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Adenine-based urea receptors in fluorescent recognition of iodide

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ABSTRACT

Adenine-based receptors **1** and **2** are designed and synthesized for selective sensing of iodide over the other halides and carboxylate anions. Both the receptors **1** and **2** use the urea motif for binding carboxylates and halides. Emissions of the naphthalene and the anthracene in **1** and **2**, respectively, are monitored in $CHCl_3$ in detecting the anions. While carboxylates, fluoride, chloride, and bromide increase the emissions of naphthalene and anthracene in both the receptors **1** and **2** during complexation, iodide quenches the emission. Such selective quenching allows iodide to be discriminated from other halides and carboxylate anions.

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The design and synthesis of fluorescent receptors for a specific task is of enormous interest in the field of supramolecular chemistry.[1] Sensing and selective recognition of ionic species are of considerable significance because of their important roles in biology.[2,3] Over the past few years, fluorescent receptors for the detection of carboxylates,[4–6] halides,[7–12] etc. have been developed. For complexation of these substrates, different types of binding sites are known, the urea motif being such an example. The hydrogen bonding properties of the urea group play an important role in herbicides, inclusion compounds, and HIV-protease inhibitors.[13] Efforts have also been devoted to establish promising hydrogen bond donor additives in Diels–Alder reactions as well as in catalysis of many important reactions.[14] It is noteworthy that urea/thiourea motifs are used extensively in synthetic receptors for anions.[6,15] We have reported urea-based fluorescent receptors in the perspective of anion recognition.[16] In connection with this, we report new adenine-based urea derivatives for selective recognition of iodide ions.

Iodide plays an important role in several biological processes such as neurological activity and thyroid function. The iodide content of urine and milk is often required to provide information for nutritional, metabolic, and epidemiological studies of thyroid disorder.[17] In this regard, there are very few reports on the fluorescent recognition of iodide.[11,12] To the best of our knowledge, adenine-based receptors have not been used in this capacity to date. Our earlier publication on the selective recognition of dicarboxylic acids[18] by the Hoogsteen (HG) site of an adenine-based receptor inspired us to explore adenine in the wider aspect of supramolecular chemistry. In this connection, we report our observations on adenine-based urea molecules **1** and **2** for fluorescent recognition of iodide ions among other halides and carboxylates.

The receptor molecules **1** and **2** were synthesized from 9-*n*-butyladenine 3 and 9-anthracenylmethyladenine **4** via coupling with 1-naphthylisocyanate (Scheme 1). Compounds **1** and **2** were isolated in 45% and 30% yields, respectively, and were fully characterized[19] by ^1H NMR, ^{13}C, MS, UV, and FTIR.

Urea/thiourea is known to form directed hydrogen bonds with spherical ions (e.g., halide ions), tetrahedral-shaped phosphate, and planar carboxylate anions.[6,15,20] To explore the scope of adenine-based urea molecules **1** and **2** in anion recognition, we performed a systematic study with a number of anionic guest species such as halides and different carboxylate anions. The interaction properties of **1** and **2** were investigated in $CHCl_3$ in the presence of these anionic species by observing the change in fluorescence, UV–vis, and ^1H NMR.

We initially studied the ^1H NMR of **1** in $CDCl_3$, which showed two sharp signals for the urea protons at 12.26 and 8.59 ppm. The downfield signal at 12.26 ppm is due to NH_b, which forms a strong and stable hydrogen bond at the Watson–Crick (WC) site. On dilution with $CDCl_3$, the position of this signal was not changed suggesting its involvement in strong intramolecular hydrogen bonding. The resonance stabilization of the six-membered hydrogen bonded ring forces the other urea proton (NH_a) of **1** to remain in the cisoid form with the urea carbonyl at the Hoogsteen (HG) site. This conformation **A** gives an ADA hydrogen bonding array at the HG site. The conformation **A** may remain in equilibrium with the form **B** in solution (Fig. 1). In the form **B**, there is an ADD

