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超分子協同行為研究(1/3)

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計畫主持人：梁文傑

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國科會專題研究計畫成果報告

超分子協同行為研究(1/3)

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Substituent Effects on Pyrid-2-yl Ureas towards Intramolecular Hydrogen Bonding and Cytosine Complexation

中英文摘要

首先研究取代基對尿素衍生物分子內氫鍵的作用。在研究取代基對尿素衍生物與 cytosine 間錯合力的影響。並發現 1-methylpyridinium-2-yl 取代基有利於 (E,Z) 構形的生成，而 1-methylpyridinium-4-yl 取代基有利於與 cytosine 的錯合。

The electronic effects of an aryl substituent on pyrid-2-yl urea towards intramolecular hydrogen bonding and intermolecular cytosine complexation were examined. Among the compounds we studied, urea containing 1-methylpyridinium-2-yl substituent greatly enhances the (E,Z) form formation while 1-methylpyridinium-4-yl substituent facilitates intermolecular cytosine complexation.

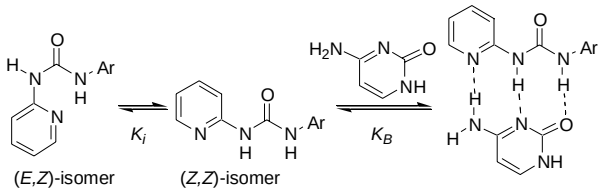
關鍵詞：尿素衍生物、氫鍵、錯合

keywords Ureas, hydrogen bond, complexation. Cytosine.

報告內容

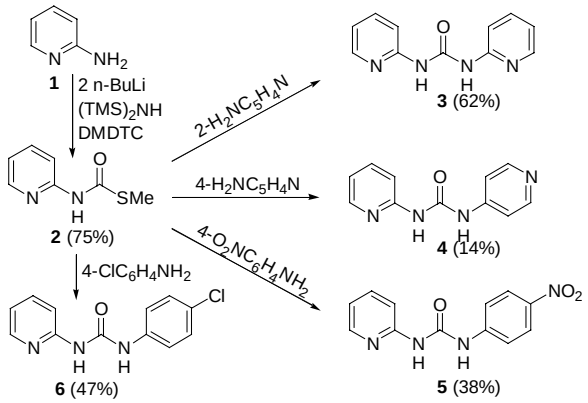
It has long been known that hydrogen bonds are responsible for the intermolecular and intramolecular order in carbohydrates,[i] proteins,[ii] and nucleic acids.[iii] Recently, many artificial receptors that employ hydrogen-bond centers as the recognition and binding elements have been designed and synthesized.[iv] As our continuous interest in the chemistry of organic urea,[v] we have examined the possibility of using pyrid-2-yl urea as a receptor to recognize cytosine (Scheme 1), an important hydrogen-bonding unit for DNA binding.[vi] Although the *Z,Z* form of pyrid-2-yl urea contains an ADD hydrogen-bonding array[vii] that is complementary to the array of cytosine, their binding is hindered by a competitive intramolecular hydrogen-bond between the pyridyl nitrogen and urea hydrogen that would stabilize the pyrid-2-yl urea in the *E,Z* form.[viii,ix] To make the binding more effective, substituents that could preferentially enhance the cytosine complexation over the intramolecular hydrogen-bonding interaction are desired.

Scheme 1



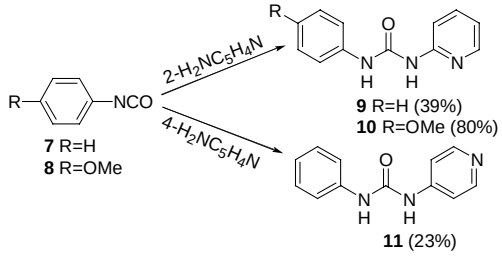
To understand the substituent effects, we explored a series of substituted pyrid-2-yl ureas **3-6**, **9**, **10**, **12**, and **13**. The syntheses of these compounds are summarized in Schemes 2-4. Since the corresponding isocyanate precursor of **3-6** is unavailable commercially, we adopted a two-step synthetic approach through thiocarbamate intermediate. On treatment of 2-aminopyridine **1** with *S,S*-dimethyl dithiocarbonate (DMDTC) under basic conditions led to thiocarbamate **2**.[x] Reaction of **2** with the corresponding amines gave pyrid-2-yl ureas **3-6** in moderate yields.

