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Anthracene-based *ortho*-phenylenediamine clefts for sensing carboxylates

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This paper is dedicated with profound regards to Professor S. P. Goswami on his 55th birthday.

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ABSTRACT

Two *ortho*-phenylenediamine-based new receptors **1** and **2** with an anthracene-coupled benzimidazolium motif have been designed and synthesized. The directed hydrogen bonds (both conventional and unconventional) and charge–charge interactions allowed the open clefts of both **1** and **2** to bind carboxylate, fluoride and dihydrogenphosphate anions with moderate binding constant values. The selectivity and sensitivity were ascertained by ^{1}H NMR, UV–vis and fluorescence spectroscopic methods. The binding cleft of **2** is found to be more effective than that of **1**.

The development of molecular receptors for recognizing cations, anions, and neutral molecules has been an emerging area of supramolecular chemistry.[1–6] Receptors capable of sensing anions are of paramount interest due to the various important roles of anions in environmental and biological processes.[7–9] Carboxylate anion recognition is important owing to its presence in various biological molecules.[7,10,11] There are various receptors which recognize both mono and dicarboxylates.[12–20] Most of them contain urea/thiourea,[10,19] guanidinium ions,[14,15] imidazolium cations,[18] etc., as potential binders of carboxylates, and they are usually placed in close vicinity of different fluorescent probes in order to report successful recognition events. In this connection, the use of imidazolium and benzimidazolium salts is worth mentioning for their effective involvement in the binding of anions through both charge–charge interactions and unconventional ionic (C–H)$^+\cdots$X (X = O, N, F$^-$, Cl$^-$, Br$^-$, I$^-$) hydrogen bonds.[21–23] The use of such hydrogen bonding features of benzimidazolium/imidazolium ions along with other hydrogen bonding motifs is one strategy in designing new receptors for a specific purpose. As a consequence, there has been recent interest in using both imidazolium and benzimidazolium motifs in devising new receptors for various analytes.[21–23] As part of our ongoing research in supramolecular chemistry,[24] we report here anthracene labelled benzimidazolium-coupled functionalized *ortho*-phenylenediamines **1** and **2**, which provide a set of convergent hydrogen bonds for recognition of carboxylates. The open clefts of **1** and **2** exhibit good recognition abilities for acetate, propanoate, benzoate and dihydrogenphosphate. In contrast to **1**, the receptor **2** shows a better recognition ability with modest selectivity towards acetate over the other anions, particularly mandelate and pyruvate, through N–H$\cdots$O, C–H$\cdots$O hydrogen bonds and charge–charge interactions.

In the designs **1** and **2**, *o*-phenylenediamine motif has been considered as basic unit with two hydrogen bond donors for anion binding. The use of such a motif for anion binding is well established.[25,26] To establish new sensor modules on the *o*- phenylenediamine motif, the inclusion of a fluorescent probe and additional hydrogen bond donors along with charge–charge interactions for effective complexation and detection of anionic guests in solution is one strategy and has been fulfilled easily in the receptors **1** and **2**.

The receptors **1** and **2** were synthesized according to the Scheme 1. In each case, anthracene-coupled benzimidazole **3** (obtained by N-alkylation of benzimidazole using 9-chloromethylanthracene in the presence of NaH in dry THF; see Scheme 1a) was attached to *o*-phenylenediamine-based synthons **5** and **7** to afford the chloride salts of **1** and **2**, respectively. Subsequent anion exchange using NH_4PF_6 gave the desired receptors **1** and **2** in appreciable yields. All the compounds were thoroughly characterized by spectroscopic techniques.[27]

To understand the conformational flexibility as well as the binding features, a conformational search on both the receptors **1** and **2** was performed.[28] The lowest energy conformation, in each

