

Five-membered heterocyclic ureas suitable for the donor–donor–acceptor hydrogen-bonding modules

Yosuke Hisamatsu*, Yuki Fukumi, Naohiro Shirai, Shin-ichi Ikeda, Kazunori Odashima*

Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho, Nagoya 467-8603, Japan

Received 29 November 2007; revised 8 January 2008; accepted 15 January 2008

Available online 19 January 2008

Abstract

Five-membered heterocyclic ureas are capable of forming the unfolded conformer without preorganization by using the intramolecular hydrogen bond, and are suitable for the DDA hydrogen-bonding modules. In contrast, six-membered heterocyclic ureas are destabilized by an effect of steric repulsion due to the closer distance of $\text{CH}^\cdots\text{O}$ and their conformational equilibria are biased toward the stable folded conformer.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Five-membered heterocyclic urea; Multiple hydrogen bond; DDA hydrogen-bonding module; Oxazol-4-yl urea; Pyrid-2-yl urea

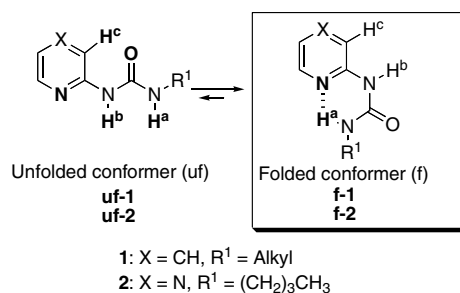
Both inter- and intramolecular hydrogen-bonding interactions play important roles in regulating the structure and the function of chemical and biological systems.¹ In supramolecular chemistry, the development of multiple hydrogen-bonding modules as building blocks for well-defined synthetic supramolecular structures and materials has attracted considerable attention.² Heterocyclic ureas including the pyrid-2-yl urea structure have been expected to provide a variety of hydrogen-bonding arrays to form stable homo- or hetero-dimers.³ However, their complexation ability is much lower than the expected values^{3,4} due to a conformational problem inherent in the pyrid-2-yl urea structures. The pyrid-2-yl urea derivatives **1** prefer a folded conformer **f-1**, which is stabilized by an intramolecular hydrogen bond, rather than an unfolded conformer **uf-1**.⁵ Thus, the stability constants of **1** to complementary guest molecules such as 1-octylcytosine^{3a} or 2-acylamino-1,8-naphthyridine derivative^{3b} are very low in CDCl_3 ($K_s = 3.0 \times 10^1 \text{ M}^{-1}$). To solve the conformational problem of the pyrid-2-yl urea structure, the unfolded conformer is

preorganized by the intramolecular hydrogen bond.⁶ Although the concept of preorganization has been widely accepted, the complexation systems are sometimes complicated by all the possible conformers/tautomers.⁶ We have been interested in the development of new heterocyclic ureas suitable for the DDA hydrogen-bonding modules without preorganization by using the intramolecular hydrogen bond.⁷

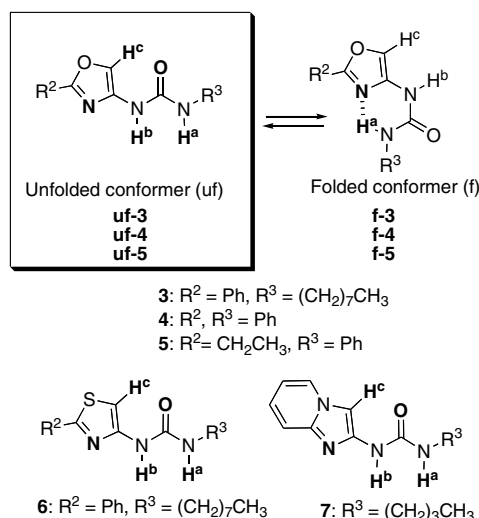
We wish to report herein the development of new five-membered heterocyclic ureas such as oxazol-4-yl urea, thiazol-4-yl urea, and imidazo[1,2-*a*]pyrid-2-yl urea. They are capable of forming the unfolded conformer, and suitable for the DDA hydrogen-bonding modules. Furthermore, we have found that the difference in ring size (six- or five-membered ring) would be the predominant factor in the equilibrium between the unfolded and the folded conformers of the heterocyclic ureas. The six- and five-membered heterocyclic ureas **2–7** used in the present study are shown in [Schemes 1 and 2](#).