Scheme 2

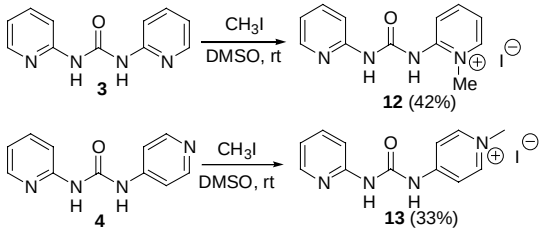


Ureas **9-11** were respectively prepared from the commercially available isocyanate precursors **7** and **8**.[xi] To know the charge effects on the bindings, we have further converted **3** and **4** to positively charged **12** and **13** by methylation of the pyridyl substituent with methyl iodide in DMSO.[xii] Interestingly, the reaction stops at monomethylation to give the desired products. Their structures were further confirmed by X-ray crystallographic analysis.

Scheme 3



Scheme 4



Intramolecular hydrogen bonding interaction was first examined by ^{1}H NMR in DMSO-d_6 at room temperature. While the N-H resonance signals of pyrid-2-yl substituted ureas **3-6**, **9-10** and **12-13** are relatively downfield shifted to 9-12 ppm, **11** shows two N-H singlets at 8.84 and 9.08 ppm. We tentatively attributed the down field shift phenomena as a result of intramolecular hydrogen bonding interactions which favor the formation of the *(E,Z)* conformers. Since **11** does not contain pyrid-2-yl group, we expected that steric repulsion between the phenyl and pyrid-4-yl group would destabilize the *(E,Z)* conformer, giving the *(Z,Z)* conformer as the predominant component. The equilibrium constants K_i, defined as [*(E,Z)*]/[*(Z,Z)*] were evaluated by ^{1}H NMR in DMF-d[7] at low temperature.[9] As shown in Figure 1, conformational exchange between the *E* and *Z* conformations of **3** at room temperature is so fast that only an average N-H proton signal was observed. However, the exchange process was significantly slowed down at –70°C and two conformers were clearly observed. We assigned the signals at δ = 12.6 and 10.4 ppm to the urea protons N_C-H and N_D-H of the (*E,Z*) conformer respectively. Since the N_c-H is intramolecularly hydrogen bonded to the pyridyl group, it

Table 1. Equilibrium constants and thermodynamic parameters for the pyrid-2yl ureas.

Urea	K_i [a]	ΔH_i^o [c]	ΔS_i^o [d]	K_B
3	3.8 (1.9)[b]	-2.3	-8.8	30
4	1.7			590
5	2.0			1100
9	1.6			390
10	2.0			340
12	14.2	-0.8	1.3	-[d]
13	1.0	-2.2	-10.6	1700

a. K_i =[(*E,Z*)]/[(*Z,Z*)]. b. Due to the symmetry of **3**, formation of intramolecular hydrogen interaction is two times of the others. c. kcal/mol. d. cal/mol-K

