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2,6-Bis(2-benzimidazolyl)pyridine receptor for urea recognition

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Abstract—The use of 2,6-bis(2-benzimidazolyl)pyridine as a neutral receptor enables the formation of highly stable supramolecular complexes with urea via self-assembly and which were characterized by spectroscopy and X-ray diffraction analysis. This receptor utilizes the imine nitrogen located on its outer core in addition to the cavity to form hydrogen-bonded adducts with high binding affinity, thus providing a unique design for chemical and biological recognition.

Noteworthy progress made to design and synthesize novel receptors capable of recognizing chemical and biological guest molecules has contributed greatly in the development of supramolecular chemistry.[1] Major challenges that need attention are the development of structurally simple and stable receptors that would have better utility and much wider applicability. Urea is toxic and a well-known pollutant that causes serious biological disorders.[2,3] Urea is an end product of nitrogen metabolism and a well-known protein denaturant that can cause damage in concentrations as low as micromolar range. Thus, the need to develop structurally simple synthetic receptors capable of detecting urea in low concentrations is important for clinical chemistry.[4]

Inspired by the few important recognition studies for urea,[5,6] we envisioned the donor–acceptor properties of 2,6-bis(2-benzimidazolyl)pyridine **1** (Fig. 1) for recognition of neutral organic guests. Herein, we report our findings on the ability of **1** to recognize and sense urea using UV/visible and fluorescence spectroscopy and the formation of stable supramolecular complexes by X-ray diffraction analysis. Compound **1** was chosen as a receptor candidate as its preparation was simple and high yielding, it possesses multiple binding sites and its stability towards air/moisture is very good.[7] Moreover, **1** also has a well-defined open cavity with a rigid overall structure that helps to predict its interaction and relative binding with guest molecules with a fair degree of accuracy.[8] These imidazole-based ligands are of considerable interest due to their presence as binding sites for metals in several biological systems, especially as mimics of histidine–imidazole systems.[9] Due to the simplicity and ease of preparation, their applications in optoelectronic devices are also being explored widely.[10] Several extended structures such as metallo-supramolecular polymers and supramolecular gels have also been developed with derivatives of **1**, thus opening newer avenues for their utilization in materials science.[11] However, their ability for molecular recognition and self-assembly with organic guests has not been reported.[12]

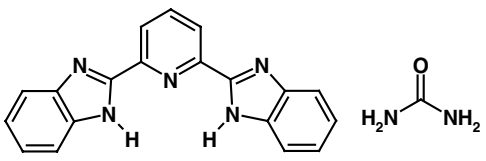

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Figure 1. 2,6-Bis(2-benzimidazolyl)pyridine, **1** and urea.

To evaluate the solution state properties of receptor **1**, a titration was performed by careful addition of 0.1 equiv of urea aliquots at regular intervals to **1**. The spectroscopic changes were recorded by means of UV/visible and fluorescence spectroscopy in acetonitrile. The choice of solvents is restricted by the insolubility of **1** in non-polar solvents. On increasing the concentration of urea, the initial absorption band (Fig. 2) having a λ_{max} at 327 nm showed a marginal but progressive decrease in intensity with broadening and formation of a clear isosbestic point at 277 nm, indicating the presence of at least one stable species at equilibrium. Due to the low basicity

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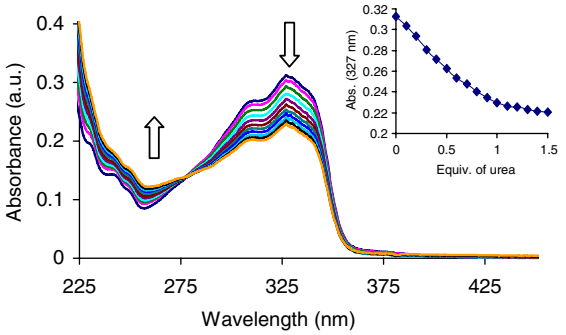

Figure 2. UV/visible spectrum of receptor **1** (6.35×10^{-6} M in dry CH_3CN) during titration with urea from 0 to 1 equiv (v/v). Inset—titration profile of the band at 327 nm corresponding to the **1**: urea H-bonded complex.

of urea, the decrease in λ_{max} intensity of **1** and the development of newer bands do not occur significantly, but the presence of a distinct isosbestic point is due to the formation of a stable donor–acceptor complex between **1** and urea. The association constant (K_a) calculated[13] for the 1:1 complex was found to be 44.38 M^{-1}, suggesting strong hydrogen bonding between **1** and urea. The inset of Figure 2 shows that a limiting value is reached on forming a 1:1 adduct between **1** and urea. The effect of solvents on hydrogen bonding was studied by performing titrations in DMSO, DMF, methanol, and ethanol. Different sets of isosbestic points were obtained in the DMSO and DMF titrations with low binding constants. However, titration in alcohols showed very minor spectral changes and the binding constants were difficult to estimate. Further complexation studies by fluorescence spectroscopy (Fig. 3) showed that the spectrum of **1** is clearly modified on the formation of a complex with urea.

