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# Adenine-based receptor for dicarboxylic acids

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**Abstract**—The adenine-based fluorescent receptor **1** was designed and synthesized for the selective recognition of dicarboxylic acids in $CH_3CN$. The recognition takes place through the Hoogsteen binding site of adenine with concomitant PET quenching of the anthracene moiety. The carboxylic acid binding to **1** was investigated by $^1H$ NMR, X-ray, UV–vis, and fluorescence spectroscopic methods. The Hoogsteen (HG) cleft of receptor **1** is found to be selective for glutaric acid.


There is currently great interest in the development of supramolecular systems that have the ability to selectively bind and sense the presence of dicarboxylic acids.[1] Sensing and selective recognition of both mono- and dicarboxylic acids are of considerable attention because of their important roles in biology.[2] Over the past few years, fluorescent chemosensors for the detection of carboxylic acids and carboxylates have been developed.[3] In this respect, one of the recent approaches for the design of fluorescent signaling systems is to exploit photoinduced electron transfer (PET) in *fluorophore-spacer-receptor* systems where the PET process is suppressed or enhanced by the introduction of a substrate into the receptor, exhibiting a fluorescent signal. To date, several receptors containing different functional groups for selective binding of both mono- and dicarboxylic acids have been reported in the literature.[4] In this regard, pyridine amine,[1d,e,5] oxazole amine,[6] cyclic amide,[7] phosphonamide,[8] the phenolic –OH of a cyclotetramer[9] etc., are well-known hydrogen bonding motifs for carboxylic acids and have been extensively used in developing carboxylic acid receptors of various architectures. The search for new hydrogen bonding motifs and their successful installation onto a fluorophore probe in order to develop sensors, for selective recognition of carboxylic acids, has been of continuous interest to the supramolecular chemistry community.

In relation to this, adenine is known to bind carboxylic acids at both the Watson–Crick (WC) and Hoogsteen binding (HG) sites (Fig. 1).[10] Engel reported the experimental differentiation between WC and HG binding sites using 6-*N*-methyl-9-*N*-ethyladenine.[11] From the analysis of data from a direct titration between a carboxylic acid and 9-butyladenine, Maitra et al. showed that aromatic carboxylic acids preferred the HG site for binding 9-butyladenine whereas aliphatic acids preferred the WC site in $CDCl_3$.[12] Rebek[13] and Zimmerman[14] have exploited these binding features of adenine in the construction of synthetic receptors for adenine recognition. The use of adenine in the construction of a synthetic sensor for carboxylic acids is unknown in the literature. Our previous report on anthracene-based PET sensors[15] for both mono- and dicarboxylic acids encouraged us to work on new designs where carboxylic cid recognition takes place at charge neutral recognition sites with concomitant changes in the photophysical properties of a fluorophore by modulation of a photoinduced electron transfer (PET) mechanism. In continu-

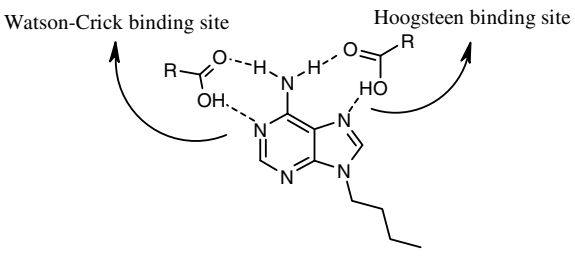


**Figure 1.** Hydrogen bonding sites of adenine with carboxylic acids.

*Keywords*: Anthracene; Adenine; Hoogsteen site; PET sensor; Glutaric acid.
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ation, we herein present our observations on new anthracene-based tweezer-like receptors **1** and **2** with flat hydrophobic surfaces bearing 9-butyl adenine as the recognition determinant, for complexation of both mono- and dicarboxylic acids of different chain lengths. To the best of our knowledge, these are the first examples of anthracene appended adenine-based charge neutral receptors that show ideal PET behavior for carboxylic acids involving the HG site as the principal binding domain. Receptor **1** can be described as a '*receptor-spacer-fluorophore-spacer-receptor*' second generation PET sensor.