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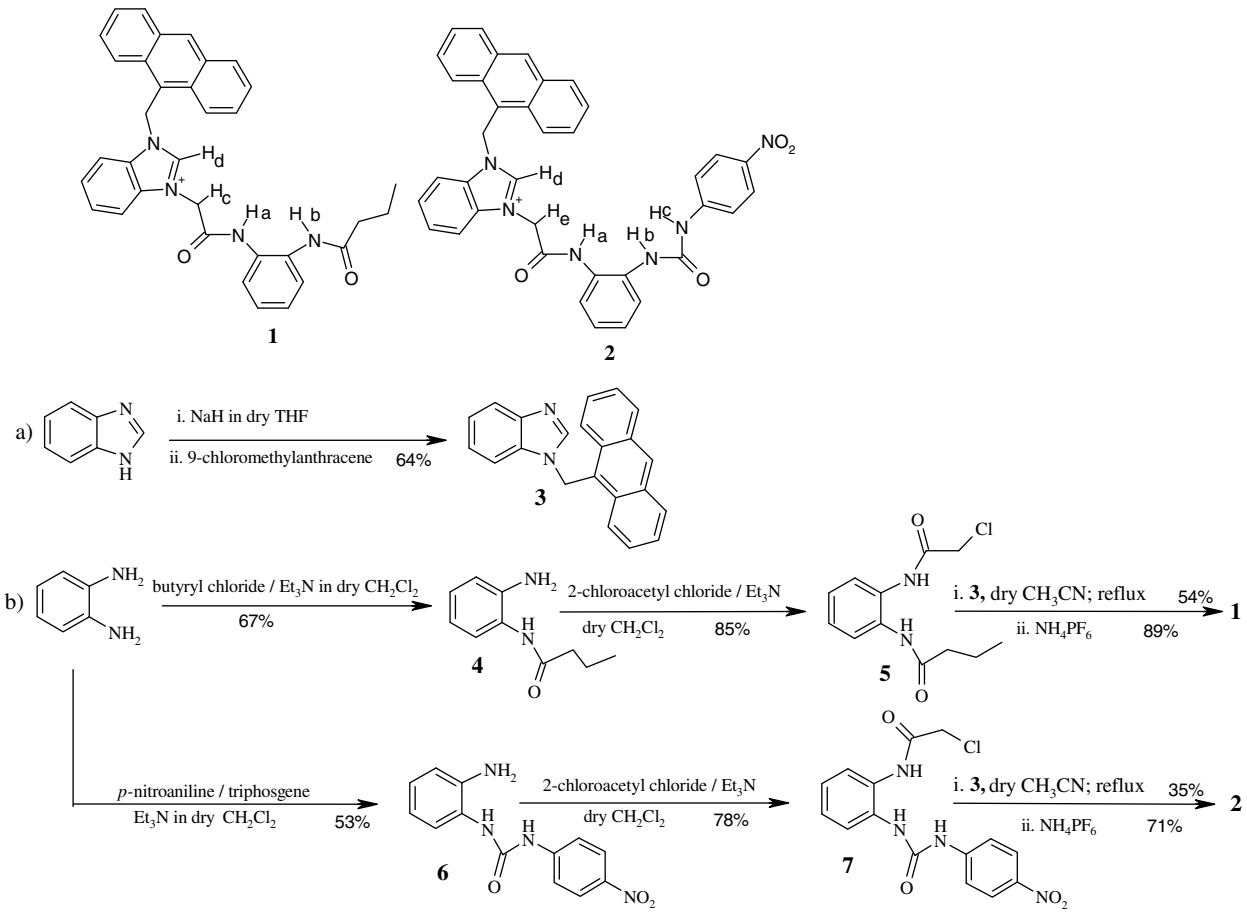

Scheme 1. Syntheses of receptors **1** and **2**.