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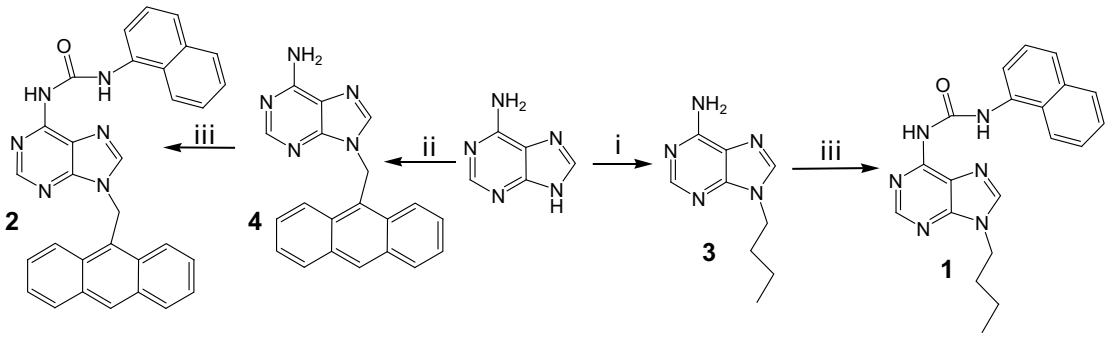

Scheme 1. Reagents and condition: (i) *n*-Butyl bromide, K_2CO_3, dry DMF, rt yield 85%; (ii) 9-chloromethylanthracene, NaH, dry THF, reflux, yield 52%; (iii) 1-naphthylisocyanate, dry THF, reflux, yield: 45% for **1** and 30% for **2**.

hydrogen-bonding array present for complexation with the complementary guest. The same was true for receptor **2**. The chemical shift value of the urea NH_b proton at 12.30 ppm in **2** also suggested the presence of a six-centered hydrogen-bonded structure at the Watson–Crick (WC) site. The urea NH_a proton of **2** appeared at 8.59 ppm. DFT (Density functional theory) calculations[21] on both the forms **A** and **B** of **1** and **2** were performed to realize their stability and conformational flexibility. Figure 2 shows the DFT optimized structures. The conformations **A** of both **1** and **2** are relatively more stable than their corresponding conformations **B** by 10.85 and 10.77 kcal/mol, respectively.

To study the binding and sensing properties of both **1** and **2** in solution, we performed fluorescence and UV–vis titrations in $CHCl_3$ containing 0.04% DMSO in the presence and absence of tetrabutylammonium salts of various carboxylates and halides. The naphthalene receptor **1** displayed a strong fluorescence emission at 395 nm in $CHCl_3$ on excitation at 300 nm. Upon addition of the tetrabutylammonium salts of carboxylates to the $CHCl_3$ solution of **1**, the fluorescence intensity increased gradually. The changes in the fluorescence intensity of **1** upon addition of the tetrabutylammonium salts of benzoic, acetic, mandelic, and pyruvic acids are shown in Figure 3.

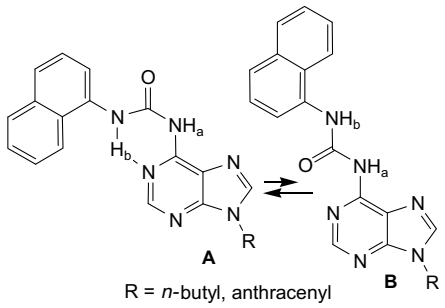

Figure 1. Possible conformations of **1** and **2**.

The increase in fluorescence during complexation is attributed to deactivation of the PET (photoinduced electron transfer) process occurring between the naphthalene moiety and the adenine-linked urea-binding site. With the tetrabutylammonium salts of halides, except iodide, the fluorescence intensity of **1** in $CHCl_3$ under similar conditions was the same as that of carboxylates. In the presence of tetrabutylammonium iodide, the emission of **1** was quenched significantly. This quenching behavior is a characteristic feature of **1** for the fluorimetric identification of iodide among the other anions in the present study. The plot of I_0/I versus [G] in Figure 4 clearly demonstrates the different fluorimetric behaviors of **1** toward halide ions. Figure 5 illustrates the change in emission of **1** in $CHCl_3$ in the presence of increasing amounts of tetrabutylammonium iodide. During titration, the emission of **1** is almost *switched off* without showing any new peak at higher wavelength either for excimer or for exciplex formation. When the experiments were repeated using **2**, where the fluorescence of anthracene was monitored on excitation of naphthalene at 300 nm, similar behavior was observed. Figure 6 shows the change in fluorescence of the anthracene moiety in the presence of the same carboxylates, considered for **1**. Here, it is also noteworthy that the emission of the anthracene unit in **2** increased in the presence of carboxylate salts as with receptor **1**. The results were also reproducible in the presence of the halide salts (Fig. 7). Upon addition of tetrabutylammonium iodide to the $CHCl_3$ solution of **2**, the structured emission of the anthracene moiety decreased steadily to a significant extent (Fig. 8).