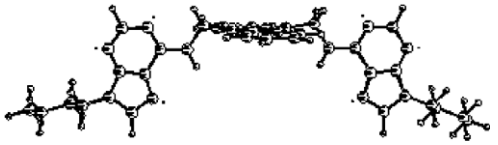
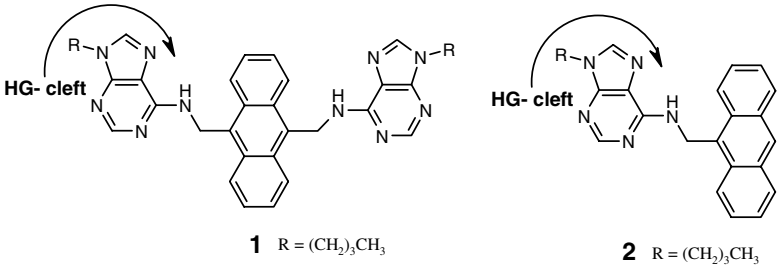


**Figure 2.** Energy minimized structure of **1**.



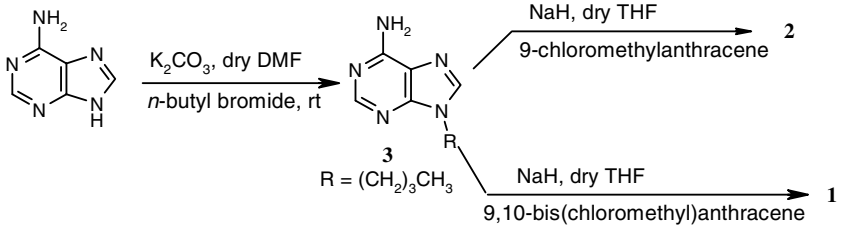

**1** R = $(CH_2)_3CH_3$ **2** R = $(CH_2)_3CH_3$

Receptor **1** was synthesized according to Scheme 1 and was obtained in low yield. Adenine was initially alkylated at the 9-position using butyl bromide in the presence of $K_2CO_3$ in dry DMF to give **3** in 85% yield, subsequent coupling of which with 9,10-bis(chloromethyl)anthracene or 9-chloromethylanthracene afforded **1** and **2**, respectively. This method gave **1** in 9% yield and **2** in 60% yield. All the compounds were characterized by $^1H$ NMR, $^{13}C$ NMR, UV–vis, and mass analyses.

A molecular modeling study[16] on **1** (Fig. 2; $E_{min} =$ 86.84 kcal/mol, $d_{NH-NH} = 6.48$ Å, $d_{N7-N7} = 10.85$ Å) shows the orientation of adenine with amine hydrogens into the HG sites around anthracene. The *syn* form out of various conformations is capable of forming a stable hydrogen bonded complex with dimensionally fitted glutaric acid (see Supplementary data).

