Anthracene-coupled Pyridine Amines: A New "Off–On" Switch for Molecular Recognition Studies on Dicarboxylic Acids

Kumaresh Ghosh* and Goutam Masanta
Department of Chemistry, University of Kalyani, Kalyani, Nadia-741235, India

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The fluorescent photoinduced electron-transfer (PET) chemosensor **1**, which can function as "off–on" fluorescence switch for dicarboxylic acids has been designed and synthesized for the first time. The carboxylic acid binding takes place through charge neutral pyridine amine receptor sites and the sensor is found to be selective for glutaric acid. The binding has been examined by fluorescence, UV–vis, and NMR spectroscopic methods.

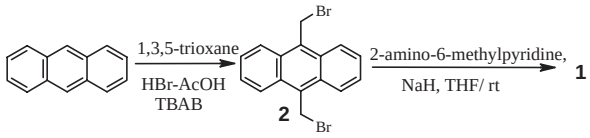
The detection of a given analyte by a chemosensor requires a receptor unit that selectively interacts with the substrate of choice and a method to read out the binding using a change in a physical signal.[1] In this aspect, one of the recent approaches to the design of fluorescent signaling systems is to exploit the 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. Over the past few years, a large number of PET sensors have been developed for various guests ranging from charged to neutral in nature.[2] In this context, the recognition and sensing of dicarboxylic acids has been attracted considerable attention owing to the important roles of both mono- and dicarboxylic acids in biology.[3] To date, several receptors containing different functional groups for selective binding of dicarboxylic acids have been reported.[4] However, the sensors based on PET process for dicarboxylic acids are still rare.[5] We, for the first time, used the anthracene-coupled pyridine amide as PET sensor for molecular recognition studies on monocarboxylic acids.[6] The results were encouraging and further tempted us to extend it for dicarboxylic acid recognition. In this paper, we, therefore, report the design and synthesis of a tweezer-like sensor **1** with a flat hydrophobic surface for size selective recognition of dicarboxylic acids where the recognition takes place at charge neutral pyridine amine sites with concomitant changes in the photophysical properties of anthracene by modulation of a photoinduced electron transfer (PET) mechanism.

Pyridine amide is a well-known hydrogen-bonding motif for carboxylic acids and has been utilized in several designs for carboxylic acid recognition.[4] As far as we are aware, there has not been any report on the introduction of such groups on to the anthracene moiety for dicarboxylic acid recognition.

The key in this design is the appropriate linker length and rigidity, and the relative orientations of the two-pyridine amine units. Molecular modeling[7] studies indicated the relative orientation of two pyridine units (*in–in* conformation) of **1** (E_{min} = 47.80 kcal/mol) with a distance of separation of 10.41 Å between two ring nitrogens.

The synthesis of this sensor **1** as being designed as "receptor–spacer–fluorophore–spacer–receptor" is outlined in Scheme 1. The simple synthesis of **1** involves the coupling of pyridine amine with 9,10-di(bromomethyl)anthracene (**2**), which was obtained from anthracene using literature procedure.[8] This method produced **1**[9] in 50% yield as yellowish solid.

The sensing property of this ditopic receptor towards a series



Scheme 1. Synthesis of receptor **1**.

of aliphatic dicarboxylic acids of various chain lengths was examined by observing the change in fluorescence emission spectra in CH_3CN. The fluorescence spectra of **1** showed bands at 406, 430, and 453 nm for anthracene when excited at 360 nm in CH_3CN. Upon addition of dicarboxylic acids (dissolved in CH_3CN containing 0.03% DMSO) of different chain lengths the emission was drastically enhanced due to formation of receptor-diacid complexes as indicated in Figure 1. During the titration, there was no other spectral change in the emission spectra. Upon addition of increasing concentration of dicarboxylic acids of various chain lengths the fluorescence of **1** was essentially "switched on" to different extents with a slight blue shift of the peaks ($\Delta\lambda$ = 4 to 6 nm) for anthracene. Figure 2 shows the change in fluorescence intensity with increasing concentration of added glutaric acid. Concurrent changes of absorption spectra (peaks at 356, 375, and 394 nm) of the anthracene moiety were only minor (Figure 2; inset) indicating the insulating role of two $-CH_2-$ spacer which minimizes the ground-state interactions between the fluorophore and the carboxylic acid receptor. This suggests that **1** behaves as a typical PET sensor; the only interaction be-

