Fluorescent sensor for α,ω-dicarboxylate anions

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The synthesis and photophysical behavior of several naphthylurea derivatives used as chemosensors for detecting anionic species is reported. In particular, compound **3** shows a photoinduced electron transfer (PET) process. The photophysical properties of **3** upon the addition of dicarboxylate anions have been studied. Results show that fluorescence quenching of the naphthyl moiety and appearance of a new emission is induced by the formation of a complex. The obtained fluorescence and ^{1}H-NMR data indicate that a 1 : 1 stoichiometry complex is formed between compound **3** and dicarboxylate anions through a hydrogen-bonding interaction. The selectivity of **3** for recognition of different dicarboxylates depends on the chain length of the anionic species.

Anions, especially dicarboxylates and hydrogen phosphate, play an important role in chemical and biochemical processes and their recognition by artificial chemosensors has been a focus of interest for chemists in the past decades.[1] The recognition of anionic species is generally based on electrochemical and ^{1}H-NMR methods through changes in redox potential and chemical shift, respectively. In recent years, a new method based on the change in fluorescence of an anionic sensor has been developed. This kind of sensor usually consists of three moieties—fluorophore, spacer and receptor. The fluorescence signal of this sensor changes when the foreign species is bound by the receptor, and the most common mechanism for fluorescence signal changes in this kind of sensor results from an intramolecular photo-induced electron transfer (PET) process.[2] The first example of this kind of chemosensor for anionic species recognition was described by the Czarnik group the for detection of phosphate and pyrophosphate.[3] More recently, other reports have appeared[4] however this kind of study is still relatively rare.

It is well known that urea and thiourea groups can interact with anionic species effectively by hydrogen bonding.[5] Several sensors containing these functional groups have been reported.[6] In a previous work, we synthesized a series of tripodal naphthylurea derivatives that were able to selectively recognize the dihydrogen phosphate anion.[7] As a part of our work, we synthesized a compound containing two urea groups, used as a chemosensor for the recognition of dicarboxylate anions in this work. To the best of our knowledge, several compounds that contain different functional groups for selective binding of dicarboxylate anions have been reported.[6a–c,8–12] These are bisphenyl urea,[6a–c] a receptor with two guanidiniums,[8] a redox-responsive bis(cobaltocenium) calix[4]arene,[9] metal-templated bisthiourea,[10] sapphyrin dimer[11] and a polynuclear metal complex.[12] Unfortunately, none of them could be attached to the fluorescence emission sensor.

In this paper, we report the synthesis and binding properties of compound **3** containing two carboxylate-binding building blocks and a flexible aminopropyl chain. Its photophysical behavior has also been investigated. The anionic recognition of this compound was monitored by fluorescence spectrometry.

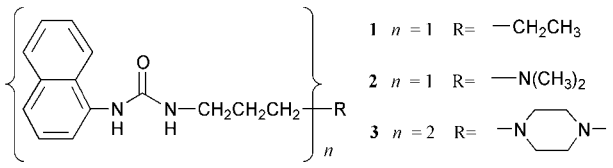
Results and discussion

The structure of compounds **1–3** is shown in Scheme 1. They are synthesized in good yields by the reaction of 1-naphthyl isocyanate and the corresponding amino compound—*n*-pentylamine, 3-dimethylaminopropylamine or 1,4-bis(3-aminopropyl)piperazine. All of these compounds were characterized by ^{1}H-NMR and elemental analysis. The HCl salts of **2** and **3** were prepared by mixing compound **2** or **3** and concentrated hydrochloric acid.

Fluorescence and absorption spectra

The fluorescence spectra were recorded from a solution (10^{-5} M) of these compounds in the absence or presence of dicarboxylate anions [$-O_2C(CH_2)_n\ CO_2^-$] such as malonate, glutarate, adipate, pimelate, suberate ($n = 1$, 3, 4, 5, 6, respectively) or acetate ($H_3CCO_2^-$). In each case the counter cation was tetrabutylammonium.