Titration experiments carried out by the addition of 0.1 equiv of urea to **1** showed that the 375 nm band in the fluorescence spectrum was diminished by over 70% of the initial intensity. A large quenching in intensity was observed up to the addition of 0.5 equiv of urea after which the changes were minor. Excess urea did not alter the spectrum signifying that the emission occurs always from the low energy electronic states. This indicates that on formation of the donor–acceptor complex between urea and **1**, the excited state is modified leading to the quenching of fluorescence. Thus, self-

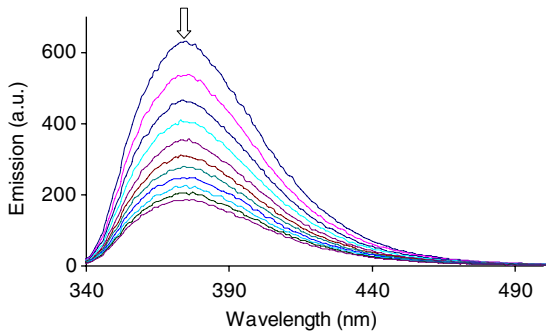

Figure 3. Emission spectrum of receptor **1** (3.54×10^{-7} M in dry CH_3CN) during the titration with urea from 0 to 1 equiv (v/v).

association has a large effect on the optical properties of **1** in solution and could be used for the sensing of neutral guests.

The crystal structures of the supramolecular complexes between **1** and urea in the ratios 1:1 and 2:1 are shown in Figure 4. As observed from the ORTEP diagram, one receptor molecule and one urea molecule combine (left) forming a stable donor–acceptor complex in a 1:1 ratio (**1**:urea).[14] The urea molecule fits into the cavity of **1** and is bound to the NH protons. In this complex, one receptor molecule donates two of its protons to the carbonyl oxygen of urea which is pointed inwards into its cavity. The donor–acceptor complex thus formed between the carbonyl oxygen of urea and NH protons of **1** is of the order (N2—H···O1) 2.85 Å and (N3—H···O1) 2.92 Å. Further, we were also successful in growing crystals of the 2:1 complex (**1**:urea) as represented in Figure 4 (right).[15] It was again observed that the urea molecule prefers the cavity of **1** in order to form the hydrogen-bonded complex. The urea molecule acts like a bridge between two receptor molecules, accepting protons from one receptor and donating one of its NH_2 protons to another receptor forming a stable donor–acceptor complex involving two molecules of **1**. The bond distances between the carbonyl oxygen of urea and the NH protons of **1** are (N6—H···O5) 2.88 Å and (N10—H···O5) 2.93 Å, respectively, which are almost identical to the bond distances in the 1:1 complex. The distance between one of the urea NH_2 protons and the imine nitrogen of the second receptor was found to be (N15—H···N1) 2.99 Å. The cavity of this second molecule of receptor **1** is utilized to bind a water molecule having bond distances of 2.93 Å for (N2—H···O3) and (N5—H···O3). This evidence indicates good association of **1** with urea, leading to 1:1 and 2:1 adducts. To the best of our knowledge, this is the first crystallographic report on the formation of stable supramolecular complexes between a neutral receptor and urea.

The X-ray structures of both 2:1 and 1:1 complexes along with the spectroscopic changes observed on the titration of urea and **1** are clear indications of the formation of supramolecular complexes in both solution and solid state. As the carbonyl oxygen of urea is pointed inwards into the cavity of receptor **1** in both the X-ray structures, the possibility of incorporating more substituted guests is greatly enhanced, which is usually very difficult with cyclic hosts.[8] Both these hydrogen-bonded complexes are readily formed by simple mixing of **1** with urea in different ratios. The simple procedure to prepare **1** and its ability to form hydrogen-bonded complexes with amide linkages and water molecules opens up its utility for the recognition of several biologically relevant molecules. Moreover, participation of the imine nitrogen in stabilizing the supramolecular structure is unique and enhances the recognition capabilities of receptor **1**.

