J Incl Phenom Macrocycl Chem (2010) 68:447–452
DOI 10.1007/s10847-010-9808-2

ORIGINAL ARTICLE

Naphthalene appended 2,5-diketopiperazine towards fluorometric response of dihydrogenphosphate

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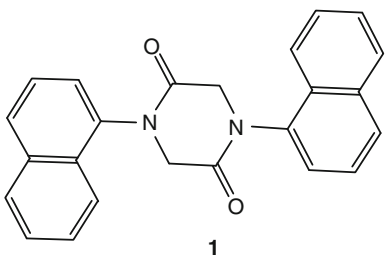
Received: 23 September 2009 / Accepted: 21 May 2010 / Published online: 8 June 2010

Abstract Naphthalene-based 2,5-diketopiperazine **1** has been synthesized in two steps with moderate yield. The compound shows water templated hydrogen bonded assemblies in the solid state and exhibits unique hydrogen bond mediated emission properties in solution. The monomer emission of **1** in $CHCl_3$ containing 0.1% DMSO is significantly quenched in the presence of large excess of dihydrogenphosphate anion and aliphatic dicarboxylic acids of different chain lengths followed by the appearance of a new peak of moderate intensity at higher wavelength for excimer. The appearance of excimer emission of moderate intensity in presence of $H_2PO_4^-$ distinguishes it from other guests in the present study.

Keywords 2,5-Diketopiperazine · Excimer · Dihydrogenphosphate recognition · Fluorometric response

Introduction

Synthesis of structurally simple and easy-to-make fluorescent compounds with hydrogen bond donor and acceptor sites is useful in the detection of important small molecules [1, 2]. Hydrogen bond formation with the guests sometimes leads to an aggregation of the host in such a way that the photophysical properties of the host molecule are changed significantly and thus becomes useful for the specific detection of guests in solution. Examples of this class are known in the literature [3, 4]. Inspite of the progress made in this area, design and synthesis of new molecular architectures is still demanding. In order to devise such molecules the different polar functionalities are required to meet the successful host–guest interaction. Amide is one the functionalities that is incorporated in the design of various hydrogen bonding hosts. It is planer and forms hydrogen bonds with well-understood geometrical constraints. In this aspect, two substituted amides which are separated by one carbon atom in the cyclic molecules is interesting [5]. Diketopiperazine (DKP) is an example of this class [6]. The geometry of the DKP rings varies as a function of the number and placement of substituents on the carbon atom adjacent to amide carbonyl of the ring. Even the substitution onto the nitrogen centre of DKP molecule has the influence in controlling the geometry of the molecule as well as supramolecular interaction with the latice solvents [7]. During the course of our work on supramolecular chemistry, we report here the synthesis and photophysical studies of naphthalene appended 2,5-diketopiperazine **1** in the presence and absence of guests.



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Compound **1** recognizes guests with two-hydrogen bond donor sites such as dihydrogen phosphate and aliphatic dicarboxylic acids of different chain lengths by showing

Electronic supplementary material The online version of this article (doi:10.1007/s10847-010-9808-2) contains supplementary material, which is available to authorized users.

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change in emission of naphthalene. Upon complexation, the monomer emission of naphthalene is decreased with simultaneous growth of a diagnostic new peak at higher wavelength. Dihydrogen phosphate is an important anion and its recognition by different receptors are known in the literature [8–11]. In the present communication, receptor **1**, which is simple and easy-to-make elegantly shows selective recognition of dihydrogen phosphate by exhibiting new emission at longer wavelength due to hydrogen bond mediated excimer formation.

Experimental

Compound 1,4-di(1-naphthyl)-2,5-piperazinedione **1** was obtained according to the Scheme 1. Reaction of 1-naphthylamine with chloroacetyl chloride gave the compound **2**, which on refluxing in CH_3CN in the presence of either K_2CO_3 or Cs_2CO_3 afforded the piperazine derivative **1** in appreciable yield.