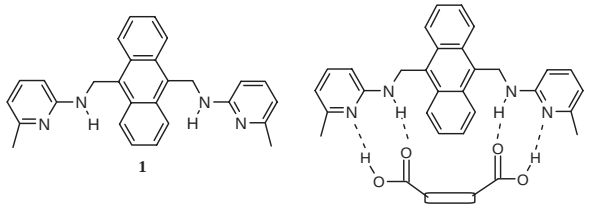


Figure 1. Hydrogen-bonded complex of dicarboxylic acids with **1**.

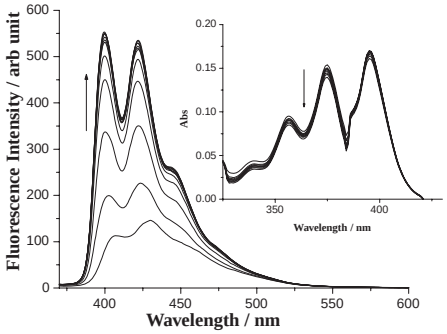


Figure 2. Fluorescence spectra of **1** ($c = 9.55 \times 10^{-7}$ M) in CH_3CN upon addition of glutaric acid (From below: 0, 0.25, 0.49, 0.74, 0.98, 1.3, 1.9, 2.7, 3.5, 4.5, 5.5, and 6.4 μM). Inset: Change of UV–vis spectra of **1** (1.91×10^{-5} M) upon addition of glutaric acid.

Table 1. Association constants by fluorescence method

Diacids	Association constants (K_a) M^{-1}
2,2-Dimethylmalonic	4.71×10^5
Succinic	3.47×10^5
Glutaric	1.49×10^6
Adipic	7.59×10^5
Pimelic	2.95×10^5
Suberic	8.06×10^4

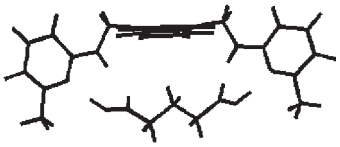


Figure 3. Energy minimized hydrogen-bonded complex of glutaric acid with **1**.

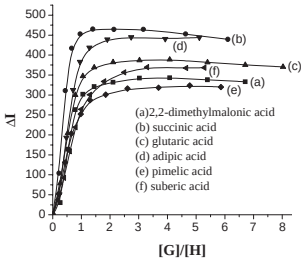


Figure 4. Fluorescence titration curves ([Guest]/[Host] vs change in fluorescence intensity) for **1** (measured at 430 nm) with the diacids.

tween the two moieties is via electron transfer. During fluorescence titration, it is believed that the hydrogen-bonded complexation prevents the thermodynamically favored PET process between anthracene and the pyridine amine moieties in **1** and as expected, retrieves the fluorescence of anthracene. The association constants[10] of sensor **1** with different aliphatic dicarboxylic acids were determined (Table 1) in order to measure the selectivity and affinity of **1** for a dicarboxylic acid of particular chain length. From Table 1, it is seen that the respective binding constants of **1** exhibit a modest dependence on the chain length of the dicarboxylic acids. The receptor **1** shows a higher affinity to glutaric acid among other diacids. Computer modeling study also indicates that in the lowest energy conformation, the two-pyridine amines bind tightly two carboxylic acid motifs of glutaric acid (Figure 3). The less dimensional match between diacids, which possess too short (malonic) or too long chain lengths (suberic) and the receptor **1** results in weaker binding. In this connection, the role of two thiourea motifs flanked by anthracene for malonate, glutarate with PET quenching of the anthracene moiety is worth mentioning.[5]

The break of the titration curves (Figure 4) indicates the stoichiometry of the complexes. We also additionally performed a continuous variation Job plot in UV to ascertain the stoichiometries. Figure 5 indicates the 1:1 complexation of glutaric acid with **1**. It is mentionable that suberic acid being longer exhibits a 2:1 stoichiometry (guest:receptor).