First, it was expected that pyraz-2-yl urea **2** might be capable of forming **uf-2** by weakening the strength of the intramolecular hydrogen-bonding, because the $\text{p}K_a$ value of the conjugated acid of pyrazine was lower than that of pyridine ([Scheme 1](#)).⁸ In a dilution study of **2** (100–2 mM) by ^1H NMR spectroscopy in CDCl_3 , the

* Corresponding authors. Tel.: +81 52 836 3461; fax: +81 52 836 3462.
E-mail addresses: ikeshin@pharm.nagoya-cu.ac.jp (Y. Hisamatsu),
odashima@pharm.nagoya-cu.ac.jp (K. Odashima).



Scheme 1.



Scheme 2.

NH^a proton signal of **2** was observed between 8.8 and 8.9 ppm. The chemical shift of the NH^a proton was significantly downfield due to the intramolecular hydrogen

bond. On the other hand, the apparent downfield shift of the NH^b proton signal ($\Delta\delta = 2.4$ ppm) with increasing concentration indicated the presence of the **f-2** dimer. In the ¹H NMR spectrum of **2** at -50 °C, only the proton signals of **f-2** were observed. These results showed that the conformational equilibrium of **2** was biased toward the stable **f-2**, similar to **1**.

Next, we attempted to develop heterocyclic ureas that preferred the unfolded conformer. In our laboratory, the adenine-selective host molecules with 2,6-bis(oxazol-2-yl)-pyridine systems have been developed.⁹ The hosts have the usefulness of oxazole system as hydrogen-bonding acceptor. So, a new heterocyclic urea **3** with the oxazole ring was prepared. A Curtius rearrangement was employed as a key step for the synthesis of **3**. A chemical shift summary from the dilution study of **3** (300–1 mM) by ¹H NMR spectroscopy in CDCl₃ is displayed in Figure 1. The NH^a proton signal was observed between 6.0 and 6.3 ppm. Interestingly, the NH^a proton signal of **3** was observed ca. 3 ppm upfield from the corresponding NH^a signals of **1**^{3a,b,5b} and **2**. The apparent downfield shift of the NH^b proton signal of **3** ($\Delta\delta = 2.1$ ppm) with increasing concentration indicated the presence of dimers ($K_{\text{dimer}} = 3.4 \times 10^1 \text{ M}^{-1}$). The proposed dimer conformations (**uf-3-uf-3**, **uf-3-f-3**, **f-3-f-3** dimers) are shown in Figure 1B.¹⁰ For the oxazole-H^c proton signal, no important shift was observed.

To study the conformational property of **3** in more detail, the ¹H NMR spectra of **3** (40 mM) were measured at 25 °C and -50 °C. As shown in Figure 2A, the average proton signals of **uf-3**, **f-3**, and their dimers were observed at 25 °C. On the other hand, the dimers constituted of **uf-3** and **f-3** were clearly observed at -50 °C as the two sets of signals (Fig. 2B). While the NH^a proton signal of **uf-3** was observed at 5.3 ppm, the NH^a proton signal of **f-3** was

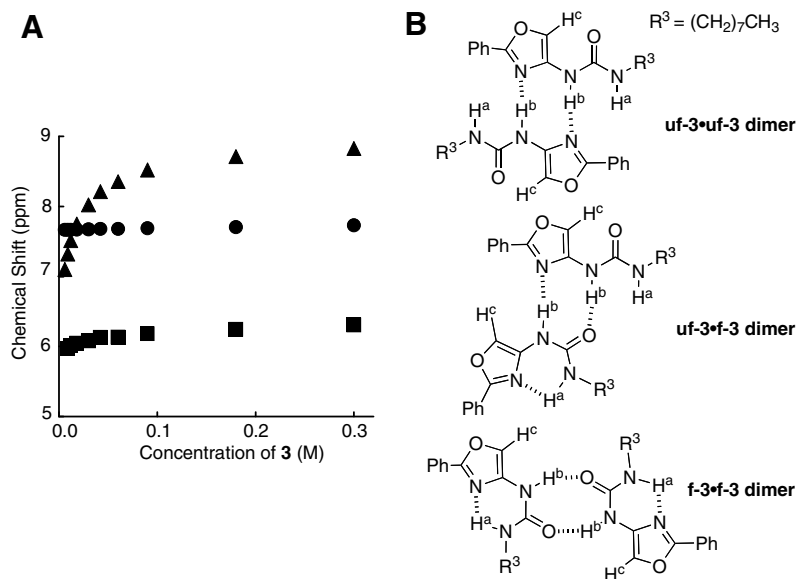


Fig. 1. (A) The chemical shift summary from the dilution study of **3**-NH^a (■), **3**-NH^b (▲) and **3**-H^c (●). The conditions: solvent, CDCl₃; temperature 25 °C. (B) The proposed dimer conformations of **3**.