2-Chloro-*N*-(naphthalen-1-yl)acetamide (**2**)

In dry CH_2Cl_2 (20 mL) 1-aminonaphthalene (250 mg, 1.75 mmol) was dissolved. To it, 2-chloroacetyl chloride (0.15 mL, 1.92 mmol) in 10 mL dry CH_2Cl_2 was added dropwise followed by measured amount of Et_3N. Reaction mixture was stirred at room temperature for 10 h. Solvent was evaporated, washed with saturated $NaHCO_3$ solution and extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified through column chromatography using 7% ethyl acetate in petroleum ether. Compound **2** was obtained as white solid (335 mg, 87% yield). Mp was recorded as 163 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (s, 1H), 8.02 (d, 1H, $J = 7.6$ Hz), 7.93–7.88 (m, 2H), 7.79 (d, 1H, $J = 8.4$ Hz), 7.62–7.51 (m, 3H), 4.38 (s, 2H); FTIR: ν cm^{-1} (in KBr) 3,256, 3,052, 2,958, 2,854, 1,666, 1,557, 1,505, 1,398, 1,248.

1,4-di(Naphthalen-1-yl)piperazine-2,5-dione (**1**)

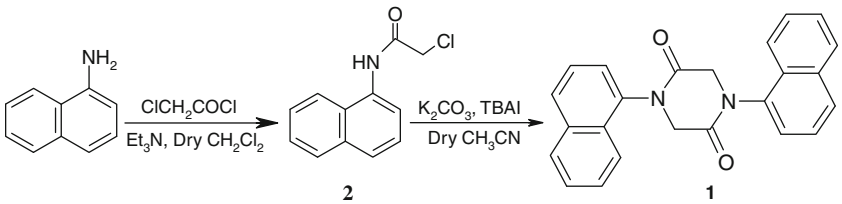
To a stirred solution of **2** (100 mg, 0.45 mmol) in CH_3CN (20 mL), K_2CO_3 (10 mg) was added and the reaction mixture was allowed to stir at room temperature for 8 h. The solvent was evaporated to dryness under vacuum. The residue was dissolved in $CHCl_3$ (30 mL), washed with water (2 × 15 mL) and dried over anhydrous Na_2SO_4. Solvent was distilled off and the crude was purified through column chromatography using 35% ethyl acetate in petroleum ether to give the expected product **1** as white solid (114 mg, 69% yield) and mp was noted as 270–272 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99–7.91 (m, 5H), 7.92 (d, 1H, $J = 8.4$ MHz), 7.68–7.56 (m, 8H), 4.78 (d, 1H, $J = 9.7$ Hz), 4.74 (d, 1H, $J = 9.7$ Hz), 4.66 (d, 1H, $J = 16.8$ Hz), 4.62 (d, 1H, $J = 16.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 Hz): δ δ 164.49, 164.19, 137.3, 134.0, 129.1, 128.4, 126.9, 126.5, 126.0, 125.4, 122.9, 53.8; FTIR: ν cm^{-1} (in KBr) 3,443, 3,049, 2,918, 1,645, 1,597, 1,480, 1,332, 1,274; Mass (EI): 389.2 ($M + Na^+$), 367.2 ($M + H^+$).

Results and discussion

Compound **1** was crystallized from $CHCl_3$ containing one drop of DMSO. Single crystal structure analysis revealed the inclusion of water in the lattice and gave the same structural information as observed previously by other [5]. Figure 1 shows the ORTEP plot of **1** where one molecule of water is present as crystal hydrate. In **1**, two naphthalenes are not in the plane of diketopiperazine ring. They are perpendicularly disposed around the planar DKP ring. The inclusion water connects the diketopiperazine units through hydrogen bonding and forms water templated hydrogen bonded polymeric chain (see supporting data). It is worth noting that the polarised C–H bonds adjacent to amide carbonyl carbons of piperazine ring are cooperatively involved in the formation of hydrogen bonds with water. In addition, the carbonyl oxygen of piperazine ring of one chain is connected with the C–H bond of piperazine ring of adjacent chain, thereby giving a bilayer hydrogen bonded network (Fig. 2). In the network, there is face-to-face and edge-to-face π-stacking interactions between the two naphthalene rings having a separation of 3.71 and 3.65 Å along the *b*-axis, respectively. The thermal stability of water molecule in **1**. H_2O was studied by thermogravimetric analysis (TGA) (Fig. 3). The weight loss for water was 4.99% that occurred in the region 89–152 °C. Looking