The fluorescence spectra of compounds **1–3**, **2** · HCl and **3** · HCl in DMSO are shown in Fig. 1. All of these compounds show a strong emission at 380 nm attributed to the naphthylurea group. At the same concentration of the naphthylurea group (10^{-5} M), the fluorescence intensity of compounds **2** and **3** is lower than that of **1**, whereas their HCl salts show a stronger emission than that of the neutral compounds. This is due to the fact that in **2** and **3** the sensor is composed of a tertiary N atom, propyl chain, and naphthylurea. The electron-rich tertiary N atom acts as an electron donor to suppress the fluorescence emission through a photo-induced electron transfer process, but this process no longer occurs in their salts owing to protonation of the tertiary N atom. On the other hand, with two naphthalene units linked by a flexible aminopropyl chain, molecule **3** would be expected to form an intra-molecular excimer by π-π* stacking. However no



Scheme 1 The structures of compounds of **1**, **2**, **3**.

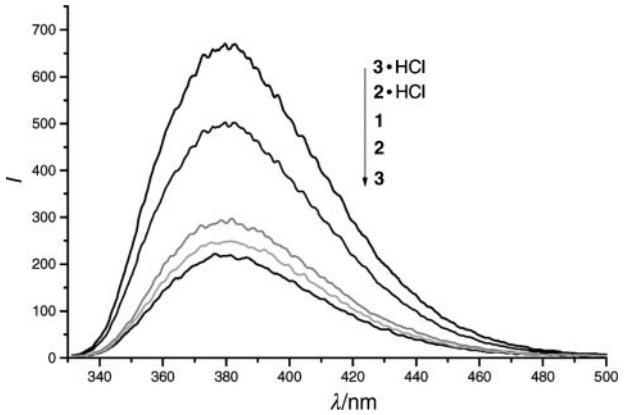


Fig. 1 Fluorescence spectra of **1** (10^{-5} M), **2** (10^{-5} M), **3** (5×10^{-6} M), **2**·HCl (10^{-5} M) and **3**·HCl (5×10^{-6} M) in DMSO. Excitation wavelength is 320 nm.

excimer emission is seen in the fluorescence spectrum of **3**. It is probable that the lowest energy chair-type conformation of piperazine should be the main one present in solution. The two linking chains connected to the tertiary N atoms these point in opposite directions and, consequently, the expected excimer fails to appear.

Fig. 2 shows that the fluorescence intensity of **3** at 380 nm is gradually quenched as the pimelate anion concentration is increased, while a new long-wavelength emission (at 500 nm) and an evident isosbestic point (at 449 nm) simultaneously appear. These results indicate that upon addition of anion, a new species is formed. As a control experiment, the effect of pimelate anion on the fluorescence spectrum of pure naphthalene (10^{-5} M) in DMSO was tested, but no significant fluorescence quenching was observed. This result indicates that the fluorescence quenching of **3** is not caused directly by the interaction of the naphthyl group and added anion, but probably by a hydrogen-bonding interaction between the urea group and the anion. Furthermore, the interaction of compounds **1** and **2** with a simple oxoanion—acetate—was also tested. Their fluorescence is quenched by acetate and a new emission at 500 nm also appears in the spectrum (Fig. 3), although the degree of quenching is not as strong as that of compound **3** with pimelate.

If the linking chains at the tertiary N's of piperazine could be forced to twist into the same direction by the H-bonding with the dicarboxylate anion, the excimer between the two naphthalene units in **3** could be formed; but, as mentioned above, the fluorescence of both **1** and **2**, which possess only one naphthalene unit, is also quenched in the presence of acetate and a new emission appears. Obviously, excimer formation is excluded. To clarify the assignment of this long-wavelength emission, the absorption spectra of compound **3**

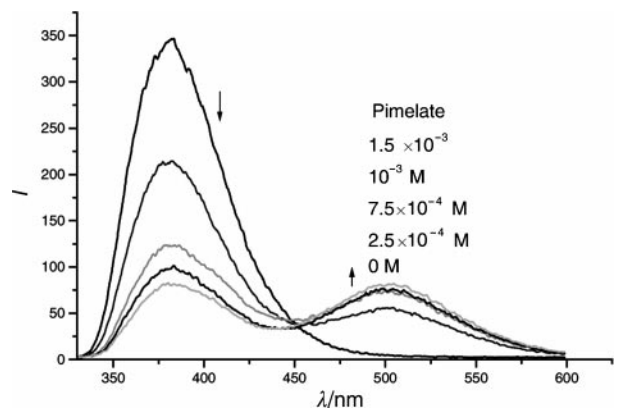


Fig. 2 The change in the fluorescence spectra of **3** (10^{-5} M, DMSO) upon successive addition of tetrabutylammonium pimelate. Excitation wavelength is 320 nm.