No additional peak at higher wavelength for excimer or exciplex was noted during the titrations. The interaction properties of **1** and

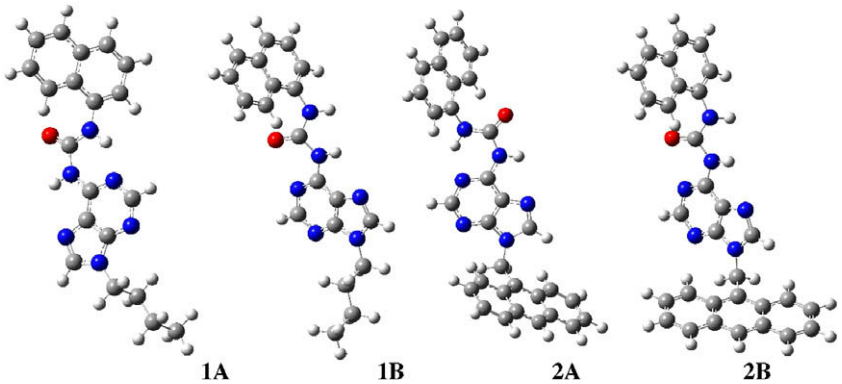

Figure 2. DFT optimized structures of **1** and **2**.

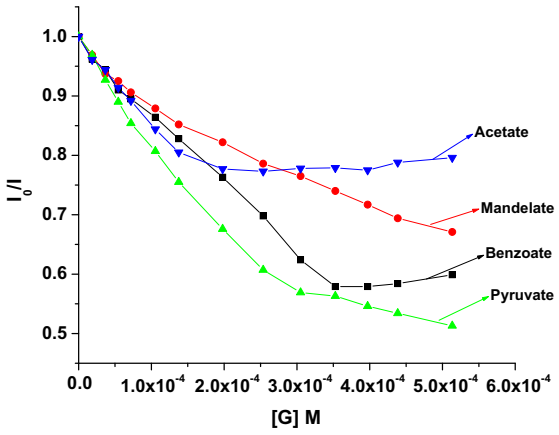

Figure 3. Plot of I_0/I versus [G] at 395 nm for receptor **1** ($c = 7.50 \times 10^{-5}$ M, $CHCl_3$) with carboxylates.

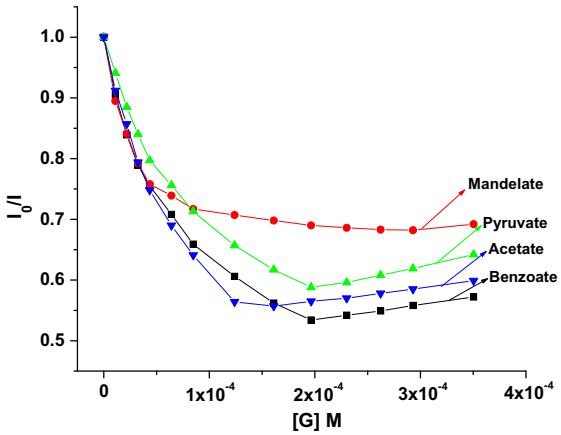

Figure 6. Plot of I_0/I versus [G] at 429 nm for receptor **2** ($c = 4.41 \times 10^{-5}$ M, $CHCl_3$) with carboxylates.