Furthermore, the binding was examined by ^{1}H NMR. The receptor **1**, in $CDCl_3$, showed a sharp peak at 4.55 ppm for the amine protons, which underwent a considerable downfield shift ($\Delta\delta =$ 1–1.30 ppm) upon addition of 1 molar equiv. of the diacids studied, suggesting that amino pyridyl moieties serve as potential binding sites for dicarboxylic acids. The large downfield shift of the amine protons indicates the complexation like that of Figure 1, neglecting the possibility of the protonation of both

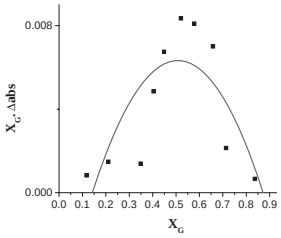


Figure 5. Job plot extracted from the UV titration indicating the 1:1 complex stoichiometry with glutaric acid.

the ring and amine nitrogens. This was proved by taking ^{1}H NMR of **1** in less polar solvent $CDCl_3$ in the presence of TFA which showed the facile protonation by exhibiting the new appearance of peaks at 7.03 and 10.97 ppm for protonated ammonium and pyridinium groups, respectively. The absence of those peaks for the diacids studied, thus ruled out the case of protonation. In this regard, the beneficial use of simple alkylated pyridine amine in recognition of dicarboxylic acids without proton transfer is well documented by Bielawski et al.[11]

In conclusion, we have thus developed a new fluorescent chemosensor **1**, which is simple, easy to make and shows good photophysical behavior upon dicarboxylic acid recognition allowing better "off–on" switchability. The open cavity of **1** shows good chain length selectivity to aliphatic dicarboxylic acids and is found to be selective to glutaric acid. Further study along this direction is under progress in the laboratory.

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7 Energy minimization was carried out by MMX (PC Model Serena Software 1993). Molecular modeling was performed using standard constants, and the dielectric constant was maintained at 1.5.

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9 Receptor **1**, mp = 168 °C, ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) 8.38 (4H, dd, $J_1 = 8$ Hz, $J_2 = 3.2$ Hz), 7.51 (4H, dd, $J_1 = 8$ Hz, $J_2 = 3.2$ Hz), 7.39 (2H, t, $J = 8$ Hz), 6.53 (2H, d, $J = 8$ Hz), 6.34 (2H, d, $J = 8$ Hz), 5.40 (4H, s), 4.56 (2H, –NH–, brs), 2.46 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 157.9, 157.1, 137.7, 130.7, 130.2, 126.0, 124.9, 112.4, 103.8, 39.0, 24.4; Mass: 419.2 $[M + H]^+$, 311.2, 299.1, 193.2. FTIR (ν cm^{-1}, KBr) 3417, 2922, 1598, 1460.

10 Binding constants were determined by using the expression $I_0/I - I_0 = [\phi_M/(\phi_M - \phi_C)](K_a^{-1} \cdot C_g^{-1} + 1)$ where ϕ_M and ϕ_C are the quantum yields of the receptor **1** and the receptor–dicaid complex, respectively. The measured fluorescence intensities $[I_0/(I - I_0)]$ as a function of the inverse of dicarboxylic acid guest concentrations are plotted. The ratio for the intercept versus slope deduces the Association constant (K_a); P. T. Chou, G. R. Wu, C. Y. Wei, C. C. Cheng, C. P. Chang, F. T. Hung, *J. Phys. Chem. B* **2000**, *104*, 7818.

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