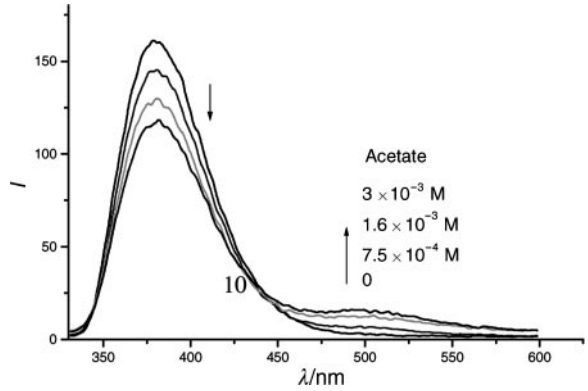


Fig. 3 The fluorescence spectra of **2** (10^{-5} M, DMSO) upon addition of tetrabutylammonium acetate.

upon the addition of pimelate ion were recorded. As shown in Fig. 4, the absorbance of **3** at 300 nm gradually decreases as the concentration of pimelate is increased; an isosbestic point at 317 nm appears, which indicates that a new complex is formed in the ground state.

Therefore, no matter which carboxylate is added, compounds **1**, **2** and **3** complex with them through hydrogen bonding; a new emission attributed to the complex is observed at 500 nm; this emission increases as more carboxylate is added and more complex is formed. On the other hand, the number of hydrogen bonds affects the stability of the complexes: the complex between **3** and a dicarboxylate dianion has more hydrogen bonds than those of **3** and acetate or **1**, **2** and acetate, thus the emissions of the latter complexes are not so strong. A proposed process leading to the new emission is shown in Scheme 2.

The effect of other dicarboxylate anions on the fluorescence spectra of **3** was also examined. The emission of the fluorophore moiety was also quenched and a new emission was again observed. But the quenching ability clearly depends on the chain length n of the dicarboxylate; the order of the quenching ability is: pimelate ($n = 5$) > suberate ($n = 6$) ≈ adipate ($n = 4$) > glutarate ($n = 3$) > malonate ($n = 1$). The obtained order demonstrates the importance of the match between the anionic chain length and the distance between the two urea units in compound **3**; the strongest hydrogen bond interaction occurs when this match is optimal. This result is also confirmed by the ^{1}H-NMR data described in the following section.

^{1}H-NMR study

^{1}H-NMR spectroscopy has been widely used to investigate receptor–substrate interactions[13] and it allows access to the

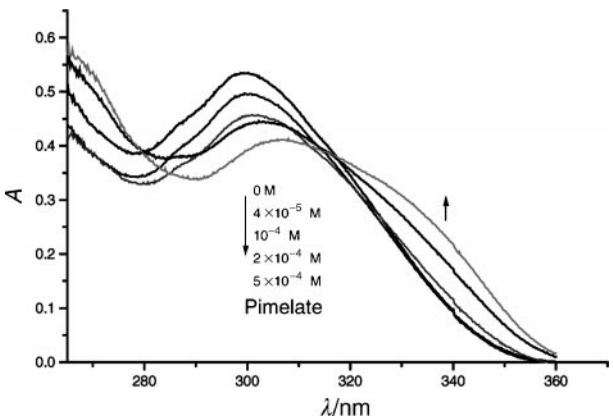
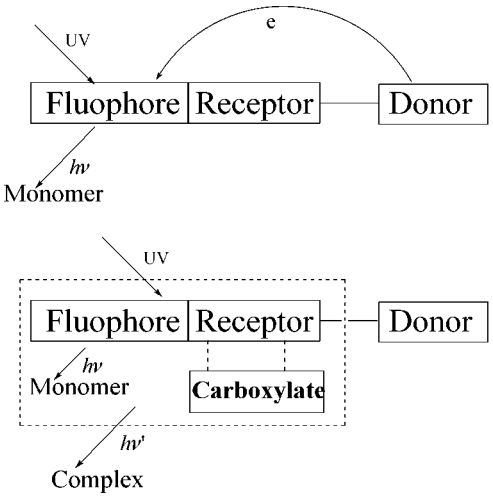


