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Highly selective imine-linked fluorescent chemosensor for adenine employing multiple hydrogen bonding

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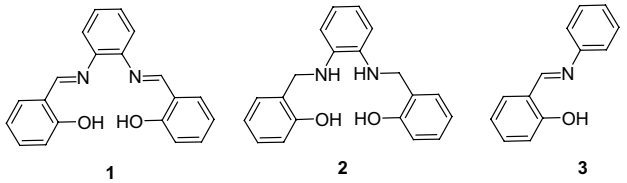
Abstract—We investigated an imine-linked fluorescent receptor bearing both the hydrogen bond donor and the hydrogen bond acceptor motifs as recognition sites in the design of the receptor. The recognition behavior of the receptor toward various nucleobases was evaluated in CH_3CN/H_2O (95:5, v/v) solution. The receptor showed significant changes in fluorescent intensity with adenine, but it showed no such changes on the addition of other nucleobases.

Over the last few years, model studies in molecular recognition have contributed to the development of a wide range of novel molecular devices.[1,2] Within this context, nucleobase recognition is an important challenge in supramolecular chemistry because of its many biological implications.[3–9] To achieve this goal in abiotic receptors, a receptor binding unit for the recognition of a guest and a signaling unit are incorporated into the receptor molecule.[10–16] However, binding of such a receptor in H_2O finds an important competitor in the solvent itself, which retards the interaction between the host and the guest through forces like H-bonding. Therefore, the alignment of receptor binding sites on a receptor platform must achieve complementarily-binding interactions toward a targeted guest. In other words, the chemical and steric features given by a guest molecule have to be matched by a sufficiently predisposed host.[17]

As part of our ongoing studies on a simple and easy-to-make receptor system,[18–21] here we present an adenine binding study of a receptor containing imine linkage. To date, there have been no reports in which an imine-linked receptor is used for the recognition of adenine. The strategy for the design of the receptor is based upon the idea that the receptor has both hydrogen bond donor and hydrogen bond acceptor sites to make a complex effectively with adenine.[22] Receptors **1**–**3** were prepared by following the procedures in the literatures (Scheme 1).[23,24]

Receptor **1** displayed a maximum at 410 nm in its fluorescence spectrum that was recorded with its 10 μM concentration in CH_3CN/H_2O (95:5, v/v) when excited at 365 nm. Receptor **2** lacks any such type of emission with its 10 μM concentration in CH_3CN/H_2O (95:5, v/v). Therefore, the imine chromophore of receptor **1** is responsible for the observed emission. The changes in fluorescence intensity of **1** upon the addition of a particular anion are shown in Figure 1, and the fluorescence ratio $(I_0 - I)/I_0$ is displayed in Figure 2.

As can be seen from Figures 1 and 2, it is clear that there is a marked enhancement in fluorescence intensity of receptor **1** upon the addition of adenine solution. There were no such significant changes in the fluorescence intensity of **1** upon the addition of guanine, thymine, and uracil. This shows that receptor **1** is highly selective



1 2 3

Scheme 1.

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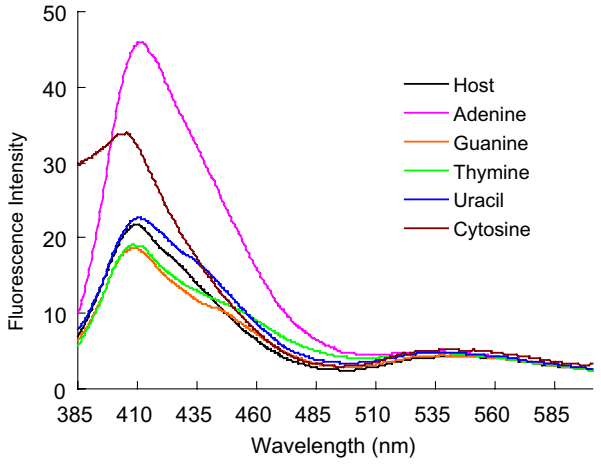

Figure 1. Changes in fluorescence intensity of receptor **1** (10 μM) upon the addition of 2.0 equiv of a particular guest in CH_3CN/H_2O (95:5, v/v) with excitation at 365 nm.