In summary, the present results demonstrate that 2,6-bis(2-benzimidazolyl)pyridine is an efficient receptor for binding urea with high affinity. Crystallographic analysis further revealed that receptor **1** utilizes its cavity and the imine nitrogen on its outer core to form

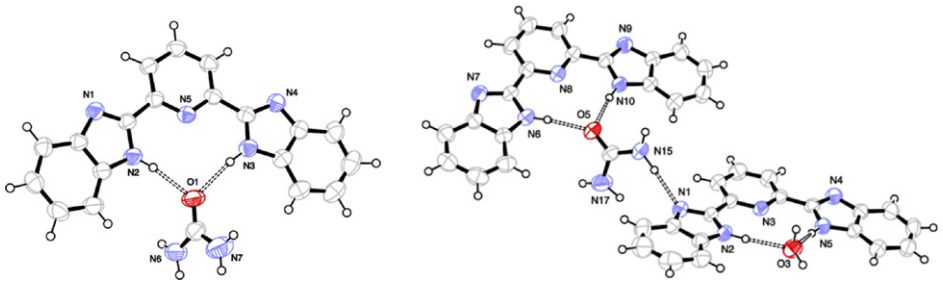

Figure 4. ORTEP diagrams of the hydrogen-bonded **1**: urea complex in the ratio 1:1 (left) and 2:1 (right). Solvent molecules omitted for clarity.

stable supramolecular complexes with urea. The low concentration at which they operate and the low synthetic cost of preparing them make them ideal candidates for designing sensors and building supramolecular complexes with well-defined geometry. Further studies on the behavior of these new receptors to bind neutral and charged guests are underway in our laboratory.

Acknowledgements

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12. A comparable receptor (in terms of binding site) is described in Ref. 8, although a quantitative association constant is not reported for urea (methylated urea derivatives are dealt with quantitatively). The structure also lacks imine nitrogens on the outer core thus restricting the binding possibilities within the cavity of the receptor.
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14. Crystal data of **1** and urea complex in the ratio 1:1. A solution of urea (0.020 g, 33.3 mmol) in methanol was added dropwise to a methanolic solution of **1** (0.104 g, 33.3 mmol) and allowed to stir for 5 min. The vial containing the clear solution of the above mixture was allowed to stand (rt) for 48 h leading to the formation of crystals that were suitable for X-ray diffraction analysis. The data collections of single crystals were performed on a Bruker Nonius Smart Apex II X-ray single crystal diffractometer (CCD). Cell constants and orientation matrices for data collection were obtained from least-square refinement with a set of 45 narrow-frame (0.5° in ω) scans. The structure was solved by direct methods and refined by full-matrix least-squares calculations with SHELX97 software. All hydrogen atoms attached to the heteroatoms were located in the difference Fourier map and refined with isotropic displacement coefficients. $C_{22}H_{25}N_7O_3$, $M = 435.49$, monoclinic, $P2_1/n$, $a = 7.4620(3)$ Å, $b = 19.7030(9)$ Å, $c = 15.0776(6)$ Å, $\beta = 97.583(3)°$, $V = 2197.38(16)$ Å^3, $Z = 5$, $\rho_{calcd} = 1.645$ g cm^{-3}, $\mu = 0.115$ mm^{-1}, $R1 = 0.0571$, $wR2 = 0.1420$. CCDC—606975 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
15. Crystal data of **1** and urea complex in the ratio 2:1. A solution of urea (0.010 g, 16.65 mmol) in acetonitrile was added dropwise to a solution of **1** (0.104 g, 33.3 mmol) in acetonitrile. The solution was allowed to stir for 5 min. The vial containing the clear solution of the above mixture was allowed to stand (rt) for 48 h leading to the formation of crystals that were suitable for X-ray diffraction analysis. C_{39} H_{32} N_{12} O_2, $M = 700.77$, monoclinic, $P2_1/n$, $a = 20.5454(6)$ Å, $b = 7.5836(2)$ Å, $c = 21.8464(6)$ Å, $\beta = 91.596(2)°$, $V = 3402.53(16)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.368$ g cm^{-3}, $\mu = 0.090$ mm^{-1}, $R1 = 0.0543$, $wR2 = 0.1308$. CCDC—604677 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.