Scheme 1 Synthesis of compound **1**



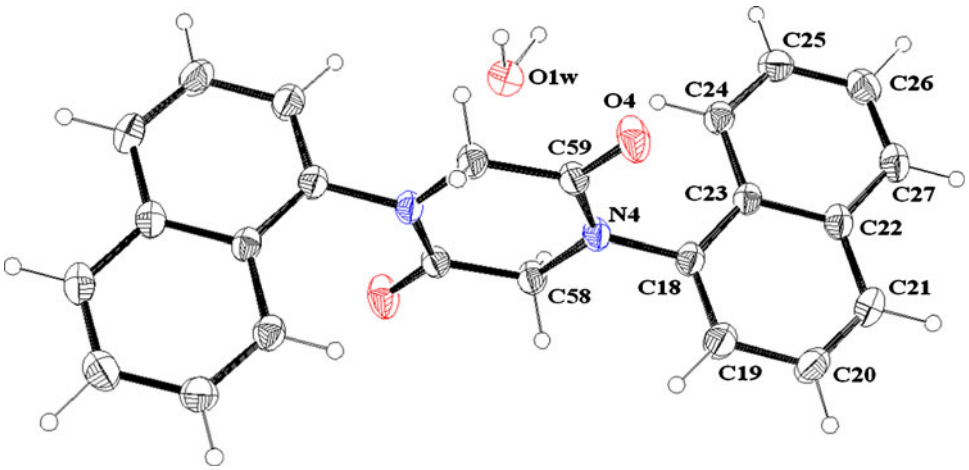


Fig. 1 ORTEP plot of **1**

at the hydrogen bonding nature of the amide carbonyl of the title compound **1** with water we thoroughly investigated the hydrogen bonding interactions of **1** with different aliphatic dicarboxylic acids, $H_2PO_4^-$ ions and strong acids such as trifluoroacetic acid, HCl, etc. The interactions were monitored by ^{1}H NMR, UV and fluorescence methods.

In ^{1}H NMR the signal for CH_2 group, appeared in the region 4.78–4.62 ppm as two doublets, underwent downfield chemical shift ($\Delta\delta = 0.01$–0.03 ppm) during complexation with $H_2PO_4^-$ and diacids such as malonic, succinic, glutaric and adipic acids. The change in chemical shift of the methylene protons of piperazine ring varied with the nature of the guest species although less in magnitude. For example, upon complexation of equivalent amount of $H_2PO_4^-$ ion the methylene protons moved downfield to the lesser extent ($\Delta\delta = 0.03$ ppm; see Fig. 4). Although this shift is less in magnitude, it cannot be ignored. This less downfield shift of the $-CH_2-$ protons in **1** is presumably either due to their direct involvement in hydrogen bonding or electron withdrawing effect of adjacent carbonyl group when it participates in hydrogen bonding with the guests. Prior to study the interaction of **1** with the guests we initially investigated the absorption (Fig. 5) and emission (Fig. 6) characteristics of **1** in different solvents.

As can be seen from Fig. 5, the structured absorbance peak in **1** shows small red shift. In the excited state, the emission intensity of **1** at 338 nm was modified and a red shift of 4 nm in THF solvent was observed (Fig. 6). In the presence of hydrogen bond donor and acceptor solvents the emission of naphthalene in **1** was much affected than in $CHCl_3$ which has neither hydrogen bond donor nor acceptor property. In CH_3OH, THF, CH_3CN-H_2O (4:1 v/v) mixture solvents, emission intensity of naphthalene in **1** increased. Importantly, in CH_3OH an additional weak emission at 445 nm was observed (Fig. 6). This is presumably due to either conformational change of the molecule in the excited

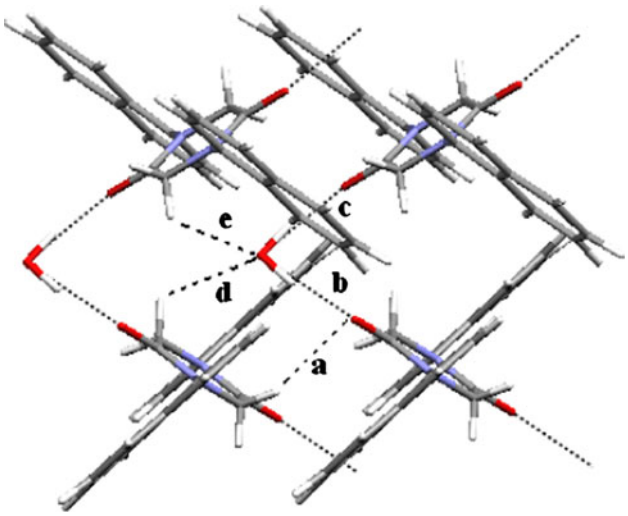


Fig. 2 Side view of the packing of **1**.H_2O ($a = 2.62$ Å, $b = 1.89$ Å, $c = 1.89$ Å, $d = 2.91$ Å, $e = 2.91$ Å)