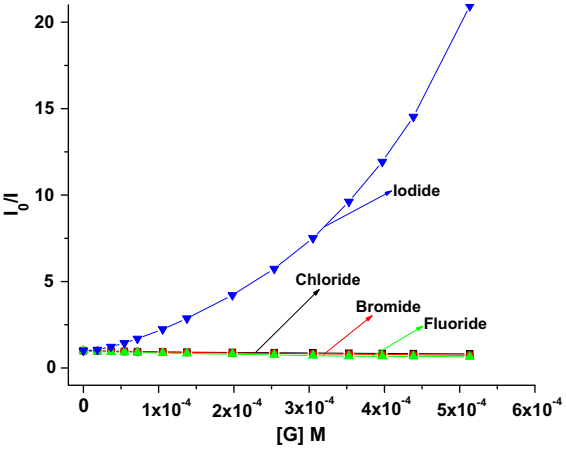

Figure 4. Plot of I_0/I versus [G] at 395 nm for receptor **1** ($c = 7.50 \times 10^{-5}$ M, $CHCl_3$) with halides.

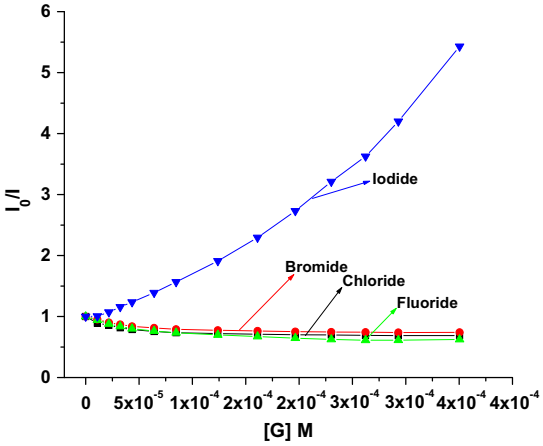

Figure 7. Plot of I_0/I versus [G] at 429 nm for receptor **2** ($c = 4.41 \times 10^{-5}$ M, $CHCl_3$) with halides.

2 with the carboxylates and halides were also monitored by UV–vis titrations. In the presence of all the anions, considered in the present study, the absorbance of **1** at 300 nm decreased to a lesser extent. For example, the change in absorbance of the naphthalene moiety in **1** during titration with tetrabutylammonium iodide is shown in the inset of Figure 5. An isosbestic point was observed which indicated the formation of a new species of **1** with iodide in solution. In contrast, the changes in absorbances of the peaks

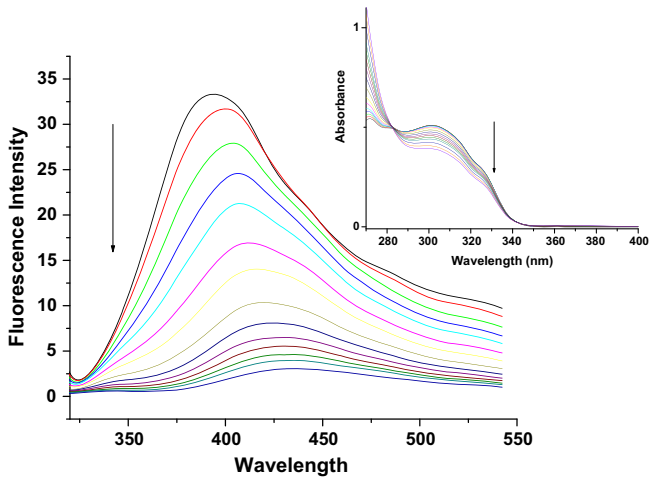

Figure 5. Change in the emission of **1** ($c = 7.50 \times 10^{-5}$ M, $CHCl_3$) at 395 nm upon addition of tetrabutylammonium iodide; inset: change in the absorbance of **1** ($c = 4.03 \times 10^{-5}$ M, $CHCl_3$) in the presence of tetrabutylammonium iodide.