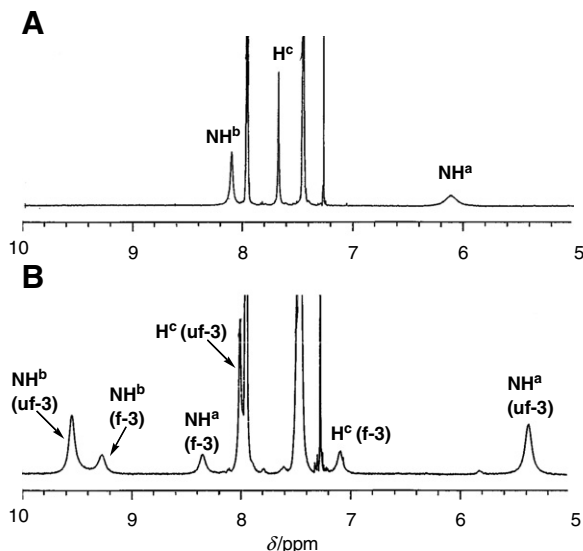


Fig. 2. ^1H NMR spectra of **3** in CDCl_3 (A) at 25°C and (B) at -50°C .

observed at 8.3 ppm due to the intramolecular hydrogen bond. The two NH^b proton signals (**f-3**: 9.3 ppm and **uf-3**: 9.5 ppm) shifted downfield by temperature-dependent dimerization. Since the H^c proton signal of **uf-3** was affected by an anisotropic effect of the carbonyl group, the H^c proton signal of **uf-3** (8.0 ppm) was observed ca. 1 ppm downfield from that of **f-3**. The ratio of **uf-3** to **f-3** at -50°C was estimated to be 3.3:1 based on the integration values of the NH^a proton signals of **uf-3** and **f-3**.

The complex formation between **3** and the *tert*-butyldimethylsilyl-protected cytosine derivative **8** was monitored by ^1H NMR spectroscopy in CDCl_3 at 25°C (Fig. 3). When **3** was titrated with **8** (0.1–3.0 equiv), significant downfield shifts were observed in both the NH^a ($\Delta\delta = 2.2$ ppm) and the NH^b ($\Delta\delta = 3.3$ ppm) proton signals. The conformational preference for **uf-3** was also supported by the significant downfield shift of the NH^a proton signal. The oxazole H^c proton signal was shifted downfield ($\Delta\delta = 0.34$ ppm) by the conformational change from minor **f-3** to **uf-3** prior to complexation with **8**. These downfield

Table 1

Stability constants of ureas **3–7** for 1:1 complexes with cytosine derivative **8** in CDCl_3 at 25°C^a

Complex	K_s (M^{-1})	ΔG_{298} (kJ/mol)
3-8	4.0×10^3	–20.6
4-8	1.1×10^4	–23.1
5-8	8.6×10^3	–22.5
6-8	1.5×10^3	–18.1
7-8	2.0×10^3	–18.8

^a Duplicate runs gave K_s values that agreed within 12%.

shifts supported the formation of a DDA·AAD complex. The stability constant (K_s) of the 1:1 complex¹¹ between **3** (400 μM) and **8** in CDCl_3 was determined to be $4.0 \times 10^3 \text{ M}^{-1}$ by the fit of the chemical shift data for the H^c proton signal to the 1:1 binding isotherm (Table 1).¹² Thus, the stability constant of **3** for the cytosine derivative was 100-fold greater than that of **1**. To improve the ability of **3** to complex with **8**, the phenylurea derivatives **4** and **5** were prepared. Unfortunately, the conformational property of **4** could not be tested because of its low solubility in CDCl_3 ($\leq 5 \text{ mM}$). The conformational property of **5** was similar to **3**. The ratio of **uf-5** and **f-5** at -50°C was estimated to be 2.4:1. The stability constant of the complex between **4** (400 μM) and **8** was increased to $1.1 \times 10^4 \text{ M}^{-1}$, which was comparable to guanine-cytosine base pairing in CDCl_3 .¹³ On the other hand, the stability constant of **5** (400 μM) was determined to be $8.6 \times 10^3 \text{ M}^{-1}$. These stability constants, higher than that of pyridine system, showed the usefulness of oxazole systems as the DDA hydrogen-bonding modules.