Fig. 4 The absorption spectra of **3** (5×10^{-5} M) in DMSO upon the addition of pimelate.



Scheme 2 Schematic representation of the PET process and emission from the complex formed by compounds **1**–**3** with carboxylate anions.

details of the interaction between compound **3** and dicarboxylate anions. ^{1}H-NMR spectra of **3** with or without dicarboxylate anions in DMSO-d_6 at 25 °C were recorded. Selected data are listed in Table 1. The NMR spectrum of compound **3** shows a small broad signal at δ 6.57 due to the NH proton of one urea group and another at δ 8.49 due to the NH proton that is adjacent to the naphthalene ring. The multiplet at 7.3–8.1 ppm is due to the naphthalene CH protons. Upon addition of dicarboxylate anion, both signals of the NH protons are shifted markedly downfield; in the case of pimelate, the H_a, H_b urea proton chemical shifts change from 6.57 to 8.04 ppm and 8.49 to 9.81 ppm, respectively, a change of almost 1.5 ppm for H_a. The naphthalene H(C8) signal also shifts downfield by up to 0.28 ppm, while the other naphthalene H signals show almost no change. These results indicate that compound **3** and pimelate form a complex *via* hydrogen-bonding interactions between the urea and carboxyl groups; the H(C8) proton in the aryl ring is also close to the carboxyl group and probably participates in the formation of hydrogen bonds. A probable structure for the complex is shown in Scheme 3.

The data in Table 1 indicate that all the dicarboxylate anions used form complexes with **3** *via* hydrogen-bonding interactions with the strongest interaction occurring with pimelate. These results are consistent with the fluorescence data.

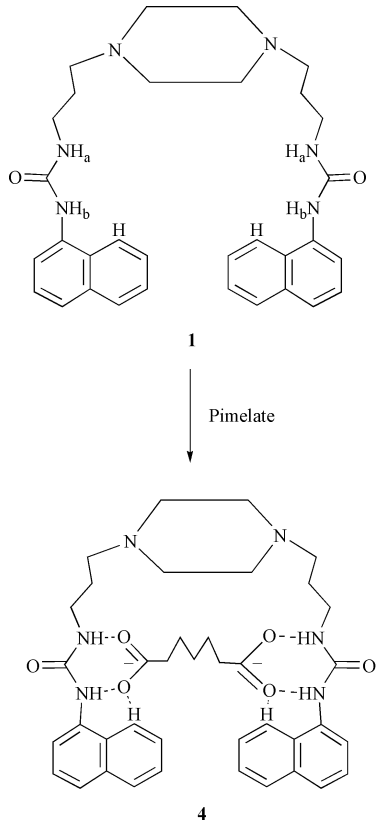
Stability constants of the complexes between 3 and dicarboxylate anions

The stability constants can be easily determined from the variation of fluorescence intensity at the appropriate observation wavelengths. For the complex of 1 : 1 stoichiometry, the stability constant K_S for the equilibrium, $H + A \rightleftharpoons HA$ can be written as:

$$K_S = \frac{[HA]}{[H][A]}$$

Table 1 ^{1}HNMR chemical shifts (ppm) for compound **3** (in DMSO-d_6) in the absence or presence of dicarboxylate anions (1 : 1)

Anion	H_a	H_b	H(C8)
None	6.57	8.49	8.06
Malonate	7.02	8.89	8.14
Glutarate	7.74	9.52	8.27
Adipate	7.72	9.51	8.29
Pimelate	8.04	9.81	8.34
Suberate	7.84	9.6	8.29



Scheme 3 Possible binding model of **3** with pimelate anion.