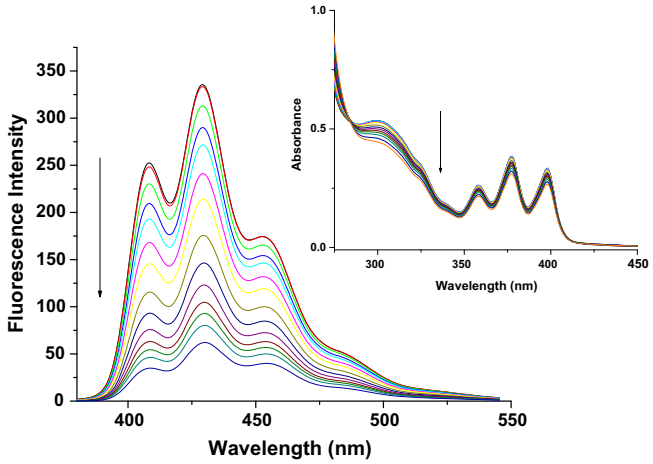

Figure 8. Change in the emission of **2** ($c = 4.41 \times 10^{-5}$ M, $CHCl_3$) at 429 nm upon addition of tetrabutylammonium iodide; inset: change in the absorbance of **2** ($c = 4.21 \times 10^{-5}$ M, $CHCl_3$) in presence of tetrabutylammonium iodide.

at 357, 377, and 398 nm for the anthracene moiety in **2** in the presence of the same guests were minor. The change in absorbance of **2** upon successive addition of tetrabutylammonium iodide is shown in the inset to Figure 8. To understand the binding potencies, emission data obtained from fluorescence titrations were used to determine the association constant values.[22] Due to minor changes in the absorbance of both **1** and **2** in the presence of the guests, the binding constant values were not determined from UV titrations. As can be seen from Table 1, both receptors **1** and **2** showed strong binding with iodide in the excited state, and were able to discriminate iodide from other halides as well carboxylates.

Figure 9 shows a comparative view of the binding constants for receptors **1** and **2** with the various anions. The binding stoichiometries of **1** and **2** with the anions, taken in the present study, were ascertained from the break in the titration curves (Figs. 10 and 11). The breaks in the curves at [G]/[H] = 1 indicate the 1:1 binding stoichiometries of the complexes. At higher concentrations, benzoate and pyruvate attain complex stoichiometries with **1**. The linear nature of the curves, obtained from UV titrations, also supported the 1:1 stoichiometries of the complexes and also intimated weak interactions of the anions in the ground states (see Supplementary data).

Finally, the ^{1}H NMR spectra of both **1** and **2** in presence of the halides and various carboxylates in their 1:1 stoichiometric ratios were recorded in $CDCl_3$ containing 0.04% DMSO-d_6 to understand the nature of the receptor–anion interactions. In the ^{1}H NMR spectra of the respective complexes of **1** and **2**, no significant measurable chemical shift of the urea protons or the adenine ring protons was found. This was due to the inherent existence of the six-centered intramolecular hydrogen bonding of the urea NH_b proton at the WC site in both **1** and **2**. During complexation with iodide, while the urea NH_b proton of **1** showed a weak downfield chemical shift ($\Delta\delta$ = 0.01 ppm), the urea NH_a proton exhibited a weak upfield shift ($\Delta\delta$ = −0.01 ppm). The adenine ring protons H_c and H_d and the naphthalene ring proton H_e underwent downfield ($\Delta\delta$ = 0.01 ppm) shifts in the complex of **1** with iodide. In the case of fluoride, the urea protons were not observed due to deprotonation caused by basic fluoride ions. This is in accordance with our previous results.[16] During complexation of fluoride, the naphthyl proton H_e underwent a large downfield shift ($\Delta\delta$ = 0.03 ppm). These results led us to assume a possible mode of interaction of the halides at the WC site as shown in Figure 12A. When the tetrabutylammonium salts of mandelate and AcO^- were added to $CDCl_3$ solutions of **1**, the urea proton NH_b showed an upfield chemical shift ($\Delta\delta$ = −0.01 ppm) and NH_a exhibited a downfield shift ($\Delta\delta$ = 0.01 ppm). This is presumably due to possible interactions of mandelate and acetate at the HG site of **1** (Fig. 12C). Similar observations were made in the case of **2**.