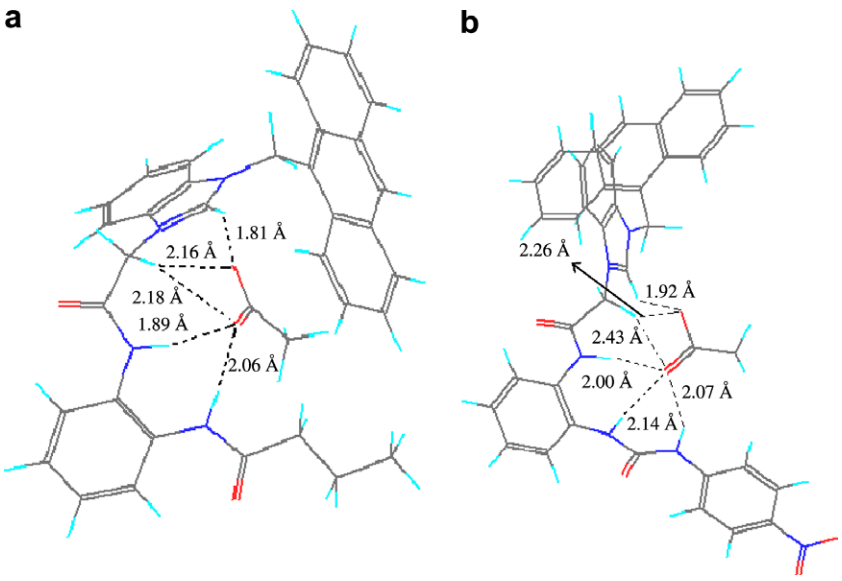

Figure 1. AM1 optimized geometries of: (a) the complex of **1** with acetate (heat of formation = 17.25 kcal); (b) the complex of **2** with acetate (heat of formation = 75.69 kcal).

case, was identified and optimized at the AM1 level. The AM1 optimized hydrogen bonding complexes of **1** and **2** with acetate are shown in Figure 1.

It is worth noting that all the N–H and C–H hydrogen bond donors of both **1** and **2** are cooperatively involved in bonding with carboxylate guests. The charge–charge interaction additionally stabilizes the complexes significantly. In each case, the hydrogens of the linker–CH_2–group also form hydrogen bonds in the gas phase during complexation (Fig. 1).

The interactions of the receptors **1** and **2** in solution with the anions (acetate, propanoate, benzoate, dihydrogen phosphate, mandalate, pyruvate and fluoride, added as their tetrabutylammonium salts) were studied using ^{1}H NMR, UV–vis and fluorescence spectroscopic techniques. The ^{1}H NMR spectra of both receptors

Table 1
Change of chemical shift ($\Delta\delta$) of the interacting protons in 1:1 complexes of the receptors **1** and **2** with anions

	Receptor **1**				Receptor **2**				
Anion	NH_a	NH_b	CH_{2c}	$(C–H_d)^+$	NH_a	NH_b	NH_c	$(C–H_d)^+$	CH_{2e}
Acetate	+1.82	+1.00	+0.11	+0.07	+2.01	+1.07	+2.22	+0.08	+0.07
Propanoate	+1.34	+0.75	+0.07	+0.04	+2.19	+ 1.28	+ 2.34	+ 0.08	+0.07
Benzoate	+1.50	+0.60	+0.14	+0.07	+2.10	+0.77	+1.77	+0.06	+0.08
Dihydrogen phosphate	+2.22	+1.35	+0.26	+0.36	+1.71	+2.12	+1.98	+0.20	+0.16
Pyruvate	+0.52	+0.28	+0.02	+0.03	+1.09	+0.49	+0.88	+0.11	+0.06
Mandelate	+0.18	+0.10	+0.0	−0.01	+1.19	+0.39	+0.88	+0.01	−0.13
Fluoride	+1.02	+0.51	−0.02	+0.02	+0.90	f	f	f	+0.06

+: Indicates downfield shift, −: indicates upfield shift, f: indicates disappearance due to deprotonation.

1 and **2** were recorded in DMSO-d_6 in the presence of anions. All the NH signals of both **1** and **2** were shifted downfield in presence of the guest anions. In addition, the hydrogens of the charged $(C–H)^+$ bond (marked as d) and the linker–CH_2–underwent downfield shifts during complexation. The different extents of the chemical shifts of those key protons of receptors **1** and **2** in their 1:1 complexes with anions are summarized in Table 1. It is evident from Table 1 that the changes in chemical shifts of the interacting protons are significant in the presence of carboxylate and dihydrogen phosphate anions. This was ascribed to their participation in hydrogen bonding and the formation of strong hydrogen bonded complexes such as **2A–B** (Fig. 2). In the presence of fluoride (1:1 stoichiometry with the receptor) the signals for the NH protons of both **1** and **2** were broad and disappeared when excess fluoride was present. This was attributed to hydrogen bonding followed by deprotonation, which we[12] and other groups[29] have noticed earlier. For example, the change in the ^1H NMR spectrum of **2** in the presence of acetate is shown in Figure 1S (see the Supplementary data). All these ^1H NMR observations during complexation clearly indicated that all the hydrogen bond donors in designs **1** and **2** are capable of forming strong complexes with carboxylate, dihydrogen phosphate and fluoride anions.

