223 °C[3f]]. ^{1}H NMR ($CDCl_3$): δ 0.80–0.83 (m, 18H), 1.30–1.33 (m, 104H), 1.48–1.51 (m, 4H), 1.68–1.72 (m, 12H), 3.68 (t, J=5.5 Hz, 8H), 3.92 (t, J=6.5 Hz, 4H), 6.89 (s, 4H), 7.08 (d, J=8.0 Hz, 2H), 7.97 (d, J=8.0 Hz, 2H), 9.82 (s, 2H), 12.50 (s, 2H). MS (maldi-tof) *m/z*: 1506 [M$^+$+H].

4.2. Binding studies

All ^{1}H NMR binding studies were carried out at 25 °C. Chloroform-*d* used in binding studies was passed through a short column of dry, activated basic alumina prior to use. DMSO-d_6 was used as provided without further purification. Volumetric flasks and syringes used in preparing solutions

were washed with dried dichloromethane and dried in vacuum before use. Samples (usually 0.6 mL) were prepared from stock solutions, transferred to the NMR tubes and diluted accordingly with syringes. For one series, usually 10–20 samples were prepared and binding constants reported are the average of two or three experiments, which were obtained by fitting chemical shift change data to 1:1 binding isotherms with standard non-linear curve-fitting procedures.[11] The non-linear equations were derived from mass-balance equations, the relationship between the concentrations of free and complexed sample and the weighted chemical shifts under the condition of rapid exchange.[11]

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References and notes

1. (a) Vögtle, F. *Supramolecular chemistry*; Wiley: Chichester, 1991. (b) Lehn, J.-M. *Supramolecular chemistry*; VCH: Weinheim, 1995. (c) Lindoy, L. F.; Atkinson, I. M. *Self-assembly in supramolecular systems*; Cambridge, RSC: Cambridge, 2000.
2. (a) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63. (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382. (c) Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139. (d) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488.
3. (a) Lüning, U.; Kühl, C. *Tetrahedron Lett.* **1998**, *38*, 5735. (b) Sessler, J. L.; Wang, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1726. (c) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761. (d) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710. (e) Gong, B.; Yang, Y.; Zeng, H.; Skrzypczak-Jankunn, E.; Kim, Y. W.; Zhu, J.; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607. (f) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475. (g) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128.
4. (a) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1991**, *113*, 2810. (b) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810.
5. (a) Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010. (b) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710.
6. (a) Corbin, P. S.; Lawless, L. J.; Li, Z.-T.; Ma, Y.; Witmer, M. J.; Zimmerman, S. C. *Proc. Natl Acad. Sci. USA* **2002**, *99*, 5099. (b) Zeng, H.; Yang, X.; Flowers, R. A., II.; Gong, B. *J. Am. Chem. Soc.* **2002**, *124*, 2903.
7. (a) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071. (b) Schmuck, C.; Wienand, W. *Angew. Chem., Int. Ed.* **2001**, *40*, 4363. (c) Qi, Z.-Q.; Shao, X.-B.; Zhao, X.; Li, X.-Q.; Wang, X.-Z.; Zhang, W.-X.; Jiang, X.-K.; Li, Z.-T. *Chin. J. Org. Chem.* **2003**, *23*, 403.
8. Wang, X.-Z.; Li, X.-Q.; Chen, Y.-Q.; Shao, X.-B.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T. *Chem. Eur. J.* **2003**, *9*, 2904.
9. Newkome, G. R.; Garbis, S. J.; Majestic, V. K.; Fronczek, F. R.; Chiari, G. *J. Org. Chem.* **1981**, *46*, 833.
10. Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487.
11. (a) Conners, K. A. *Binding constants: the measurement of molecular complex stability*; Wiley: New York, 1987. (b) Wilcox, C. S. In *Frontiers in supramolecular organic chemistry and photochemistry*; Schneider, H. J., Dürr, H., Eds.; VCH: New York, 1991; p 123.
12. A K_{dim} of less than 5 M^{-1} had been reported for a molecule with similar structure, see Ref. 3f.
13. Complex **2′·4** had been mentioned, without detailed characterization or quantitative binding study, in a previous paper (Ref. 8).
14. An example of complexation-induced isomerization has been reported for 3*H*-pyrido-(2,3-*d*)pyrimidin-4-one-2-urea derivatives, see Ref. 3d.
15. Sandstroom, J. *Dynamic NMR spectroscopy* Academic: New York, 1982; Chapter 6.
16. Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929.
17. Brown, E.; Moudachirou, M. *Tetrahedron* **1994**, *50*, 10309.