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Zhen-Ya Zeng[a]; Yong-Bing He[a]; Jin-Long Wu[a]; Lan-Hua Wei[a]; Shun-Ying Liu[a]; Yan-Yan Huang[a]; Ling-Zhi[a]; Ling Hu[a]
[a] Department of Chemistry, Wuhan University, Hubei, P. R. China

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A Multi-armed Neutral Receptor for α,ω-Dicarboxylate Anions

ZHEN-YA ZENG, YONG-BING HE*, JIN-LONG WU, LAN-HUA WEI, SHUN-YING LIU, YAN-YAN HUANG, LING-ZHI MENG and LING HU

Department of Chemistry, Wuhan University, Wuhan, Hubei 430072, P. R. China

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A multi-armed neutral anion receptor (1) bearing multiple amide and thiourea binding sites was synthesized. Receptor 1 forms 1:2 complexes with dicarboxylate anions, and the sensitivity for recognition of dicarboxylate depends strongly on the chain length of these dicarboxylate anions. Addition of the anions caused a considerable change in the absorbance and fluorescent intensity of the host solution and a consequent visible color change.

Keywords: Anion receptor; Dicarboxylate; Recognition; UV–vis spectrum; Fluorescence

INTRODUCTION

During the past few decades, the development of receptors for recognizing and sensing cationic, neutral and anionic species has attracted increasing interest in supramolecular chemistry [1–6]. In particular, the design and synthesis of anion receptors and sensors are of great importance [7–11] because of the significance of anionic species in clinical diagnosis, environmental monitoring and biological processes. However, the study of anion receptors remains relatively unexplored compared to the more extensively studied recognition of cations [12–14]. The current focus of the field has been on synthetic receptors with amide [15–18] and thiourea [19–22] groups, because the hydrogen bonds between these functional groups and guests are directional in character and result in strong complexes with biologically important anions. The cooperative act of these two kinds of functional groups and multiple hydrogen bonds with anions could effectively enhance binding selectivity and affinity.

In this paper, we report the synthesis of a multi-armed neutral receptor (**1**) that contains four amide and four thiourea groups, and that can provide multiple hydrogen bonds to form strong complexes with anionic guests. Upon addition of dicarboxylate anions to a solution of **1**, the absorbance and fluorescence intensity of the solution were changed and, even more dramatically, a significant color change was observed.

RESULTS AND DISCUSSION

Receptor **1** was synthesized in good yields by the method outlined in Scheme 1. The key intermediate **2** was synthesized from 9,10-bis(chloromethyl)anthracene in anhydrous DMF and purified easily by recrystallization from toluene, although the bis(chloromethyl) compound is almost insoluble in most solvents [23]. Initially, bis(bromomethyl)anthracene was chosen for its relatively good solubility, but unfortunately the products were too difficult to separate. Intermediate **2** and hydrazine hydrate were heated in ethanol under reflux, and then the collected precipitate **3** was allowed to react with *p*-nitrophenyl isothiocyanate in DMF to give the target receptor molecule **1**.

Addition of dicarboxylate anions to the solution of receptor **1** induced a visible color change from yellow to red. The color of the solution, however, became only slightly darker upon the addition of 100 equivalents of halogen anions (Cl^-, Br^-, I^-).

*Corresponding author. E-mail: ybhe@whu.edu.cn

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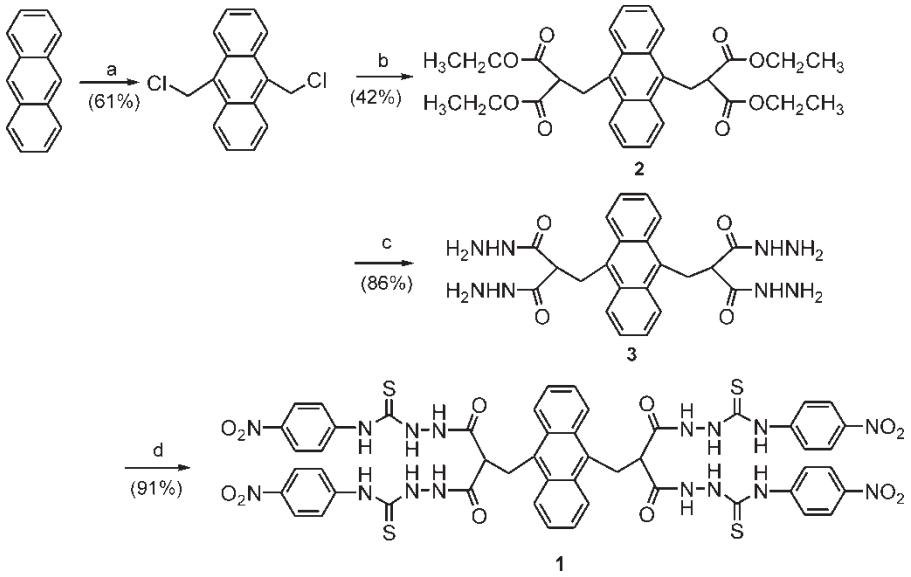