For other five-membered heterocyclic ureas, thiazol-4-yl urea **6** and imidazo[1,2-*a*]pyrid-2-yl urea **7** were investigated. From the variable-temperature NMR studies of **6** (40 mM), the ratio of **uf-6** and **f-6** (40 mM) at -50°C was estimated to be 0.8:1. The stability constant of the 1:1 complex between **6** (400 μM) and **8** in CDCl_3 was determined to be $1.5 \times 10^3 \text{ M}^{-1}$. On the other hand, the ratio of **uf-7** and **f-7** (40 mM) at -50°C was estimated to be 1.9:1. The stability constant of the 1:1 complex between **7** (400 μM) and **8** in CDCl_3 was determined to be

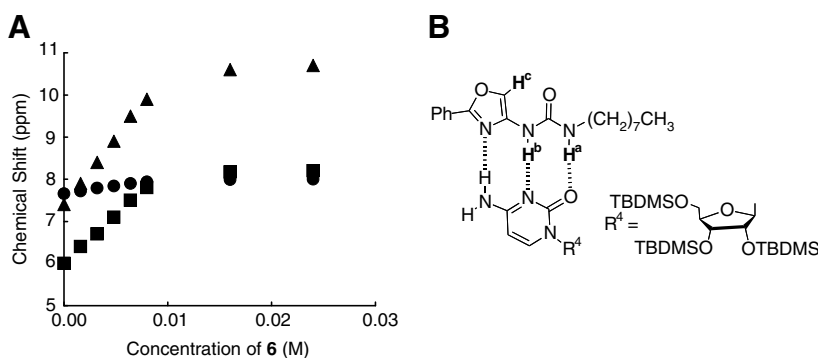


Fig. 3. (A) The chemical shift summary from the titration of **3** (8 mM) with cytosine derivative **8**: 3- NH^a (■), 3- NH^b (▲) and 3- H^c (●). The conditions: solvent, CDCl_3 ; temperature 25°C . (B) The proposed structure of the complex between **uf-3-8**.

$2.0 \times 10^3 \text{ M}^{-1}$. Thus, these five-membered heterocyclic ureas were capable of forming both the unfolded and folded conformers at each ratio, and suitable for the DDA hydrogen-bonding modules.

From these results, it was suggested that the difference in ring size (six- or five-membered ring) was a predominant factor in the conformational equilibrium of the heterocyclic ureas. Although the strength of the intramolecular hydrogen bond in the folded conformer affected the equilibrium, it would not be the predominant factor. Indeed, the ratios between the unfolded and the folded conformers in the heterocyclic ureas were not in accord with the order of the $\text{p}K_{\text{a}}$ values of conjugated acid in each heteroaromatic ring.^{9,14} Thus, we focused on the heterocyclic urea structures of the unfolded conformer optimized by computational study (B3LYP/6-31+G^{**}).¹⁵ Ureas **uf-1a**, **uf-2a** ($\text{R}^1 = \text{CH}_2\text{CH}_3$), **uf-3a**, **uf-6a**, and **uf-7a** ($\text{R}^3 = \text{CH}_2\text{CH}_3$) were used as the model compounds. The distances between the hydrogen H^{c} on the heteroaromatic ring and the oxygen on the urea carbonyl substitute of each heterocyclic urea are shown in Table 2. The $\text{CH}^{\text{c}} \cdots \text{O}$ distances of six-membered heterocyclic ureas (2.2 Å) were clearly shorter than those of five-membered heterocyclic ureas (2.4–2.5 Å). In addition, as shown in Table 2 and Figure 4, the angle of three nitrogen atoms ($\angle \text{N-N-N}$) of six-membered heterocyclic ureas (**uf-1a** and **uf-2a**) were smaller than that of five-membered heterocyclic ureas (**uf-3a**, **uf-6a** and **uf-7a**). The slightly concave shape^{3d,e} of **uf-1a** and **uf-2a** suggested the presence of a steric strain. Thus, the six-membered heterocyclic ureas **1** and **2** would be destabilized as an effect of steric repulsion due to the closer distance between $\text{CH}^{\text{c}} \cdots \text{O}$ and their conformational equilibria were biased toward the stable folded conformer. In contrast, the longer distance in the five-membered heterocyclic ureas decreased such unfavourable interactions. Generally, the distance of $\text{CH}^{\text{c}} \cdots \text{O}$ in the six-membered heterocyclic ureas suggested the presence of a weak intramolecular hydrogen bond.¹⁶ In this case, if the