To obtain an insight into the binding properties of neutral receptor **1**, we investigated the change in the $^1H$ NMR spectrum of the receptor upon addition of dicarboxylic acids in $CDCl_3$. The –NH– and C(8)–H protons in **1** moved downfield ($\Delta\delta = 0.32$–$0.8$ ppm for NH and 0.01–0.03 ppm for C(8)–H) whereas C(2)–H underwent an upfield ($\Delta\delta = 0.01$–$0.02$ ppm) shift upon complexation with different aliphatic dicarboxylic acids (malonic, succinic, glutaric, adipic, and pimelic). The upfield shift of C(2)–H results from the binding-promoted π-polarization which induces a partial negative charge on the adjacent N-1. The downfield shift of the C(8)–H proton and upfield shift of the C(2)–H proton in **1** during complexation with the diacids in $CDCl_3$, suggests a competitive mode of complexation between the WC and HG sites. To substantiate the site selectivity in complexation, we isolated a single crystal of a 1:1 complex of **1** with adipic acid (Fig. 3a).[17a] The disposition of the HG clefts of **1** in opposite directions led to 1:1 dynamic supramolecular hetero association with adipic acid. The N3 atom of each adenine is coordinated to methanol, which was used for crytallization. In the molecular assembly, the carboxyl moieties are selectively held in the HG clefts of **1** without showing any proton transfer. This observation intimates that the binding of the aliphatic acids in the present case occurs preferentially in the HG site over the WC site. The HG site prefers to bind aromatic acid. Figure 3b, in this connection, further substantiated the binding proposition.[17b] The involvement of the WC site in complexation, although negligible, cannot be ruled out in solution. Benzoic acid in receptor **2** is complexed into the HG site over the WC site through more hydrogen bonds.

With the propensity of the HG site as the preferred binding site for carboxylic acids established, the selectivity and sensitivity of receptor **1** toward a series of aliphatic dicarboxylic acids, as mentioned in Table 1, was evaluated by observing the change in their fluorescence emission in $CH_3CN$. When a solution of **1** ($c = 5.480 \times 10^{-6}$ M) in $CH_3CN$ was excited at 375 nm, the




**Scheme 1.** Synthesis of sensors **1**and **2**.

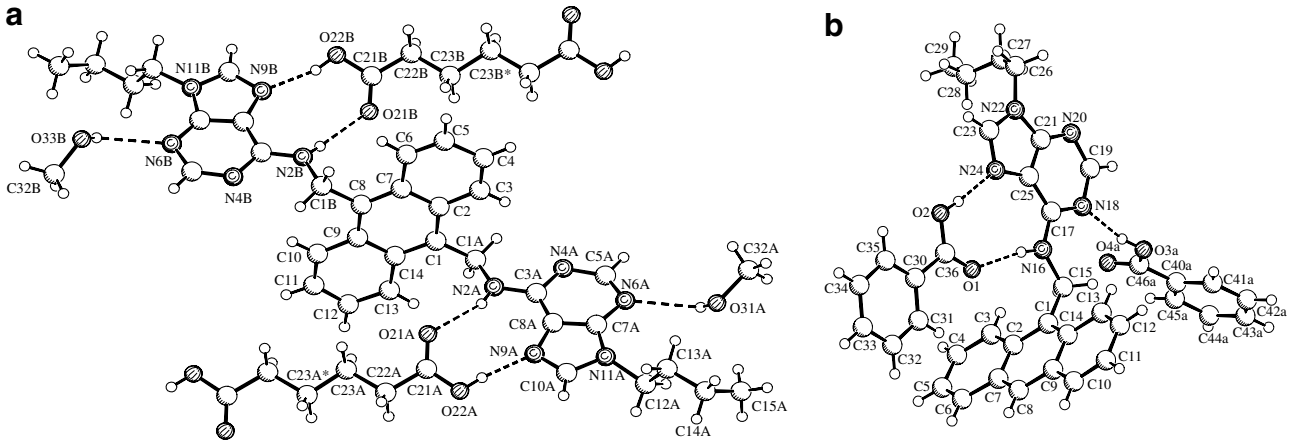



**Figure 3.** Single crystal X-ray structure of (a) **1** with adipic acid and (b) **2** with benzoic acid.

**Table 1.** Association constants of **1** with guest acids

| Diacids[a] | $K_a$ ($M^{-1}$)[b] | $K_a$ ($M^{-1}$)[c] |
|---|---|---|
| Malonic | $1.35 \times 10^4$ | $4.50 \times 10^2$ |
| Succinic | $1.31 \times 10^4$ | $6.52 \times 10^2$ |
| Glutaric | $3.49 \times 10^4$ | $8.27 \times 10^3$ |
| Adipic | $1.03 \times 10^4$ | $9.56 \times 10^2$ |
| Pimelic | $1.49 \times 10^4$ | $3.25 \times 10^3$ |

