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Molecular Recognition: A Simple Dinaphthyridine Receptor for Urea

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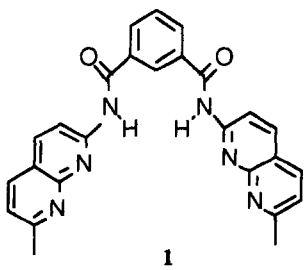
Abstract: A new dinaphthyridine receptor **1** is designed that efficiently binds to urea probably by six hydrogen bonds forming a chloroform soluble 1:1 complex and selectively extracts urea into chloroform from its mixture with thiourea. The receptor **1** has fifteen fold higher binding constant for urea than the truncated receptor **2** possibly due to formation of greater number of hydrogen bonds in complexation.

Hydrogen bonding[1] plays a key role in molecular recognition.[2] In the design of artificial receptors, the most important task is to place the hydrogen bonding groups (as hydrogen donor or acceptor) in a rigid or semirigid cavity.[3] Compared to similar hydrogen bonding groups between two alternative hosts and a particular guest, greater number of hydrogen bonds that a host can make with the guest, stronger complex it generally forms. On complexation, the solubility of the complex becomes more in less polar solvents and water soluble substrates can become soluble in solvent like chloroform. This has relevance to the nonpolar interior of an enzyme similar to the low dielectric constant of an organic solvent.

Urea, a product of protein metabolism[4] is an interesting target for binding studies. Urea inclusion compounds have important applications.[5] Ordinary crystalline urea is tetragonal, but it forms an inclusion compound with a guest, crystallising in a hexagonal lattice[6] containing the guest in long channels. However it is difficult to recognise urea as a guest with a synthetic receptor to solubilise it in less polar solvents like chloroform because of its notorious insolubility in chloroform and high affinity for water. Efficient complexation of urea is more difficult compared to alkyl urea derivatives[7] which are soluble in chloroform and also their receptor design will be simpler as the receptor has to make less hydrogen bonds. We report here the design and synthesis of the dinaphthyridine receptor **1** for urea which binds more efficiently than the



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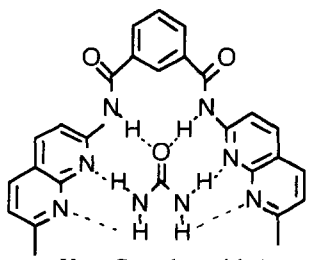
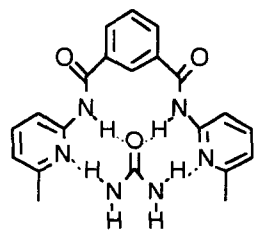
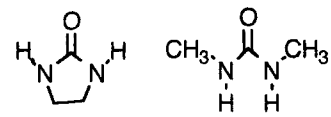


Urea Complex with **1**



Urea Complex with **2**

truncated bipyridyl receptor[2] **2**. Interestingly both receptors **1** and **2** bind well with imidazolidone (**3**) but they do not bind with N,N'-dimethylurea (**4**).



3 4

Previous receptors for urea interaction with crown ethers by Pedersen[8], with tetra-aza polynuclear diketone receptor by Bell[9] (complexing only the urea protons leaving the urea oxygen uninvolved), with macrocycles containing intraannular acidic groups by Reinhoudt[10] are all structurally more complicated. Our simple design is based on the observation by Hamilton et al. in the binding of barbituric acids[2] with macrocyclic tetramides from two pyridine diamines separated by isophthaloyl spacer. Replacement of the bottom hydrogen bond donor[2] by an hydrogen bond acceptor to bind urea is simply achieved by taking two naphthyridine moieties in place of pyridines to get the receptor **1**.

The addition of powdered urea to $CDCl_3$ solution of receptor **1** shows its facile dissolution as evidenced by the new appearance of urea NH peaks at δ 6.63 and significant downfield shift of the receptor amide protons (from δ 9.61 to δ 10.75, Δδ = 1.2 ppm) in the NMR spectrum of the complex (Fig.1 and 2).[11] From the integration ratio of urea protons to the receptor amide protons in NMR spectrum of the complex revealed the clear formation of 1:1 complex (Fig. 2). The binding constant of urea and the receptor **1** was found to be $6.6x10^4$ M^{-1} (Table1) as determined by the gravimetric method of Horman[12] as well as by Stoddart method[13] which gave similar results. That **1** is a superior receptor for urea in chloroform than the truncated bipyridyl receptor **2** is supported by significantly more downfield shift of the key amide protons in **1** on complexation with urea [Δδ 1.2 compared to 0.5 (from δ 9.18 to δ 9.68)] in the complex of **2**] and also the appearance of urea protons at more downfield in the complex with **1** (δ 6.63 compared to δ 5.93 in the complex with **2**). This is also corroborated from more than fifteen fold higher binding constant of **1** compared to **2** with urea which suggests that all naphthyridine nitrogens are probably participating in hydrogen bondings in complexation. The extra naphthyridine nitrogen responsible for the increase in binding is equidistant from two urea hydrogens. The additional stability in the urea complex with **1** compared to that with **2** may also be due to long range electrostatic interactions instead of hydrogen bonds, with all four urea hydrogens. The results are therefore an example of secondary electrostatic effects which occur in multiple hydrogen bonded systems. Interestingly, in the complex of ethyleneurea **3** with **1** and **2**, large downfield shifts occur with the amide protons of **1** (from δ 9.37 to δ 11.28, Δδ =1.9 ppm) and **2** (from δ 8.81 to δ10.33, Δδ = 1.5 ppm) as well as the urea protons of **3** (Δδ = 3.4 and 2.14 ppm

Table 1. Binding Constants (K_{as} M^{-1}) of Receptor **1** and truncated receptor **2** with urea, **3** and **4**.