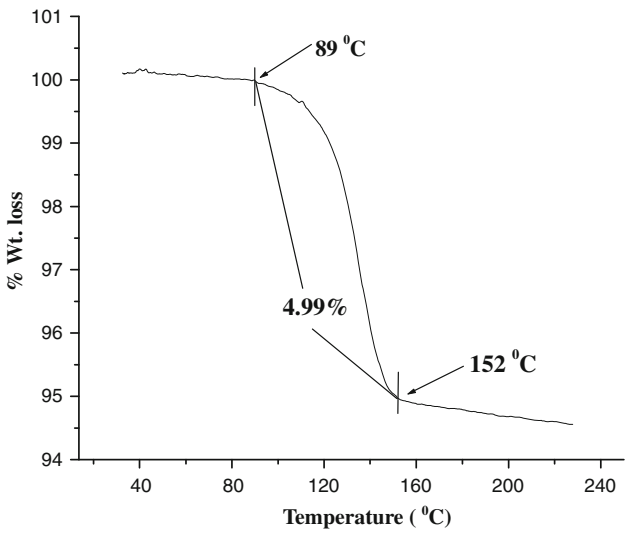


Fig. 3 TGA plot showing the weight loss of the compound **1**.H_2O

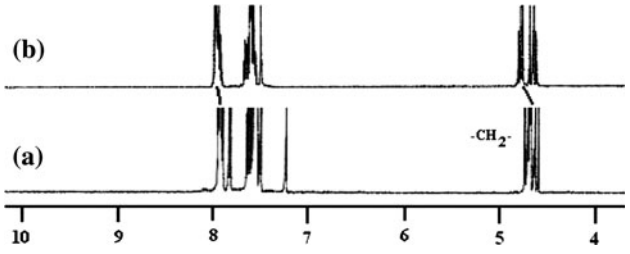


Fig. 4 Partial ^{1}H-NMR (500 MHz) spectra of **1** ($c = 8.19 \times 10^{-3}$ M) (*a*) and 1:1 complex with $H_2PO_4^-$ (*b*) in $CDCl_3$ containing 0.2% d_6-DMSO

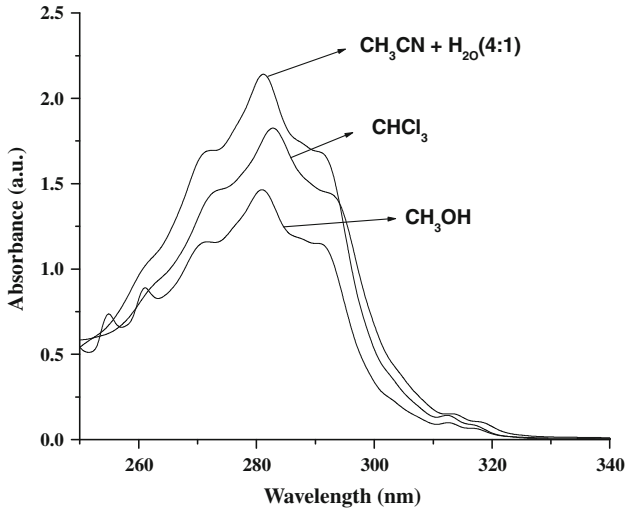


Fig. 5 Absorption spectra of **1** ($c = 8.87 \times 10^{-5}$ M) in different solvents