[a] All the diacids were dissolved in $CH_3CN$ containing 0.5% DMSO.
[b] Determined by the UV method in $CH_3CN$.
[c] Determined by the fluorescence method in $CH_3CN$.

characteristic emissions at 402, 424, and 448 nm for monomeric anthracene were quenched or '*switched off*' to different extents in the presence of dicarboxylic acids without showing any other noticeable changes. Figure 4 shows the changes in fluorescence of **1** upon gradual increase of the concentration of glutaric acid. The extent of quenching (24–31%) with different diacids of different chain lengths, though small (Fig. 5), is of great significance. The quenching is attributed to the hydrogen bonding interactions of the adenine moieties with the carboxylic acid groups of the diacids into the cleft of **1** either in mode A or mode B as shown in Figure 6.

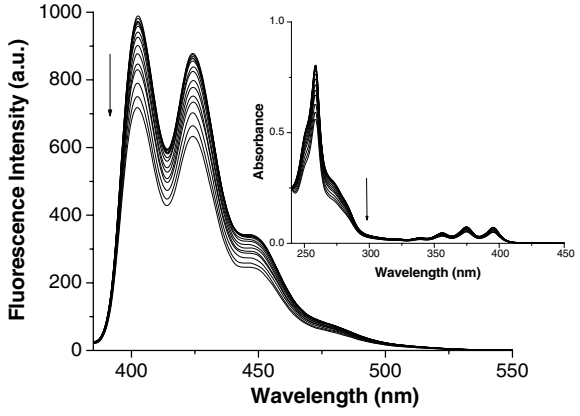



**Figure 4.** Fluorescence spectra of **1** ($c = 5.48 \times 10^{-6}$ M) in $CH_3CN$ and the change in the UV–vis spectra of **1** ($c = 5.48 \times 10^{-6}$ M) (inset) upon addition of glutaric acid.

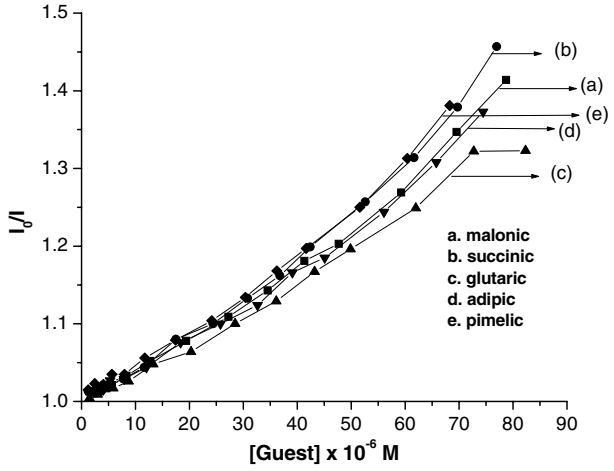



**Figure 5.** Stern–Volmer plot of $I_0/I$ versus concn of carboxylic acid (M).

The diminished fluorescence emission intensity of **1** is due to a thermodynamically favored primary PET between the adenine binding site and the excited chromophore (*Anth). Complexation of adenine will prevent the primary PET and fluorescence of **1**, which in principle, will be switched 'On' on the basis of the normal logic of a fluorescent PET sensor. At the same time, the opposite situation of 'On–Off' switching can be arranged by a secondary PET process (*Anth to adenine site). The present example undoubtedly represents a combination of these two opposite situations resulting in the quenching of fluorescence leading to an 'Off' mode. The same was true for **2** also.