To gain an insight on the selectivity and sensitivities of both receptors **1** and **2** towards the anions mentioned in Table 1, fluorescence and UV titrations were performed in DMSO. When receptor **1** was titrated with varying concentrations of guests in DMSO, the emission of anthracene at 421 nm was quenched. Figure 3 indicates the change in fluorescence of **1** ($c = 1.00 \times 10^{-5}$ M) upon addition of acetate ions in DMSO.

Similar observations with significant quenching of the emission of anthracene were observed in the case of receptor **2**. During titration, no additional peaks for **1** and **2** at higher wavelengths due to

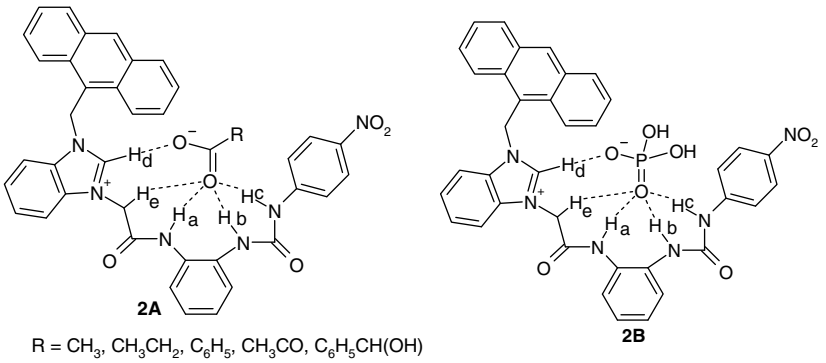

Figure 2. Possible hydrogen-bonding structures of the complexes of receptor **2** with carboxylate and dihydrogen phosphate anions.

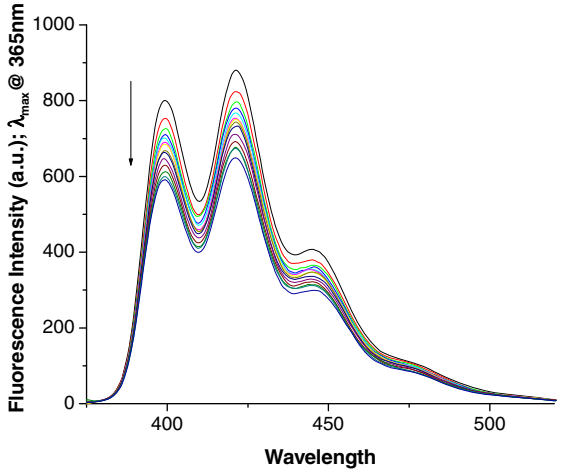

Figure 3. Change in emission of **1** ($c = 1.00 \times 10^{-5}$ M) in DMSO upon addition of tetrabutylammonium acetate.

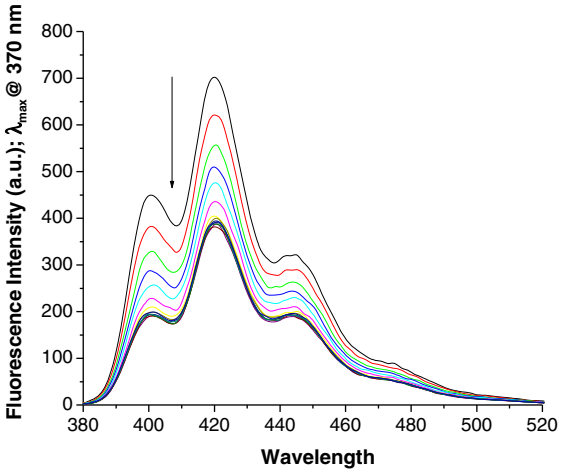

Figure 4. Change in emission of **2** ($c = 4.59 \times 10^{-5}$ M) in DMSO upon addition of tetrabutylammonium acetate.

excimer or exciplex formation were observed. The degree of quenching of the emission varied with the nature of the anions. As shown in Figure 4, receptor **2** displayed a large fluorescence quenching effect upon addition of acetate and dihydrogenphosphate (Figure 2S, see Supplementary data) in DMSO. The fluorescence quenching effect was possibly due to the photo-induced electron transfer (PET) process between the anthracene moiety and the binding site.