These results indicate that the fluorescence change is caused by weak hydrogen-bonding interactions between the adenine-based urea and the anions. The quenching of fluorescence of the naphthalene and anthracene units in **1** and **2** in presence of iodide ions is presumably due to an increase in the reduction potential of the adenine-linked urea after anion recognition. This affects the rate of electron transfer from the HOMO of the receptor site to the

Table 1
Binding constant values from fluorescence titrations in $CHCl_3$

Anion[a]	Receptor **1** log*K*	Receptor **2** log*K*
Benzoate	3.74	5.56
Mandelate	4.00	6.24
Acetate	5.69	5.80
Pyruvate	5.56	5.59
F^-	3.14	5.17
Cl^-	4.00	6.01
Br^-	6.19	6.09
I^-	7.59	6.87

[a] Tetrabutylammonium salts were used.

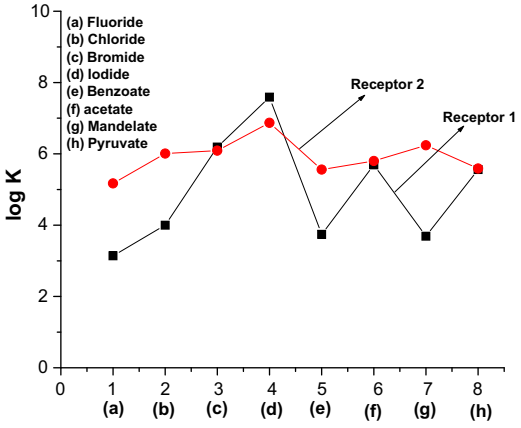

Figure 9. Graphical representation of the association constants log*K* of the complexes formed by receptors **1** and **2** with the anions.

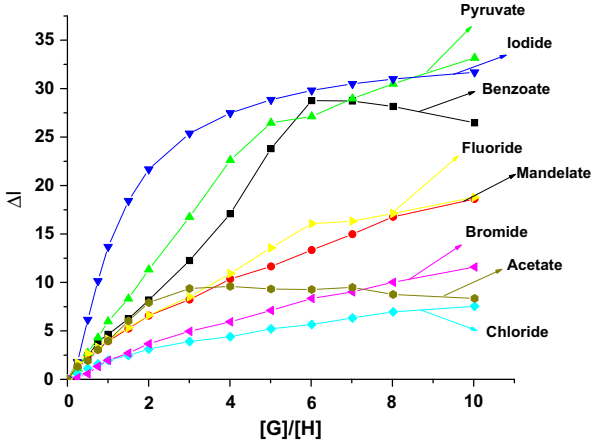

Figure 10. Fluorescence titration curves ([guest]/[host] vs change in emission) for **1** (measured at 395 nm).

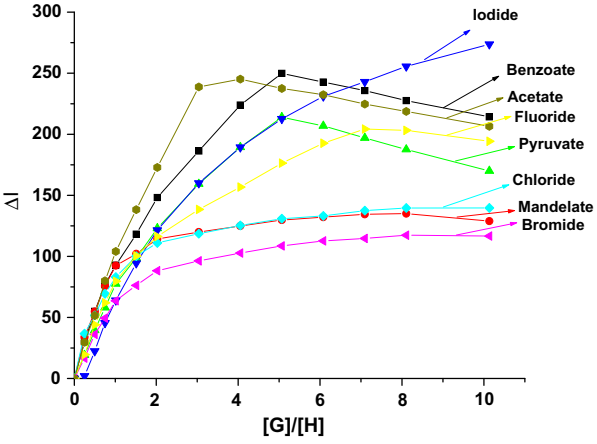

Figure 11. Fluorescence titration curves ([guest]/[host] vs change in emission) for **2** (measured at 429 nm).