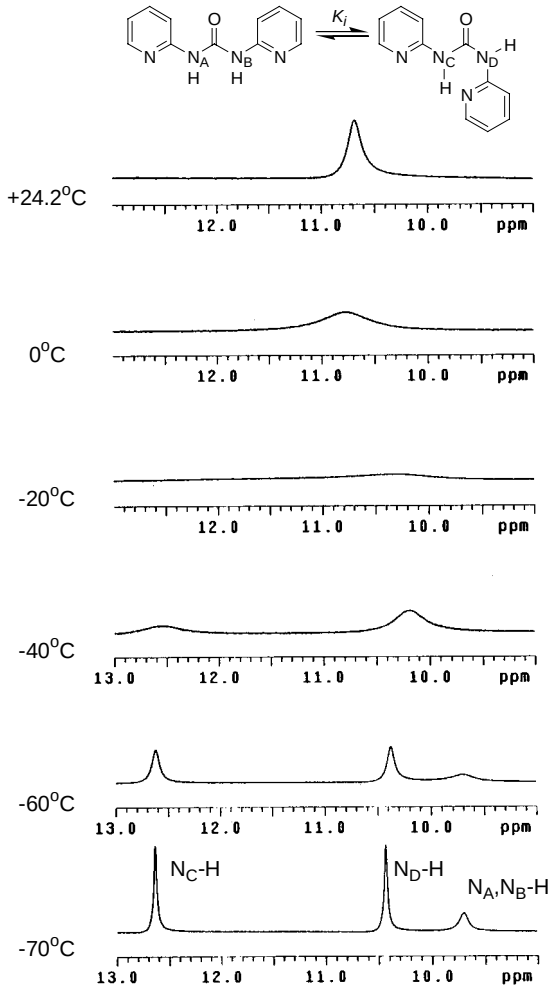


Figure 1. ^{1}H NMR spectra of **3** at different temperatures.

is supposed to be relatively downfield shifted. The smaller signal at 9.7 ppm was assigned to the N-H protons of the symmetrical (*Z*,*Z*) conformer. Perhaps due to steric hindrance, no evidence for the (*E*,*E*) conformer was observed. The equilibrium constant K_i was evaluated on the basis of the NMR integrations. Similar spectra were obtained for **4**, **5**, **9**, **10**, **12**, and **13**. Perhaps due to the relatively low rotational energy barrier that leads to faster N-C=O bond rotation, the N-H proton signals of **4**-**6**, **9**, and **10** are broad in comparison to those of **3**, **12**, and **13**. Except for **6**, nevertheless, their equilibrium constants could be reasonably estimated and are summarized in Table 1. Among the organic ureas we studied, most of them have the K_i value around 1-2, indicating that there is only a small preference for the (*E*,*Z*) form over the (*Z*,*Z*) form. However, the K_i for **12** is unusually high and is almost one order of magnitude larger than the others. The results of the temperature dependent experiments revealed that the preference for the intramolecular hydrogen bonding interaction is arising from the entropy factors. The (*E*,*Z*)-conformation of **12** is indeed less exothermic but entropically favored in comparison to **3** and **13**.

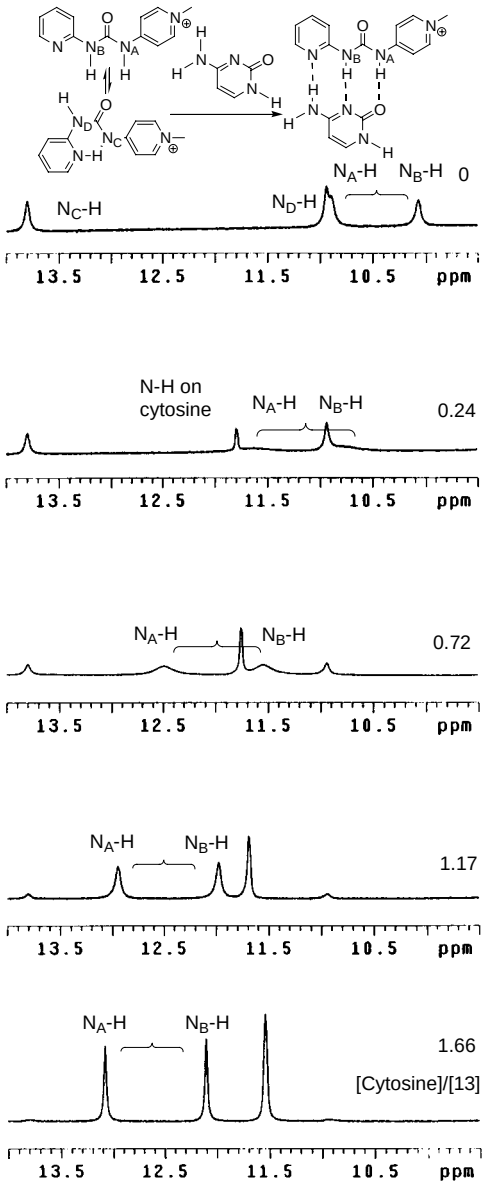


Figure 2. ^{1}H NMR spectra of **13** in the presence of different equivalents of cytosine at –70 C^o in DMF-d^7.