The Stern–Volmer plots (Figs. 5 and 6) clearly demonstrate the quenching phenomena. The significant differential quenching of emission of the anthracene moiety of **2** compared to **1** is due to strong non-covalent interactions of the binding site with different complementary guests. The linear nature and the close spacing of the curves in Figure 7 indicate the weak interaction of **1** with the anions. The breaks at [G]/[H] = 1 in the titration curves of Figure 8 indicated the 1:1 stoichiometries of the complexes with the receptor **2**.

To determine the association constants for the complexes formed between receptors **1** and **2** with the anions, UV titrations were performed in DMSO. Receptor **1** ($c = 3.96 \times 10^{-5}$ M) showed absorption bands at 336, 353, 372 and 392 nm for anthracene in DMSO. Upon titration with acetate, significant changes were observed in its UV–vis spectra. On increasing the amount of acetate, the absorbances of the peaks due to the anthracene moiety of **1** decreased in a regular fashion. The changes in absorbance of **1** at 372 nm in presence of other anions were minor (Fig. 9).

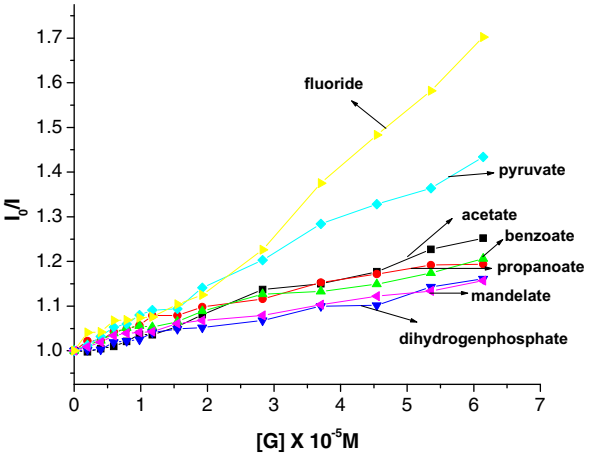

Figure 5. Stern–Volmer plot of **1** at 421 nm.

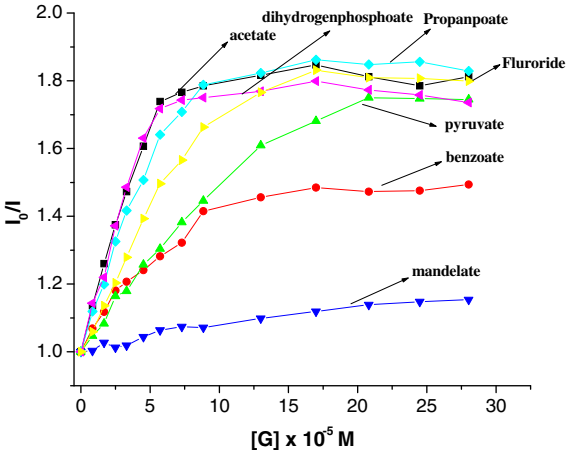

Figure 6. Stern–Volmer plot of **2** at 420 nm.

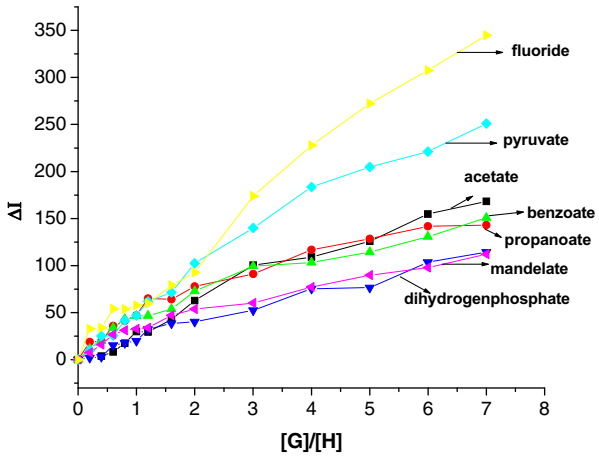

Figure 7. Fluorescence titration curves ([Guest]/[Host] vs change in emission) of **1** (measured at 421 nm).