$\text{CH}^{\text{c}} \cdots \text{O}$ intramolecular hydrogen bond influenced conformational stabilization, the conformational preference of **uf-2** for the unfolded conformer would be higher than that of oxazol-4-yl urea **3**.

In conclusion, it was demonstrated that the new five-membered heterocyclic ureas **3–7** were capable of forming both the unfolded and the folded conformers at each ratio, and suitable for the DDA hydrogen-bonding modules.¹⁷ In this case, the greater usefulness of the five-membered ring as the hydrogen-bonding acceptor is clearly shown, compared with the six-membered ring. Additionally, we propose that the distance between $\text{CH}^{\text{c}} \cdots \text{O}$ in the unfolded conformer is the predominant factor in the equilibrium between the unfolded and the folded conformers of the heterocyclic ureas. Understanding of the conformational equilibria inherent in heterocyclic ureas is broadening the potential of multiple hydrogen-bonding modules. By employing our concept, the development of new quadruple hydrogen-bonding modules including five-membered heterocyclic urea structures is ongoing.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Ms. S. Kato (Graduate School of Pharmaceutical Sciences) for technical support with NMR measurements.

Supplementary data

Experimental details describing the synthesis of the heterocyclic ureas, characterization of all new compounds, the ^1H NMR measurements and the calculation studies. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.068.

References and notes

- (a) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997; (b) Watson, J. D.; Baker, T. A.; Bell, S. P.; Gann, A.; Levine, M.; Losick, R. *Molecular Biology of the Gene*, 5th ed.; Benjamin-Cummings: San Francisco, 2003.
- For reviews, see: (a) Zimmerman, S. C.; Corbin, P. S. *Struct. Bond.* **2000**, *96*, 63–94; (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426; (c) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5–16; (d) Sessler, J. L.; Lawrence, C. M.; Jayawickramarajah, J. *Chem. Soc. Rev.* **2007**, *36*, 314–325; (e) Sivakova, S.; Rowan, S. J. *Chem. Soc. Rev.* **2005**, *34*, 9–21; (f) Sessler, J. L.; Jayawickramarajah, J. *Chem. Commun.* **2005**, 1939–1949; (g) Cooke, G.; Rotello, V. M. *Chem. Soc. Rev.* **2002**, *31*, 275–286; (h) Wilson, A. J. *Soft Matter* **2007**, *3*, 409–425.
- (a) Papadopoulos, M. V.; Goswami, S.; Hamilton, A. D. *J. Heterocycl. Chem.* **1995**, *32*, 675–681; (b) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475–10488; (c) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2000**, *122*, 3779–3780; (d) Quinn, J. R.; Zimmerman, S. C. *Org. Lett.* **2004**, *6*, 1649–1652; (e) Mayer, M. F.; Nakashima, S.; Zimmerman, S. C. *Org. Lett.* **2005**, *7*, 3005–3008; (f) Lüning, U.;

Table 2

Calculated $\text{CH}^{\text{c}} \cdots \text{O}$ distances and $\angle \text{N-N-N}^{\text{a}}$

Ureas	Ring size	$\text{CH}^{\text{c}} \cdots \text{O}$ (Å)	$\angle \text{N-N-N}$ (°)
uf-3a	5	2.52	173
uf-7a	5	2.45	171
uf-6a	5	2.37	169
uf-2a	6	2.24	166
uf-1a	6	2.23	165

^a Calculated with DFT at the B3LYP/6-31G^{**} level.

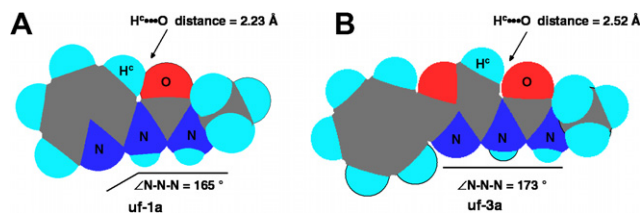


Fig. 4. Optimized structures of (A) **uf-1a** and (B) **uf-3a**, obtained by DFT at the B3LYP/6-31G^{**} level.