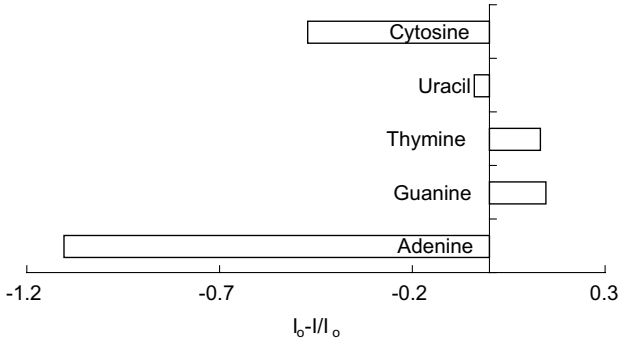

Figure 2. Fluorescence ratio $(I_0 - I/I_0)$ of receptor **1** (10 μM) at 410 nm upon the addition of 2.0 equiv of a particular guest in CH_3CN/H_2O (95:5, v/v).

in its response to adenine in comparison to other nucleobases. The receptor- nucleobase binding strength follows the order of adenine > cytosine ≫ guanine ≈ thymine ≈ uracil. This implies that sp^2 nitrogens of imine linkage of receptor **1** act as hydrogen bond acceptors to form additional hydrogen bonds with the N–H of adenine and cytosine in addition to the hydrogen bonding between receptor O–H and nitrogens of the nucleobase.[25–28]

To confirm our point, we investigated the recognition properties of another compound **3**, which resembles the single pod of receptor **1**. We selected a 20 μM concentration of compound **3** (a 20 μM concentration of **3** has approximately the same number of binding sites as that of a 10 μM concentration of **1**) to investigate the recognition properties. No significant changes in the fluorescence intensity were observed in the typical experiment. This proved that although **1** and **3** have the same type of binding sites only an appropriate size of the pseudocavity of **1** can bind adenine, and a guest is believed to be bound cooperatively in the cavity of **1**.

To learn more about the properties of **1** as a receptor for adenine, fluorescence titrations were carried out. The fluorescence intensity of a 10 μM solution of **1** was enhanced as the concentration of adenine increased as shown in Figure 3. The fluorescence enhancement of receptor **1** may be a consequence of an increase in the conformational restriction of receptor **1** upon the complexation of receptor with adenine. According to this system, as a consequence of the guest coordination, the rigidity of the formed complex increases making the non-radiative decay from the excited state less probable; consequently, the emission intensity increases.[29–31] The association constants K_a of **1** for adenine and cytosine were calculated on the basis of Benesi–Hildebrand plot,[32] and it was found to be $(3.8 \pm 0.3) \times 10^4\ M^{-1}$ and $(2.0 \pm 0.2) \times 10^3\ M^{-1}$, respectively. Thus, receptor **1** can be used for selective recognition of adenine and it can detect adenine as little as a low concentration of 2.1 μM.[33] The stoichiometry of the complex formed was determined by Job's plot,[34] and it turned out to be 1:1.

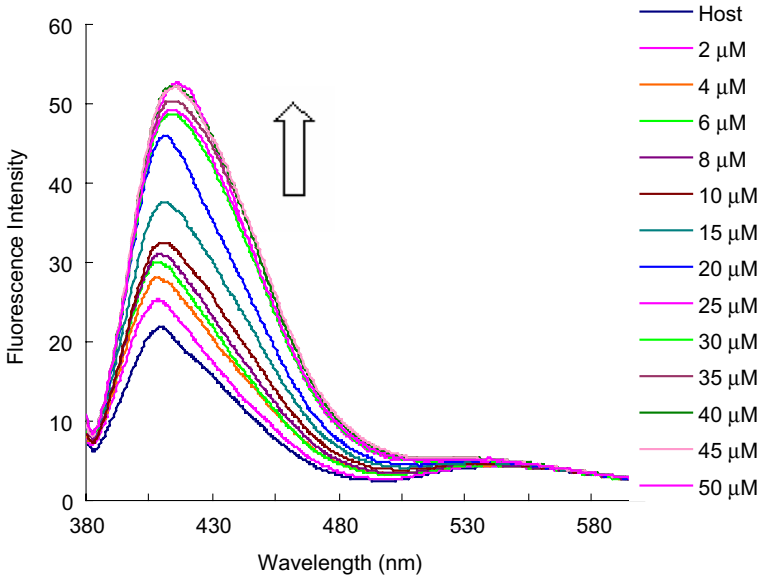

Figure 3. Fluorescence intensity changes of receptor **1** (10 μM) upon the addition of adenine (0–50 μM) in CH_3CN/H_2O (95:5, v/v).