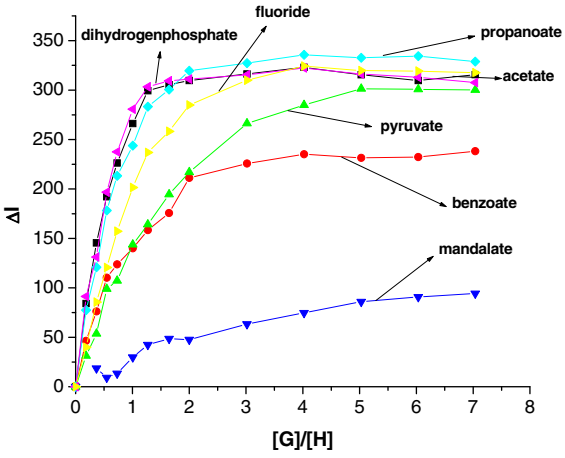

Figure 8. Fluorescence titration curves ([Guest]/[Host] vs change in emission) of **2** (measured at 420 nm).

However, the changes in absorbance of receptor **2** in the presence of acetate, under similar conditions, were appreciable compared to **1**. The initial change in absorbance upto 1:1 stoichiometry was regular and then a downward trend (Fig. 10) was noticed in the presence of excess acetate. This is presumably either due to deprotonation by the basic acetate ions which were

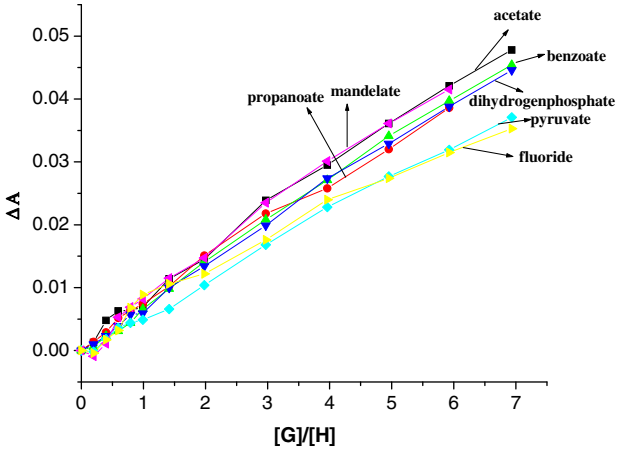

Figure 9. UV titration curves ([Guest]/[Host] vs change emission) for **1** (measured at 372 nm).

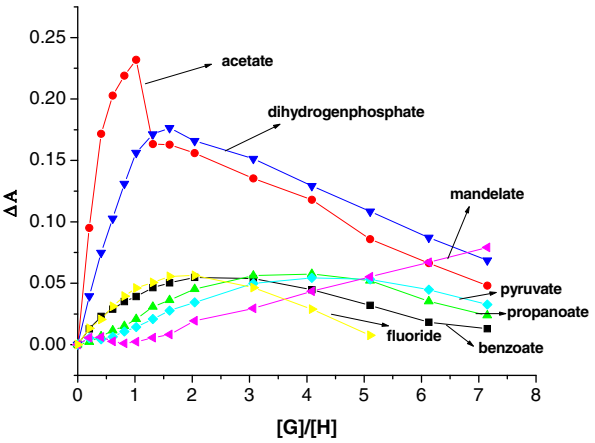

Figure 10. UV titration curves ([Guest]/[Host] vs change emission) for **2** (measured at 371 nm).

Table 2
Binding constant values (K_a) determined by UV–vis titration in DMSO

Anion	Receptor **1** (K_a) in M^{-1}	Receptor **2** (K_a) in M^{-1}
Acetate	2.33×10^4	3.91×10^4
Propanoate	1.98×10^3	1.04×10^4
Benzoate	2.25×10^3	2.36×10^4
Dihydrogenphosphate	1.73×10^3	1.12×10^4
Mandelate	1.00×10^3	4.37×10^3
Pyruvate	5.02×10^2	5.95×10^3
Fluoride	3.79×10^3	1.87×10^4

held less strongly to the binding site or due to decomplexation in the presence of excess acetate. The same was true for fluoride and dihydrogenphosphate (Fig. 10). The binding constants were determined using the Benesi–Hildebrand equation,[30] and the values are given in Table 2.