A concurrent study of the absorption spectra of **1** in the presence of the same carboxylic acids show small changes in the anthracene absorption indicating typical PET behavior. The Benesi-Hildebrand analysis of the fluorescence changes observed at 424 nm gave a 1:1 stoichiometry for the complex formed between **1** and glutaric acid with an association constant of $8.27 \times 10^3$ $M^{-1}$.[18] A similar analysis using absorbance at 375 nm also gave 1:1 stoichiometry for the complexes of all the acids with **1**. The association constants are

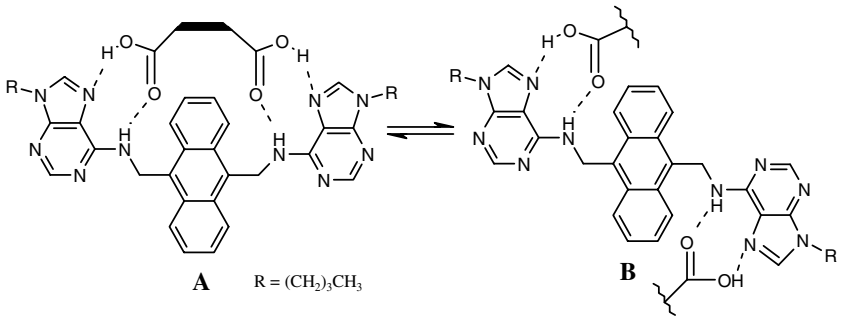



**Figure 6.** Possible hydrogen bonded complex modes of dicarboxylic acids in the HG cleft of **1**.

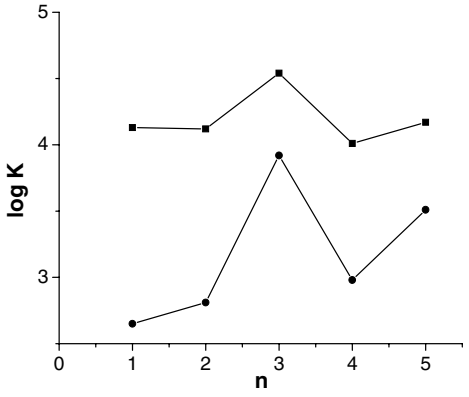



**Figure 7.** Graphical representation of the association constants $\log K$ of the complexes formed by receptor **1** with $HO_2C$–$(CH_2)_n$–$CO_2H$ against the number ($n$) of atoms connecting the two carboxylic acids (solid cubes: UV titration; solid circles: fluorescence titration).

accumulated in Table 1. Figure 7 shows the calculated stability constants as a function of the aliphatic chain lengths connecting the two carboxyl ends for a series of linear aliphatic dicarboxylic acids $HO_2C$–$(CH_2)_n$–$CO_2H$, with $n$ ranging from 1 to 5 and clearly predicts a preference for glutaric acid over both the short and long chain diacids. The preference is greater in the excited state. This is due to the formation of a stable 1:1 hydrogen bonded complex. The stoichiometry of the complexes was also confirmed by a Job plot analysis (see Supplementary data). In addition, a plot of emission changes in fluorescence at 424 nm versus [G]/[H] for all the diacids as mentioned in Table 1, gave almost linear instead of sigmoidal responses. We believe this is probably due to the interaction of the individual adenine unit with the carboxylic acid motif in mode B instead of A as shown in Figure 6. The possibility of formation of hydrogen bonded complexes A (Fig. 6) with dimensionally fitted dicarboxylic acids in solution also cannot be ruled out.

The fluorescence sensitivity of **2** ($c = 1.26 \times 10^{-5}$ M) with the monocarboxylic acids was also observed and **2** exhibited the same 'On–Off' switching behavior as **1** in $CH_3CN$. It was found that receptor **2** binds benzoic and acetic acids with association constants of $4.29 \times 10^3\ M^{-1}$ and $2.71 \times 10^3\ M^{-1}$, respectively. The values are slightly less in magnitude than those obtained for dicarboxylic acids with **1** and also indicate that the cleft in **2** has a marginal preference for an aromatic acid.