The following equation can be derived from the relation between fluorescence intensity and the concentration of host or complex:[14]

$$\frac{I_0}{I_0 - I} = \frac{a}{b - a}\left(\frac{1}{K_S[A]} + 1\right)$$

where I_0, I (at 380 nm, in this case) are the fluorescence intensity of host without and with anion, respectively, and [A] is the total concentration of anion. Both a, b are constants and K_S is the stability constant. A plot of $I_0/(I_0 - I)$ against the recipropal of anionic concentration $[A]^{-1}$ allows the stability constant K_S to be calculated from the ratio intercept/slope.

In this work, the fluorescence titration was carried out by the successive addition of anion to a solution of **3** (10^{-5} M) in DMSO. As shown in Fig. 5, the plots of $I_0/(I_0 - I)$ against $[A]^{-1}$ for all dicarboxylate anions show a good linear relationship (all correlation coefficients obtained are larger than 0.998). The good fits to the equation confirm that compound **3** forms a 1 : 1 stoichiometric complex with dicarboxy-

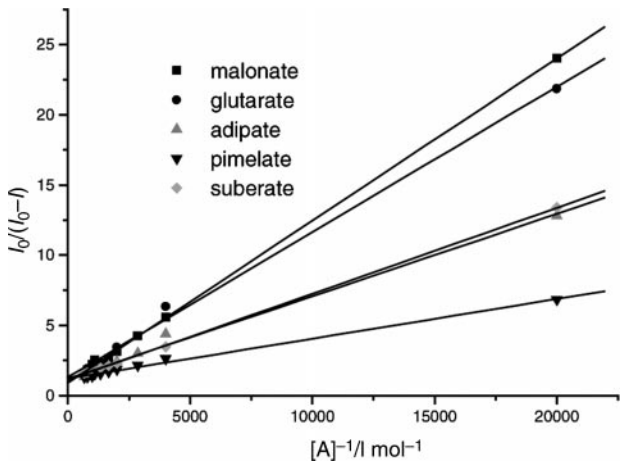


Fig. 5 Plots of $I_0/(I_0—I)$ of **3** (10^{-5} M, DMSO) *vs.* $[A]^{-1}$ of different dicarboxylate anions.

Table 2 The binding constants of compound **3** with the dicarboxylate anions[a] $^{-}O_2C(CH_2)_nCO_2^{-}$

Anion	n	K_S/l · mol^{-1}	Sensitivity[b]
Malonate	1	940 ± 140	1
Glutarate	3	1270 ± 250	1.35
Adipate	4	1940 ± 194	2.06
Pimelate	5	4337 ± 172	4.61
Suberate	6	2106 ± 42	2.24

[a] Calculated from the fluorescence data for a 1 : 1 complex. [b] Relative to the worst binding substrate, malonate.

late anions. The stability constants are listed in Table 2. Choosing the lowest stability constant for malonate as a reference the relative selective values for the other dicarboxylate anions can be calculated; the largest belongs to pimelate. This result coincides with that from the ^{1}H-NMR data discussed above.

Conclusion

In the present work, the fluorescence quenching of compound **3** by different dicarboxylate anions through hydrogen-bonding interactions have been studied. The fluorescence quenching and the appearance of a new emission in the spectrum are caused by the formation of a complex between **3** and the dicarboxylate. These results indicate that **3** could be used as a fluorescent chemosensor to recognize dicarboxylate anions. Its sensitivity for recognition of α,ω-dicarboxylates depends strongly on the chain length of these dicarboxylates. This demonstrates that it is possible to design a suitable receptor for recognition of specific anion species with a definite shape and size. Results also indicate that the multiple hydrogen-bonding interactions may affect the stability of the complex and play an important role in molecular recognition.