The 1:1 stoichiometries of the complexes were further realized from the break in the UV-titration curves at [G]/[H] = 1 (Fig. 10). The almost linear nature of the curves in Figure 9 again demonstrated the weak interactions of **1**. As we move from receptor **1** to receptor **2**, the binding constant values are improved significantly and become higher for acetate ions. This is corroborated by the presence of more hydrogen bonds, and the directed nature of the urea linkage of **2** forming a six-membered hydrogen bonding arrangement with the carboxylate oxygen (see Fig. 1). The role of the basicity of the anions in the binding process cannot be ignored.

In conclusion, this Letter demonstrates a rational way to design and synthesize anthracene-coupled benzimidazolium-based *ortho*-phenylenediamine derivatives **1** and **2** and describes the binding properties towards various anions. The cleft of receptor **2** shows preferred binding with acetate, fluoride and dihydrogenphosphate anions over receptor **1** where the complexes are stabilized by both conventional (N–H···O) and unconventional hydrogen bonds [C–H···O, $(C–H)^+$···O] and charge–charge interactions. Further optimization of the binding site of **2** for other anions is underway in our laboratory.

Acknowledgement

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Supplementary data

^{1}H NMR spectra of receptor **2** and its 1:1 complex with acetate, change in emission of receptor **2** in DMSO upon addition of tetrabutylammonium dihydrogenphosphate, changes in the UV spectra of **1** and **2** in DMSO in presence of varying amounts of tetrabutylammonium acetate and the binding constant curves for **2** with acetate, benzoate, dihydrogenphosphate, fluoride are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.096.

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27. *Receptor* **1**: Mp 176–180 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.78 (s, NH, 1H), 9.19 (s, NH, 1H), 8.93 (s, 1H), 8.92 (s, 1H), 8.44 (d, 1H, J = 8 Hz), 8.39 (d, 2H, J = 8 Hz), 8.27 (d, 2H, J = 8 Hz), 8.06 (d, 1H, J = 8 Hz), 7.85 (t, 1H, J = 8 Hz), 7.78 (t, 1H, J = 8 Hz), 7.67–7.60 (m, 4H), 7.51 (d, 1H, J = 8 Hz), 7.33 (d, 1H, J = 8 Hz), 7.14 (t, 1H, J = 8 Hz), 7.08 (t, 1H, J = 8 Hz), 6.80 (s, 2H), 5.29 (s, 2H), 2.19 (t, 2H, J = 7.2 Hz), 1.52 (q, 2H, J = 7.2 Hz), 0.86 (t, 3H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 171.1, 163.5, 142.0, 132.0, 131.3, 131.2, 131.1, 130.9, 130.5, 129.4, 128.9, 127.8, 127.0, 126.7, 125.6, 125.0, 124.6, 124.4, 123.2, 121.6, 114.2, 113.8, 48.9, 43.3, 37.7, 18.3, 13.5 (1 carbon is less); FT-IR: ν cm^{-1} (Nujol): 3597, 3385, 1680, 1651, 1555, 1462; HRMS (TOF MS ES$^+$) $C_{34}H_{31}N_4O_2PF_6$ $(M-PF_6)^+$ requires 527.2442, found 527.2441; *Receptor* **2**: Mp 165 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.12 (s, NH, 1H), 9.81 (s, NH, 1H), 8.95 (s, 1H), 8.93 (s, 1H), 8.41–8.36 (m, 3H including NH), 8.26 (d, 2H, J = 8 Hz), 8.20 (d, 2H, J = 8 Hz), 8.06 (d, 1H, J = 8 Hz), 7.81 (t, 1H, J = 8 Hz), 7.67–7.62 (m, 9H), 7.25 (d, 1H, J = 8 Hz), 7.19 (t, 1H, J = 8 Hz), 7.07 (t, 1H, J = 8 Hz), 6.78 (s, 2H), 5.34 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 163.9, 152.1, 146.3, 142.0, 140.8, 132.2, 132.0, 131.2, 131.0, 130.9, 130.4, 129.3, 128.3, 127.8, 126.9, 126.6, 126.1, 125.5, 125.3, 125.0, 123.8, 123.6, 123.2, 121.6, 117.2, 114.1, 113.8, 48.8, 43.3; FT-IR: ν cm^{-1} (Nujol): 3277, 1721, 1681, 1598, 1552, 1537, 1500, 1329; HRMS (TOF MS ES$^+$) $C_{37}H_{29}N_6O_4PF_6$ $(M-PF_6)^+$ requires 621.2245, found 621.2242.
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