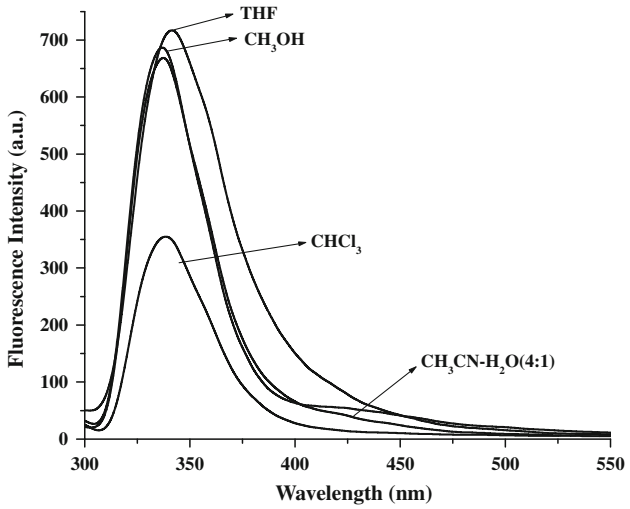


Fig. 6 Emission spectra of **1** ($c = 8.87 \times 10^{-5}$ M) in different solvents

state or hydrogen bonding interaction of **1** with CH_3OH which can act as both hydrogen bond donor and acceptor. Therefore, we studied the hydrogen bonding interaction of **1** with the guests in $CHCl_3$ solvent.

Compound **1** ($c = 8.91 \times 10^{-6}$ M) in $CHCl_3$ containing 0.1% DMSO (for clear solution) showed emission peak centered at 338 nm when excited at 290 nm. Upon addition of increasing amounts of $H_2PO_4^-$ ions the monomer emission of naphthalene decreased gradually. Although the initial change in monomer emission was negligible, on progression of the titration it was effectively decreased with simultaneous growth of a new peak at 420 nm. Similar observations were noticed in the presence of aliphatic dicarboxylic acids such as malonic, succinic, glutaric and adipic acids. Figure 7 shows the change in emission of **1** in the presence of 40 equiv. of different guest species. As from Fig. 7, the growth of the peak at 421 nm is considerable in the presence of $H_2PO_4^-$ ion. This is also true for the dicarboxylic acids. Surprisingly, this situation was not aroused in presence of benzoic acid. In presence of TFA, monomer emission of **1** decreased but there was no intense band at higher wavelength (Fig. 7). Figure 8 demonstrates the change in emission of **1** in $CHCl_3$ containing 0.1% DMSO upon gradual addition of tertrabutylammonium dihydrogenphosphate. The appearance of isosbestic point both in the ground (Fig. 8; inset) and excited states (Fig. 8) indicated the formation of new species in solution which remains in equilibrium with the uncomplexed **1**. Similar findings were observed in the presence of dicarboxylic acids such as adipic and succinic acids. For example, Fig. 9 shows the emission and absorption characteristics of **1** upon gradual addition of adipic acid. It is worth mentioning that the intensity of the peak at 421 nm increased drastically when excess solid tetrabutylammonium dihydrogenphosphate ($\sim$2 equiv. with respect to **1**) was added to the $CHCl_3$ solution of **1** followed by sonication (see supplementary data). Thus the appearance of structured emission peak at 421 nm in the presence of $H_2PO_4^-$ ion and

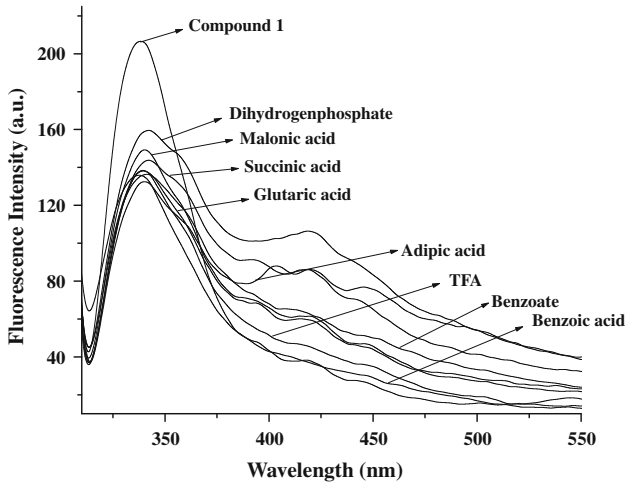


Fig. 7 Change in emission of **1** ($c = 8.91 \times 10^{-6}$ M) in the presence of 40 equivalent amounts of different guests ($\lambda_{ex} = 290$ nm) in $CHCl_3$ containing 0.1% DMSO