SCHEME 1 The synthesis of anion receptor **1**. a: HCl, $(CH_2O)_n$, dioxane; b: diethyl malonate, EtONa, DMF, reflux 20 h; c: $NH_2NH_2{\cdot}H_2O$, EtOH, reflux 40 h; d: *p*-nitrophenyl isothiocyanate, DMF, rt, 10 h.

In this type of donor–acceptor chromophore, the origin of the color might be ascribed to the charge-transfer interactions between the donor nitrogen of the thiourea and the acceptor *p*-nitrophenyl moieties of the chromophore [24–26]. Introduction of an electron-withdrawing substituent (—NO_2) into the thiourea moiety enhances the acidity of thiourea and improves the hydrogen bonding ability [27]. It could be postulated that while the receptor binds anions effectively, hydrogen bonds were constructed to form stable complexes, and the excited state of the charge transfer would be more strongly stabilized, resulting in a visible color change [28].

Figure 1 shows the changes in the UV–vis spectra of **1** at a concentration of $2.5 \times 10^{-5}\,\mathrm{mol\,l^{-1}}$ in DMSO upon the addition of adipate anion. In the absence of anions, **1** had absorbance peaks at 362 nm ($\varepsilon = 5.46 \times 10^4\,\mathrm{cm^{-1}\,mol^{-1}\,l}$), 382 nm ($\varepsilon = 5.11 \times 10^4\,\mathrm{cm^{-1}\,mol^{-1}\,l}$) and 404 nm ($\varepsilon = 3.64 \times 10^4\,\mathrm{cm^{-1}\,mol^{-1}\,l}$). In the presence of adipate anion, the absorbances at 382 nm and 404 nm increased, and the absorbance at 362 nm decreased. All the peaks were slightly red-shifted by about 6–8 nm. In particular, the absorbance increase at the longer wavelength, which was in the visible region, resulted in the change in color. Clear isosbestic points at 298 nm and 372 nm were observed. The plot in the top right corner of Fig. 1 illustrates the absorbance change of the receptor solution upon the addition of adipate at 404 nm. Addition of adipate to the solution of receptor **1** caused a linear absorbance change before adding two equivalents of the anion, and after that there was only a slight absorbance change. The results suggested that a 1:2 complex was formed between the receptor and the anion guest; in addition, the associate constant was fairly large ($>10^5\,\mathrm{M^{-1}}$) [29,30]. Similar phenomena were observed when other α,ω-dicarboxylate anions (malonate, succinate, glutarate) were added to a solution of **1**. However, introducing large amounts of halogen anions (Cl^-, Br^-, I^-) respectively into the solution of receptor **1** did not cause such a distinct change as that observed with the dicarboxylate anions.

Continuous variation methods were used to determine the stoichiometric ratio of the receptor **1** and anion guests. Fig. 2 shows the UV–vis spectra of a series of solutions in which the total concentration of host and adipate anion guest was constant

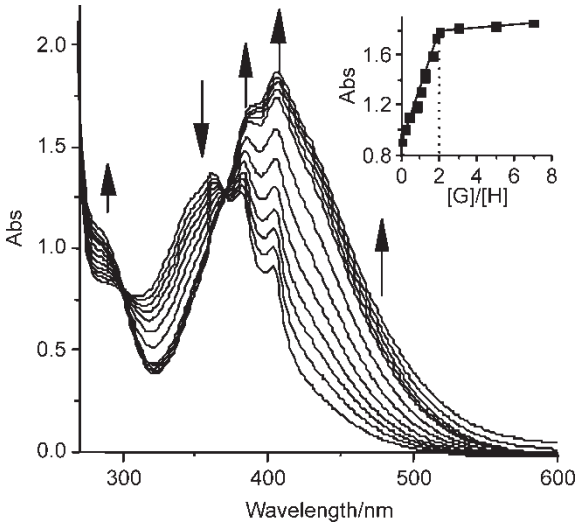


FIGURE 1 UV–vis spectra of **1** ($2.5 \times 10^{-5}\,\mathrm{mol\,l^{-1}}$) in the presence of adipate in DMSO. The equivalents of adipate anion are: 0, 0.2, 0.4, 0.8, 1, 1.2, 1.6, 1.8, 2, 3, 5 and 7.