Intermolecular complexation of pyridyl ureas with cytosine has also been studied by ^{1}H NMR at –70 ^{o}C. In each series of studies, concentration of cytosine was gradually increased while the concentration of the target pyridyl ureas was kept constant at 0.01M. Example spectra of **13** are shown in Figure 2. On increasing the amount of cytosine, the N-H chemical shifts δ_{zz} of the *(Z,Z)*-**13** gradually shifted from 10.1 ppm and 10.9 ppm to 12.1 and 13.1 ppm respectively, indicating complex formation between cytosine and **13**. On the other hand, the N-H signal intensities of *(E,Z)*-isomer at 13.8 and 10.9 ppm progressively dropped without any shift of the δ values. These observations are consistent with our assumption that only *(Z,Z)*-**13** would bind with cytosine. However, binding between cytosine and the *(Z,Z)*-**13** would shift the equilibrium towards the *(Z,Z)*-**13** side, reducing the amounts of *(E,Z)*-**13** in solution.

As shown in Figure 3, the tendency of the δ_{zz} values follows a mathematical expression of $\delta_{zz} = (\delta_i + \delta_f K_B[C])/(1+K_B[C])$, where [C] is the concentration of free cytosine in solution, δ_i is the initial chemical shift before addition of cytosine, and δ_f is the final chemical shift in the presence of large excess of cytosine. The binding constants K_B were evaluated on the basis of non-linear least square fitting of δ_{zz} versus concentration of free cytosine and are summarized in Table 1.

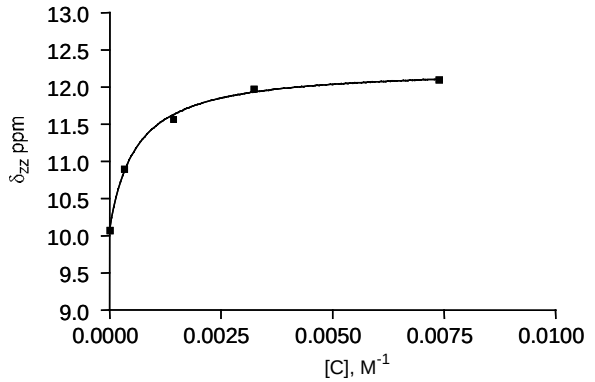
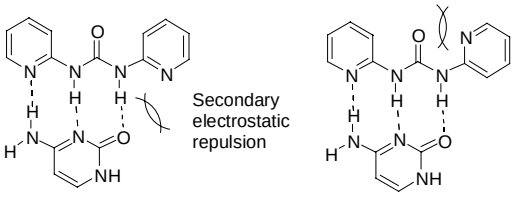


Figure 3. A plot of the N-H chemical shifts δ_{zz} of the *(Z,Z)*-**13** versus [C], the concentration of free cytosine in solution.

Pyridyl ureas containing electron deficient or electron withdrawing group such as **5** or **13** show relatively large binding constant K_B. In particular, **13** is the strongest receptor for cytosine in the studied series, indicating the significance of the charge effects on the binding. However, the binding constant measurement of **12** with cytosine was hampered by formation of an unidentified compound and could not be evaluated.

The K_B value for **3** is particularly small in comparison to the others in the series. We tentatively attribute this phenomenon to the secondary electrostatic repulsion between the pyridyl nitrogen and the carbonyl group of cytosine in **14**. The secondary electrostatic repulsion model has been proposed by Jorgenson and later on quantified by Schneider. [xiii] Although one may suggest that rotation of the pyridyl group away from the cytosine would lead to less repulsion, as shown in **15**, this will create another electrostatic repulsion between the pyridyl nitrogen and the ureyleno carbonyl group.



14 **15**

In summary, we report herein the unexpected substituent effects on aryl pyrid-2-yl ureas towards intramolecular hydrogen bonding and cytosine complexation. *N*-Methylpyridinium derivative **12** shows unexpectedly strong tendency towards intramolecular hydrogen bond interactions. On the other hand, introduction of an electron withdrawing substituent at the para position of aryl pyrid-2-yl ureas particularly benefits the intermolecular cytosine binding. Application of this concept to the design of DNA binders is ongoing.