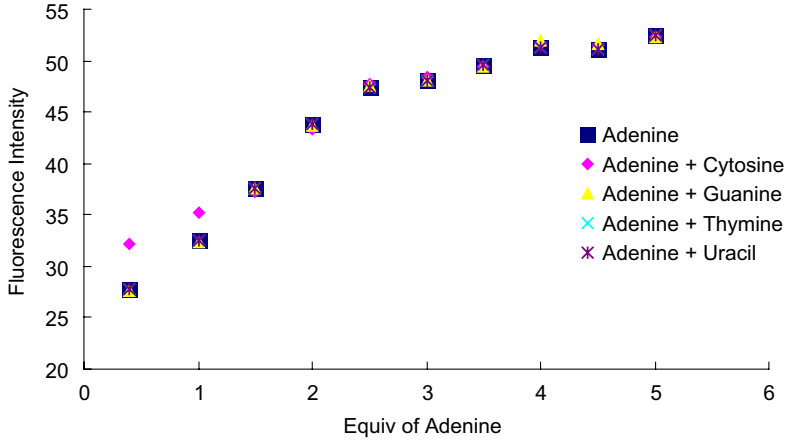

Figure 4. Estimation of adenine in the presence of other nucleobases in CH_3CN/H_2O (95:5, v/v).

To evaluate the effect of polar solvent like water, we carried out titrations between receptor **1** and adenine in different composition of solvent systems. It was found that in a $CH_3CN:H_2O$ (8:2, v/v) solvent system, the water fraction is sufficient to retard hydrogen bonding completely between receptor **1** and adenine.

The system was further extended to estimate adenine in the presence of other nucleobases, which may interfere with estimation (Fig. 4). Experiments were performed to measure the fluorescence intensity in a series of solutions containing receptor **1**, different amounts of adenine, and other nucleobase having a concentration 10 times greater than that of adenine in the CH_3CN/H_2O (95:5, v/v) solvent system. The fluorescence titration of **1** for adenine in CH_3CN/H_2O (95:5, v/v) solution was carried out in the presence of cytosine, guanine, thymine, and uracil. The fluorescence intensity was almost identical to that obtained in the absence of nucleobases with the exception of cytosine. Cytosine caused a small interference when the sample contained a small amount of adenine (up to 10 μM), whereas other nucleobases did not cause any interference with the estimation of adenine.

Every attempt failed to obtain a single crystal of the complex suitable for crystal structure determination. The structure of complex formed between receptor **1** and adenine was determined from energy minimization studies with MacroModel v 9.0 using MM-2* force field (Fig. 5).[35] The structure reveals the binding of adenine in the cavity of receptor **1** through an imine nitrogen of one pod and a hydroxyl hydrogen of the other pod. This binding mode of the complex is further confirmed with

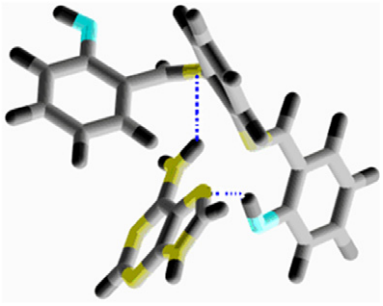

Figure 5. Energy minimized structure of the complex formed between receptor **1** and adenine obtained by MacroModel calculation.

^1H NMR titration that explains the character of the receptor–guest interactions. A series of ^1H NMR spectra of receptor **1** upon the addition of 1.0 equiv of adenine in DMSO-d_6/D_2O (95:5, v/v) are shown in Figure 6. Upon the addition of 1.0 equiv of adenine, the hydrogen of imine signal at δ 8.93 ppm split into two signals with $\Delta\delta = 0.2$ ppm, confirming that two imine protons are in different environment. On the other hand, the C–H proton signal of adenine also shifted with $\Delta\delta = 0.1$ ppm. All the aromatic protons of receptor **1** split and shifted upfield drastically. This illustrates that hydroxyl groups of receptor **1** also undergo asymmetric binding. These synchronized shifts in the signals of receptor **1** and adenine show the strong binding between the host and the guest.

In conclusion, we developed an easy-to-make neutral fluorescent receptor bearing imine linkages and investigated its binding properties toward nucleobases. The

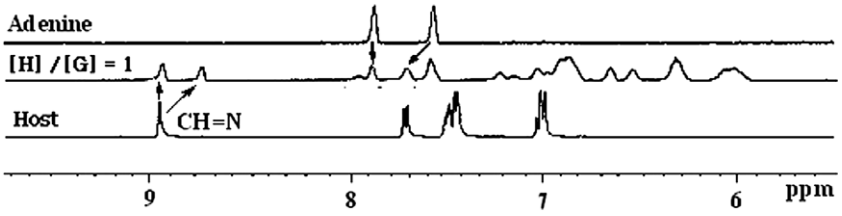

Figure 6. Plot of ^1H NMR spectra of receptor **1** on the addition of adenine in DMSO-d_6/D_2O (95:5, v/v).

newly developed fluorescence receptor shows a high selectivity for adenine over other commonly occurring nucleobases. The receptor acts as a selective sensor for adenine even in the presence of other nucleobases in CH_3CN/H_2O (95:5, v/v) without interference.

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Supplementary data

Supplementary data (spectroscopic measurements) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.027.

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