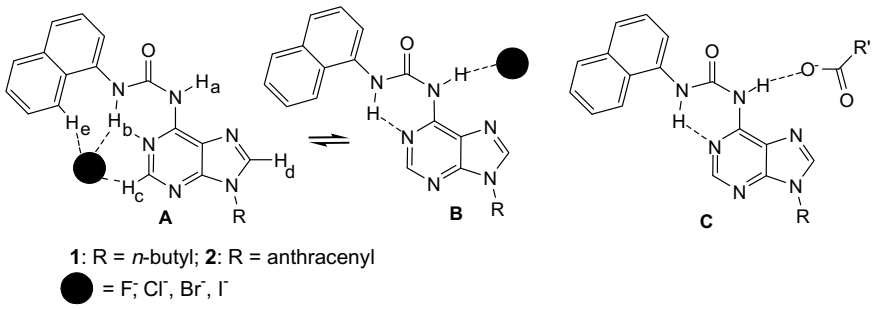

Figure 12. Possible hydrogen bonding structures of the complexes of halide **A** and **B**, carboxylate anions **C** with the receptors **1** and **2** in solution.

excited states of the naphthalene and anthracene moieties of **1** and **2**, respectively.

In conclusion, we have reported the design and synthesis of adenine-based urea derivatives **1** and **2** for the study of adenine in anion recognition for the first time. Both the receptors selectively detect iodide in $CHCl_3$ by showing quenching of the fluorescence of the naphthalene and anthracene units in **1** and **2**, respectively. Other anions in the present study are discriminated from iodide by an opposite effect in the fluorescence. Although the NMR responses of **1** and **2** to anions are weak, the substantial changes in fluorescence of the systems are promising for the detection of iodide. Further investigation and optimization of these adenine-based urea molecules are underway, and will be reported in due course.

Acknowledgments

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Supplementary data

Plots of the changes in absorbance of receptors **1** and **2** with the [Guest]/[Host] ratio and binding constant curves for iodide with receptors **1** and **2** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.009.

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19. Compounds **1** and **2** are partially soluble in $CDCl_3$. Compound **1**: Mp 156 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.26 (s, 1H, –NH–), 8.63 (s, 1H), 8.59 (s, 1H, –NH–), 8.17 (d, 1H, J = 8.40 Hz), 8.12 (d, 1H, J = 8.40 Hz), 7.99 (s, 1H), 7.80 (d, 1H, J = 8 Hz), 7.58 (d, 1H, J = 8 Hz), 7.51 (t, 1H, J = 8 Hz), 7.46–7.39 (m, 2H), 4.21 (t, 2H, J = 8 Hz), 1.16 (q, 2H, J = 8 Hz), 1.30 (m, 2H), 0.88 (t, 3H, J = 7.60 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): 152.2, 150.8, 150.5, 150.0, 143.6, 134.0, 133.3, 128.6, 126.6, 126.1, 125.9, 125.8, 124.4, 121.2, 118.8, 43.8, 31.9, 19.7, 13.3 (one carbon in the aromatic region is missing); FTIR: ν cm^{-1} (KBr): 3396, 3342, 2917, 2848, 1633, 1619, 1585, 1564; HRMS (TOF MS ES$^+$) $C_{20}H_{20}N_6O$ requires 361.1777, found 361.2453. Compound **2**: Mp 210 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 12.30 (s, 1H), 8.61 (s, 1H), 8.59 (s, 1H), 8.42 (d, 2H, J = 8 Hz), 8.24–8.21 (m, 2H), 8.18 (s, 1H), 8.05 (d, 2H, J = 8 Hz), 7.84–7.82 (m, 2H), 7.65 (d, 1H, J = 8 Hz), 7.59–7.43 (m, 7H), 7.23 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): 153.5, 151.6, 151.1, 150.3, 144.6, 133.5, 129.4, 128.2, 128.1, 128.0, 127.1, 126.1, 125.8, 125.5, 125.4, 125.2, 124.9, 124.8, 123.9, 122.7, 121.7, 120.9, 120.7, 117.7, (one carbon in the aliphatic region is missing); FTIR: ν cm^{-1} (KBr): 3423, 3268, 2925, 1635, 1619, 1559; HRMS (TOF MS ES$^+$) $C_{31}H_{22}N_6O$ requires 495.1933, found 495.2811.
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22. Binding constants ($\log K$) were determined using the equation: $\log[(I_{max} - I_F)/(I_F - I_{min})] = \log[\text{guest}] - \log K$ (a) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Biomol. Chem.* **2005**, *3*, 48; (b) Cooper, C. R.; James, T. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 963.