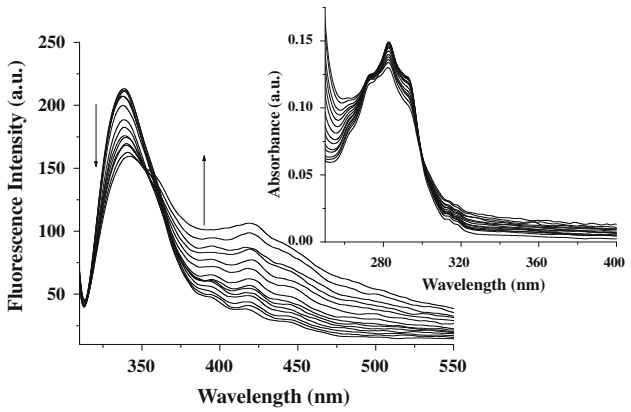


Fig. 8 Change in emission of **1** ($c = 8.91 \times 10^{-6}$ M) upon gradual addition of tertrabutylammonium dihydrogen phosphate in $CHCl_3$ containing 0.1% DMSO; inset: Change in absorption of **1** ($c = 8.91 \times 10^{-6}$ M) upon addition of tertrabutylammonium dihydrogen phosphate in $CHCl_3$ containing 0.1% DMSO

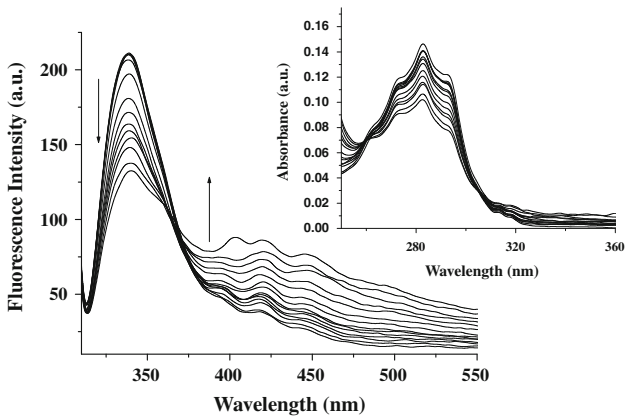


Fig. 9 Change in emission of **1** ($c = 8.91 \times 10^{-6}$ M) upon gradual addition of adipic acid in $CHCl_3$ containing 0.1% DMSO; *inset* change in absorption of **1** ($c = 8.91 \times 10^{-6}$ M) upon addition of adipic acid in $CHCl_3$ containing 0.1% DMSO

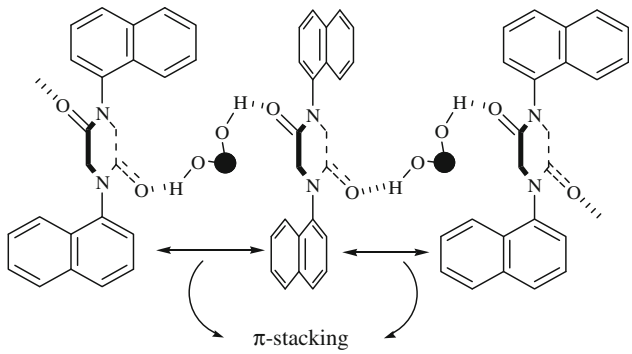


Fig. 10 Suggested mode of complexation of **1** with $H_2PO_4^-$ ion and dicarboxylic acids

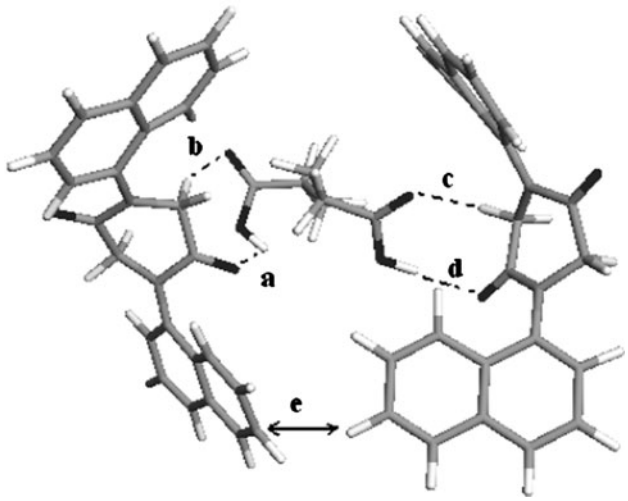


Fig. 11 MM2 optimized geometry of **1** with adipic acid, $E = 11.95$ kcal/mol, $a = 2.70$ Å, $b = 2.77$ Å, $c = 2.63$ Å, $d = 2.03$ Å, $e = 3.24$ Å

aliphatic dicarboxylic acids can be explained due to complexation induced formation of intermolecular excimer between the closely spaced naphthalenes of **1**.