	Receptor	
Guest	**1**	**2**
Urea	$6.6x10^4$	$4.2x10^3$
3	$1.0x10^3$	$1.5x10^3$
4	<10	<10

respectively) but urea protons moved upfields on excess additions of **3** until they appeared at similar chemical shift as in the uncomplexed **3** which may be due to fast exchange average of free and bound species and so should approach the free value at high concentration of excess **3**.

The selective extraction of urea from its mixture with thiourea by receptor **1** was confirmed by extracting only urea and no thiourea (identity was proved by comparison with authentic sample as well as by NMR of the complex) in water from chloroform solution of the complex of the receptor with a mixture of urea and thiourea. This selectivity may be due to the bigger size of sulphur (complexation sterically more unfavourable) and its less electronegativity and hence poor hydrogen bond accepting capability in comparison to oxygen as well as the decreased acidity of thiourea hydrogens.

The receptor **1** was synthesised by the simple reaction of isophthaloyl dichloride and 2-amino-7-methyl-1,8-naphthyridine[14] prepared by condensing 2,6-diaminopyridine and 2-oxobutyryldehyde dimethylacetal (H_3PO_4, 90 °C).

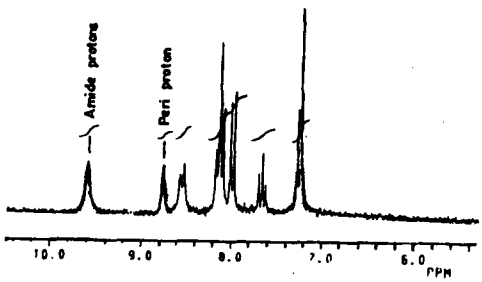


Fig 1

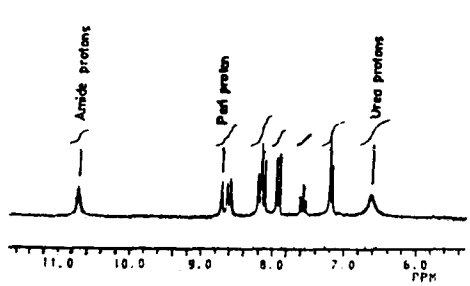


Fig 2

In summary, we have shown the new simply designed receptor **1** binds strongly and selectively to urea over thiourea or N,N'-dimethylurea forming a chloroform soluble 1:1 complex. The ability of **1** to bind **3** but not **4** may be due to *anti, anti* conformation of cyclic **3** in contrast to *syn, syn* conformation[7] of **4** unfavourable for binding. However the two hydrogen bonds involving the bottom hydrogens of urea and the naphthyridine nitrogens at 8 positions may be weaker due to some nonplanarity because of repulsion between the lone pairs on peri nitrogens. 1,8-naphthyridines are known to become planar[15,16] on complexation with metal ions due to chelation and also the peri nitrogens of naphthyridines having 2- alkoxy group are reported[17] to be involved in hydrogen bond formation with guanosine. This report is another illustration of hydrogen bonds involving naphthyridines and the first example of their hydrogen bondings[18] and electrostatic attractions[18] with urea evidenced by formation of stronger 1:1 complex (more than fifteen fold higher binding constant) with receptor **1** compared to **2** and thus **1** has improved specificity for urea.