In conclusion, we have shown that the selective recognition of a dicarboxylic acid by the HG cleft of an adenine-based receptor is possible. Further optimization of the HG binding pocket using a combinatorial approach can now be used to improve both the affinity and selectivity. Such work is in progress in our laboratory.

## Acknowledgments

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## Supplementary data

Job plot of **1** with glutaric, adipic, and pimelic acids, energy minimized structure of the complex of **1** with glutaric acid, experimental procedures for the syntheses of **1** and **2**, $^1$H NMR, $^{13}$C NMR, and mass spectra of 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.2007.07.110.

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16. Energy minimization was carried out using MMX (PC Model Serena Software 1993). Molecular modeling was performed using standard constants, and the dielectric constant was maintained at 1.5.
17. (a) *Crystal data of the 1:1 complex of adipic acid with* **1**: $C_{34}H_{36}N_{10}\cdot 2/2C_6H_{10}O_4\cdot 2/2CH_3OH$, monoclinic, $P2_1/n$ (No. 14), $a = 14.321(1)$, $b = 14.814(1)$, $c = 18.512(1)$ Å, $\beta = 98.80(1)^{\circ}$, $V = 3881.1(4)$ Å$^3$, $T = 198(2)$ K, $Z = 4$, $\rho_{calcd} = 1.306$ mg m$^{-3}$, 25,333 total reflections of which 6811 were independent, 3690 observed [$I > 2\sigma$ ($I$)]. Structure solution and refinement with SHELXS-97 and SHELXL-97, final refinement against $F^2$ with 601 parameters, $R_1$ [$I > 2\sigma$ ($I$)] = 0.114, $wR^2 = 0.268$.; (b) *Crystal data of the complex of benzoic acid with* **2**: $C_{24}H_{23}N_5\cdot C_7H_6O_2\cdot 1/2C_7H_6O_2$, triclinic, $P\bar{1}$ (No. 2), $a = 10.492(1)$, $b = 11.247(1)$, $c = 13.288(1)$ Å, $\alpha = 76.45(1)$, $\beta = 82.04(1)$, $\gamma = 74.42(1)^{\circ}$, $V = 1463.6(2)$ Å$^3$, $T = 223(2)$ K, $Z = 2$, $\rho_{calcd} = 1.281$ mg m$^{-3}$, 20,123 total reflections of which 5151 were independent, 4487 observed [$I > 2\sigma$ ($I$)]. Structure solution and refinement with SHELXS-97 and SHELXL-97, final refinement against $F^2$ with 418 parameters, $R_1$ [$I > 2\sigma$ ($I$)] = 0.069, $wR^2 = 0.182$. CCDC Nos. 648928 and 648929.
18. Binding constants were determined using the expression $A_0/(A_0 - A) = [\varepsilon_M/(\varepsilon_M - \varepsilon_C)]\,(K_a^{-1}\cdot C_g^{-1} + 1)$ where $\varepsilon_M$ and $\varepsilon_C$ are the molar extinction coefficients of receptor **1** and hydrogen bonding complex, respectively, at a selected wavelength. $A_0$ denotes the absorbance of free receptor **1** at that specific wavelength and $C_g$ is the concentration of carboxylic acid guest. The measured absorbance [$A_0/(A_0 - A)$] as a function of the inverse of carboxylic acid guest concentrations fits a linear relationship, indicating 1:1 stoichiometry of the receptor/carboxylic acid complex. The ratio for the intercept versus slope determines the binding constant ($K_a$) and the binding constant values using fluorescence intensity were calculated using the expression $F_0/(F_0 - F) = [\phi_M/(\phi_M - \phi_C)]\;(K_a^{-1}\cdot C_g^{-1} + 1)$. Chou, P. T.; Wu, G. R.; Wei, C. Y.; Cheng, C. C.; Chang, C. P.; Hung, F. T. *J. Phys. Chem. B* **2000**, *104*, 7818–7829.