- Kühl, C.; Uphoff, A. *Eur. J. Org. Chem.* **2002**, 4063–4070; (g) Brammer, S.; Lüning, U.; Kühl, C. *Eur. J. Org. Chem.* **2002**, 4054–4062; (h) Söntjens, S. H. M.; Meijer, J. T.; Kooijman, H.; Spek, A. L.; van Genderen, M. H. P.; Sijbesma, R. P.; Meijer, E. W. *Org. Lett.* **2001**, 3, 3887–3889; (i) Lüning, U.; Kühl, C. *Tetrahedron. Lett.* **1998**, 39, 5735–5738; (j) Chien, C.-H.; Leung, M.-K.; Su, J.-K.; Li, G.-H.; Liu, Y.-H.; Wang, Y. *J. Org. Chem.* **2004**, 69, 1866–1871.
4. Sartorius, J.; Schneider, H.-J. *Chem. Eur. J.* **1996**, 2, 1446–1452.
5. (a) Singha, N. C.; Sathyanarayana, D. N. *J. Chem. Soc., Perkin Trans. 2* **1997**, 157–162; (b) Sudha, L. N.; Sathyanarayana, D. N. *J. Mol. Struct.* **1984**, 125, 89–96.
6. (a) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, 120, 6761–6769; (b) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, 120, 9710–9711; (c) Baruah, P. K.; Gonnade, R.; Phalgune, U. D.; Sanjayan, G. J. *J. Org. Chem.* **2005**, 70, 6461–6467.
7. The substituent effects on pyrid-2-yl ureas toward the intramolecular hydrogen bond were reported.^{3j} The ratio between the unfolded and folded conformation of 1-methyl-4-(3-(pyrid-2-yl)ureido)pyridinium iodide at –70 °C in DMF-*d*₇ was 1:1.
8. The pK_a values of conjugated acid: Pyridine (5.23),^a Pyrazine (0.65),^a Oxazole (0.8),^a Thiazole (2.5),^a Imidazo[1,2-*a*]pyridine (6.79).^b See, (a) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 83rd ed.; CRC Press: LLC, Boca Raton, 2002; (b) Catalan, J.; Elguero, J. *J. Heterocycl. Chem.* **1984**, 21, 269–270.
9. (a) Hisamatsu, Y.; Hasada, K.; Amano, F.; Tsubota, Y.; Wasada, Y.; Shirai, N.; Ikeda, S.; Odashima, K. *Chem. Eur. J.* **2006**, 12, 7733–7741; (b) Hisamatsu, Y.; Takami, H.; Shirai, N.; Ikeda, S.; Odashima, K. *Tetrahedron Lett.* **2007**, 48, 617–621.
10. The proposed dimer conformations were supported by NOE studies.
11. The 1:1 complexation was confirmed by the Job's plot: Job, P. *Ann. Chim. Appl.* **1928**, 9, 113–203.
12. Connors, K. A. *Binding Constants*; Wiley-Interscience: New York, USA, 1987.
13. Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, 114, 4010–4011.
14. The pK_a values of conjugated acid of imidazo[1,2-*a*]pyridine ring was higher than that of pyridine ring,⁹ although imidazo[1,2-*a*]pyrid-2-yl urea **7** was capable of forming the unfolded conformer.
15. The calculation was carried out with the GAUSSIAN-98 program on the IBM 7038-6M2 pSeries650 computer system of the Library and Information Processing Center of Nagoya City University. GAUSSIAN-98: Gaussian 98, Revision A.11.3.
16. (a) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, 104, 5063–5070; (b) Desiraju, G. R. *Acc. Chem. Res.* **1996**, 29, 441–449.
17. Recently, Wilson and co-workers reported 'Conformer independent heterodimerisation of linear arrays using three hydrogen bonds'. See, McGhee, A. M.; Kilner, C.; Wilson, A. J. *Chem. Commun.* **2008**, 344–346. In this Letter, the ureidoimidazole was suitable for DDA hydrogen-bonding module since the linear array of three hydrogen bonds was prorganized by the intramolecular hydrogen bond. In contrast, our five-membered heterocyclic ureas were suitable for the DDA hydrogen-bonding modules without preorganization by using the intramolecular hydrogen bond.