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REFERENCES AND NOTES

1. Jeffrey. G. A.; Saenger, W. Hydrogen Bonding in Biological Structures. Springer-Verlag; New York, 1991.; Schneider, H. J. *Angew.Chem. Int. Ed. Engl.* **1991**, *30*, 1417; Simanek, E. E.; Mammen, M.; Gordon, D. M.; Chin, D.Mathias, J. P.; Seto, C. T.; Whitesides, G. M. *Tetrahedron* **1995**, *51*, 607; Platts, J. A.; Howard, S.T.; Bracke, B. R. F. *J. Am. Chem.Soc.* **1996,** *118*, 2726; Ge, Y.; Lilienthal, R. R.; Smith, D.K. *J. Am. Chem.Soc.* **1996,** *118*, 3976; Goswami, S., Ghosh, K.; Dasgupta, S. *Tetrahedron* **1996**, *52*, 12223.
2. Lehn, J. M. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304; Rebek, J. *Science* **1987,** *235*, 1478.; Van Engen, D. Hamilton, A. D. *J. Am. Chem. Soc.* **1987,** *109*, 5035.; Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988,** *110*, 1318.; Chang, S. K.; Van Engen, D.; Fan, E.; Hamilton, A. D., *J. Am. Chem. Soc.* **1991**, *113*, 7640; Goswami, S.; Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 3425.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1990,** *112*, 7269.; Sheridan, R. E.; Whitlock, H. W. *J. Am. Chem. Soc.* **1986**, *108*, 7120; Vicent, C.; Fan, E.; Hamilton, A. D. *Tetrahedron Lett.* **1992**, *33*, 4269.
3. Cram, D. J. *Science* **1983**, *219*, 1177; Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549.; Diederich, F. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 362; Perreault, D. M.; Chen, X.; Anslyn, E. V. *Tetrahedron* **1995,** *51*, 353; Rebek, J.; Nemeth, D.; Ballester, P.;Lin, F. T. *J. Am. Chem. Soc.* **1987**, *109*, 3474; Davis, A. P.; Menger, S.; Walsh, J. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1996,** 453.
4. Schmidtchen, F. P. *J. Am. Chem. Soc.* **1986**, *108*, 8249.
5. Stryer, L.; W. H. Freeman and Company; New York, 3rd ed. 1988, p. 500.
6. Ten Hoor, M. J. *J. Chem. Ed.* **1996**, *73*, 42.
7. Hegde, V.; Madhukar, P.; Madura, J. D.; Thummel, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 4549; Hegde, V.; Hung, C. Y.; Madhukar, P.; Cunningham, R.; Hopfner, T.; Thummel, R. P. *J. Am. Chem. Soc.* **1993**, *115*, 872; Hung, C. Y.; Hopfner, T.; Thummel, R. P.*J. Am. Chem. Soc.* **1993**, *115*, 12601; Wilcox, C.S.; Kim, E.; Romano, D.; Kuo, L. H.; Burt, A.L.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621.
8. Pedersen, C.J. *J. Org. Chem.* **1971,** *36*, 1690.
9. Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673.
10. Aarts, V. M. L. J.;. Van Staveren, C. J.; Grootenhuis, P. D. J.; Van Eerden, J.; Kruise, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035; Van Staveren, C. J.; Aarts, V. M. L. J.; Grootenhuis, P. D. J.; Droppers, W. J. H.; Van Eerden, J.; Harkema, S.; Reinhoudt, D. N.*J. Am. Chem. Soc.* **1988**, *110*, 8134.
11. All the compunds have spectroscopic data consistent with the assigned structures. **Receptor 1** (M^+ 448, 21%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.61 (2H, bs, amide NH), 8.78 (1H, s), 8.54 (2H, d, J=8Hz), 8.17 (2H, d, J=8 Hz), 8.14 (2H, d, J=8 Hz), 8.01 (2H, d, J=8 Hz), 7.67(1H, t, J=8 Hz), 7.28 (2H, d, J=6.5 Hz), 2.7 (6H, s);.^{13}C NMR (50 MHz $CDCl_3$): δ 165.5, 162.3, 154.0, 153.7, 138.4, 135.9, 133.4, 131.7, 128.6, 126.2, 121.0, 117.9, 114.3, 25.0; **Urea Complex with 1**: ^{1}H NMR: δ 10.74 (2H, bs, amide NH), 8.72 (1H, s), 8.63 (2H, d, J=8Hz), 9.19 (2H, d, J=8Hz), 8.14 (2H, d, J=8 Hz), 7.93 (2H, d, J= 8Hz), 7.58 (1H, t, J=8 Hz), 7.19 (2H, d, J=6.5Hz), 6.63 (4H,bs, urea NH), 2.6 (6H, S). **Urea complex with 2**: δ 9.68(2H, bs, amideNH), 8.67(1H, s), 8.20(2H, d, J=2Hz), 8.17(2H,d,J=2Hz), 7.66(2H,t, J=8Hz), 7.62(1H,t,J=8Hz), 6.93(2H,d,J=8Hz), 5.93(4H, bs, urea NH), 2.45(6H,s).
12. Horman, I.; Dreux, B. *Anal. Chem.* **1983,** *55*, 1219.
13. Colquhoun, H. M.; Goodings, E. P.; Maud, J. M.; Stoddart, J. F.; Wolstenholme, J. B.; Williams, D. J. *J. C. S. Perkin II*, **1985**, 607; Alston, D.R.; Slawin, A.M.Z.; Stoddart, J.F.; Williams, D. J. *Ang. Chem. Int. Ed.* **1985**, *24*, 786.
14. Brown, E. V. *J. Org. Chem.*. **1995,** *30*, 1607.
15. Clearfield, A.; Sims, M. J.; Singh, P. *Acta Crystallographica, Part B* **1972**, *28*, 350.
16. Cavanaugh, M. A.; Cappo, V. M.; Alexander, C. J.; Good, M. L. *Inorganic Chem.* **1976**, *15*, 2615.
17. Hamilton, A. D.; Pant, N. J. Chem. Soc., Chem. Commun. **1988**, 765; Murray, T. J.; Zimmerman, S. C. *Tetrahedron Lett* . **1995**, *42*, 7627.
18. Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008; Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 3744.

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