This was supported by the absence of the peak at 421 nm in the presence of benzoic acid. Even in the presence of stronger acid TFA this emission at longer wavelength was not observed (see supplementary data). Thus it is quite reasonable that guests having bifunctional hydrogen bond donor sites are only able to form intermolecular excimer by bring naphthalenes closely via hydrogen bond formation according to the suggested mode in Fig. 10. Molecular modeling studies were performed in the gas phase to understand the binding mode [12]. Figure 11, for example, shows the energy optimized structure of the complex of **1** with adipic acid and supports the proposed mode as shown in Fig. 10. However, the distance between the two naphthalenes in edge-to-face orientation in the complexes is within the stacking distance. The concomitant decrease in monomer emission of naphthalene during complexation is presumably attributed to the activation of photoinduced electron transfer either from amide nitrogen to the excited state of naphthalene or from the guest to the excited state of naphthalene.

The stoichiometry of the complexes of **1** with the diacids and dihydrogenphosphate in the excited state was 3:2 type as evidenced from fluorescence Job plots (see supplementary data). Figure 12, for example, shows the Job plot for **1** with $H_2PO_4^-$. It is mentionable that compound **1** formed 1:1 complexes with all the guests in the ground state as evidenced from UV Job plots in Figure 4S (see supplenatary data). To understand the stability of the complexes we determined the binding constant values [13] from UV titration data (Table 1). From Table 1 it is evident that **1** shows weak binding with the guests. No measurable selectivity is observed.

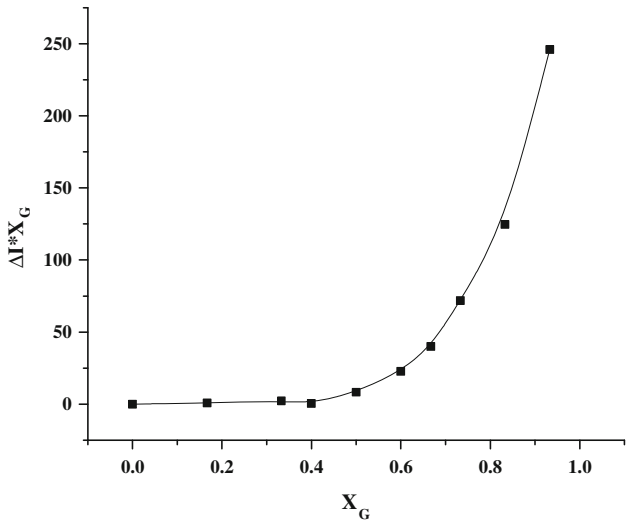


Fig. 12 Fluorescence Job plot for **1** ($c = 8.16 \times 10^{-5}$ M) with $H_2PO_4^-$ ion

Table 1 Binding constant values determined by UV method

Guests	K_a (M^{-1})
Dihydrogenphosphate[a]	4.73×10^2
Malonic acid	2.75×10^2
Succinic acid	2.11×10^2
Glutaric acid	3.63×10^2
Adipic acid	2.70×10^2

[a] Tetrabutylammonium salt was taken

Conclusion

Thus, in conclusion, we have shown that naphthalene appended 2,5-diketopiperazine **1** can easily be achieved via two steps. Fluorophore labeled any optically pure 2,5-diketopiperazine ring can be constructed by this simple methodology. Hydrogen bonding behavior of this simple system in the solution is interesting in the recognition of $H_2PO_4^-$ ion. Upon complexation, appearance of more intense peak at higher wavelength characteristically distinguishes $H_2PO_4^-$ from the other guests in the present study. Exploration of this system with various substituents is underway in our laboratory.

Acknowledgments We thank CSIR, New Delhi for financial support and DST, New Delhi for providing facilities in the department under DST FIST program. T.S. thanks CSIR, New Delhi for a fellowship. We also thank Matthias Zeller, Youngstown State University, 1 University Plaza, Youngstown, USA for a help on the crystallographic work.

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