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Supporting Information Available: Derive of the equation for binding constant K_B evaluation, Table for the N-H chemical shifts for **3-6** and **9-13** in DMSO-d_6, CIF and ORTEP X-ray crystallographic data for **12-13**, synthetic procedures for **3-6** and **9-13** (32 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

[i] (a) Wong, C.-H. *Acc. Chem. Res.* **1999**, *32*, 376 (b) Poveda, A.; Jime´nez-Barbero J. *Chem. Soc. Re*v. **1998**, *27*, 133.

[ii] (a) Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (c) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**; *101*, 3131.

[iii] (a) Majumdar, A.; Patel, D. J. *Acc. Chem. Res.* **2002**, *35*, 1. (b) Pirrung, M. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1276. (c) Capila, I.; Linhardt, R. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 390. (d) Niemeyer, C. M. *Angew. Chem. Int. Ed.* **2001**, *4*0, 4128.

[iv] (a) Zhu, P.; Kang, H.; Facchetti, A.; Evmenenko, G.; Dutta, P; Marks, T. J. *J. Am. Chem. Soc.* **2003,** *125*, 11496. (b) Hunter, C. A.;. Low, C. M. R.; Vinter, J. G.; Zonta, C. *J. Am. Chem. Soc.* **2003,** 125, 9936. (c) Al-Sayah, M. H.; Branda, N. R. *Org. Lett.* **2002**, *4*, 881. (d) Archer, E. A.; Sochia, A. E.; Krische, M. J. *Chem. Eur. J.* **2001**, *7*, 2049. (e) Mancin, F.; Chin, J. *J. Am. Chem. Soc.* **2002**, *124*, 10946. (f) Pedireddi, V. R.; Ranganathan, A.; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 99. (g) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487. (h) Archer, E. A.; Goldberg, N. T.; Lynch, V.; Krische, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 5006. (i) Bisson, A. P.; Carver, F. J.; Eggleston, D. S.; Haltiwanger, R. C.; Hunter, C. A.; Livingstone, D. L.; McCabe, J. F.; Rotger, C.; Rowan, A. E. *J. Am. Chem. Soc.* **2000**, *122*, 8856.

[v] (a) Chen, J.-A.; Lai, J.-L.; Lee, G. H.; Wang, Y.; Su, J. K.; Yeh, H.-C.; Lin, W.-Y.; Leung, M.-k. *Org. Lett.* **2001**, *3*, 3999. (b) Liao, C.-F.; Lai, J.-L.; Chen, J.-A.; Chen, H.-T.; Cheng, H.-L.; Her, G.-R.; Su, J. K.; Wang, Y.; Lee, G. H.; Leung, M.-k.; Wang, C.-C. *J. Org. Chem.* **2001**, *66*, 2566. (c) Lai, J.-L.; Leung, M.-k.; Lee, G. H. *J. Org. Chem.* **1996**, *61*, 8364.

[vi] (a) Rajeev, K. G.; Maier, M. A.; Lesnik, E. A.; Manoharan, M. *Org. Lett.* **2002**, *4*, 4395. (b) Glaser, R.; Lewis, M. *Org. Lett.* **1999**, *1*, 273. (c) Sakurai, K.; Shinkai, S. *J. Am. Chem. Soc.* **2000**, *122*, 4520.

[vii] Lüning, U.; Kühl, C.; Uphoff, A. *Eur. J. Org. Chem.* **2002**, 4063

[viii] Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475.

[ix] Jiménez Blanco, J. L.; Benito, J. M.; Ortiz Mellet, C.; García Fernández, J. M. *Org. Lett.* **1999**, *1*, 1217.

[x] Leung, M.-k.; Lai, J.-L.; Lau, K.-H.; Yu, H.-h.; Hsiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175.

[xi] The compounds were purchased from Acros and were used without further purification.

[xii] Mayr, H.; Ofial, A. R. ; Sauer, J.; Schmied, B. *Eur. J. Org. Chem.* **2000**, 2013.

[xiii] (a) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810. (b) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc*. **1990**, *112*, 2008. (c) Sartorius, J.; Schneider, H.-J. *Chem.-Eur. J.* **1996**, *2*, 1446.