Experimental

General

Solvents were dried and distilled before use according to standard procedure. All other reagents were purchased from either Aldrich or Acros. Melting points were measured on a micro-melting-point apparatus (uncorrected). Elemental analyses were performed on a Heraeus CHN-Rapid analytical instrument. The fluorescence spectra were measured on a Hitachi F-4500 fluorescence spectrophotometer at 25 °C (the excitation wavelength was 320 nm, the excitation and emission slit widths were 2.5 nm). The fluorescence titration was performed with a series of 10^{-5} M solutions of compound **3** containing different amounts of dicarboxylate anion. ^{1}H-NMR spectra were recorded on a Varian GEMAN 300 (300 MHz) spectrometer at 25° C using TMS as an internal standard; the solutions in DMSO-d_6 were prepared with a concentration of 1 mM and the measurements of the chemical shift changes of **3** were performed with an equivalent amount of dicarboxylate anion (as the tetrabutylammonium salt).

Syntheses

Preparation of tetrabutylammonium salts. To a stirred solution of a dicarboxylic acid (2.5 mmol) in dry methanol (5 ml), 1.0 equiv. of a 1.0 M solution of tetrabutylammonium hydroxide in methanol (5 ml) was added. The resulting mixture was stirred for 2 h at room temperature. The solvent was evaporated *in vacuo* over P_2O_5 and the solid was further dried for several days under high vacuum over P_2O_5. The resulting tetrabutylammonium salt was stored under anhydrous conditions before use.

***N*-Naphthyl-*N*-pentylurea (1).** To a solution of *n*-pentylamine (2.57 g, 29.6 mmol) in dry CH_2Cl_2, 1-naphthyl isocyanate (5 g, 29.6 mmol) was added at room temperature. The resulting mixture was stirred overnight and the precipitate was filtered off and dried in vacuum to obtain pure **1**. Yield: 90%, mp: 130–132 °C. ^{1}H-NMR (DMSO-d_6): δ 8.47 (1H, s, NH_a), 8.08 (1H, d, J = 7.9, ArH), 8.00 (1H, d, J = 7.2, ArH), 7.88 (1H, d, J = 7.1, ArH), 7.54–7.47 (3H, m, ArH), 7.42–7.37 (1H, t, J = 7.8, ArH), 6.57 (1H, s, NH_b), 3.12 (2H, t, NCH_2), 1.46 (2H, m, NCH_2CH_2), 1.30 (4H, m, CCH_2CH_2C), 0.88 (3H, t, $-CH_3$).

***N*-(1-Naphthyl)-*N'*-(3-dimethylaminopropyl)urea (2).** The synthetic procedure is similar to that of compound **1**. Yield 86%, mp: 149-151 °C. ^{1}H-NMR (DMSO-d_6): δ 8.52 (1H, s, ArNH), 8.08 (d, 1H, ArH, J = 8.03), 7.96 (d, 1H, ArH, J = 7.48), 7.89 (d, 1H, ArH, J = 8.12), 7.57–7.49 (m, 3H, ArH), 7.42 (t, 1H, ArH, J = 7.88), 6.60 (t, 1H, CONH), 3.19–3.15 (m, 2H, $NHCH_2$), 2.27 (t, 2H, CH_2N, J = 7.07 Hz), 2.13 (s, 6H, CH_3), 1.60 (m, 2H, CH_2).

1,4-Bis(1-naphthylureylenepropyl)piperazine (3). The synthetic procedure is similar to that of compound **1.** To a stirred solution of 1,4-bis(3-aminopropyl)piperazine (0.296 g, 1.48 mmol) in dry CH_2Cl_2, 1-naphthyl isocyanate (0.5 g, 2.96 mmol) was added at room temperature. After addition, the resulting mixture was stirred overnight, then the precipitate was filtered off, washed with CH_2Cl_2, and dried *in vacuo* to obtain **3** (0.732 g, 92%) as a white solid. Mp > 300 °C. ^{1}H-NMR (DMSO-d_6): δ 1.60 (m, 4H, $CH_2CH_2CH_2$), 2.31 (t, 8H, CH_2N), 2.42 (t, 4H, CH_2N), 3.15 (t, 4H, CH_2NHCO), 6.57 (s, 2H, NHCO), 7.37–8.08 (m, 14H, ArH), 8.49 (s, 2H, $CONH_aAr$). Anal. calc. for $C_{32}H_{38}N_6O_2$: C 71.34, H 7.11, N 15.60; found: C 70.11, H 7.26, N 15.60%.

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