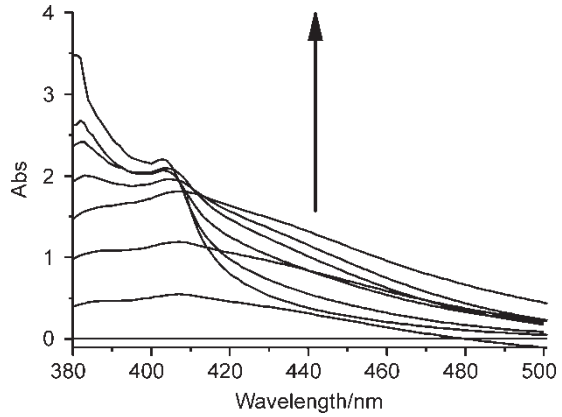


FIGURE 2 UV–vis spectra of **1** (H) with adipate anion (G) in DMSO. $[H] + [G] = 1.0 \times 10^{-4}\,mol\,l^{-1}$, $[H]/([H] + [G])$: 0, 0.1, 0.2, 0.33, 0.4, 0.5, 0.6, 0.8 and 1.

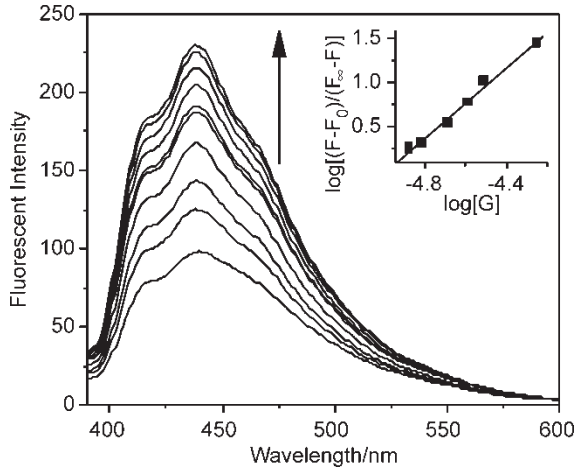


FIGURE 4 Fluorescent spectra of **1** ($5 \times 10^{-6}\,mol\,l^{-1}$) with adipate in DMSO. The equivalents of adipate are: 0, 0.2, 0.4, 0.8, 1.2, 2.6, 3, 4, 5, 6 and 11. $\lambda_{ex} = 361\,nm$.

($1.0 \times 10^{-4}\,mol\,l^{-1}$), with the molar fraction of the host $[H]/([H] + [G])$ continuously variable. Figure 3 shows the Job plot of the difference between observed absorbance and absorbance of the free receptor **1** at 408 nm of the solutions with the molar fraction of the host, which illustrates that the receptor-anion complex concentration approaches a maximum when the molar fraction of the host $[H]/([H] + [G])$ is about 0.33, indicating that the receptor and the adipate anion formed a 1:2 complex of **1** [31]. In the same way, it was deduced that receptor **1** and the other dicarboxylate anions formed 1:2 complexes.

The binding properties of receptor **1** with dicarboxylate anions were also investigated by fluorescence titration. When the adipate anion was added to a solution of receptor **1**, the fluorescence intensity increased (Fig. 4). A similar phenomenon was also observed upon addition of other dicarboxylate anions to the solution of **1**.

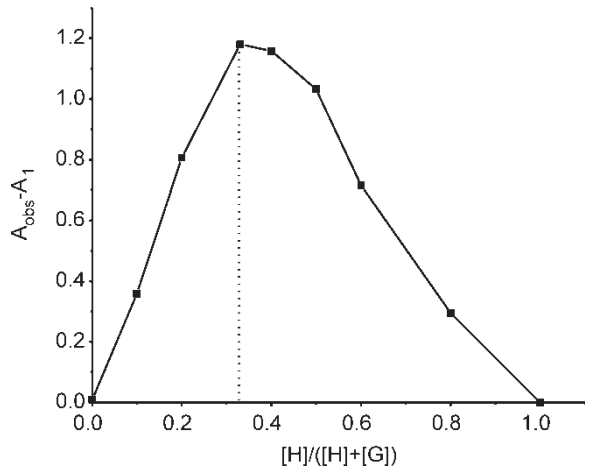


FIGURE 3 Continuous variation curves of **1** with adipate anion. The total concentration of the host and guest is $1.0 \times 10^{-4}\,mol\,l^{-1}$.

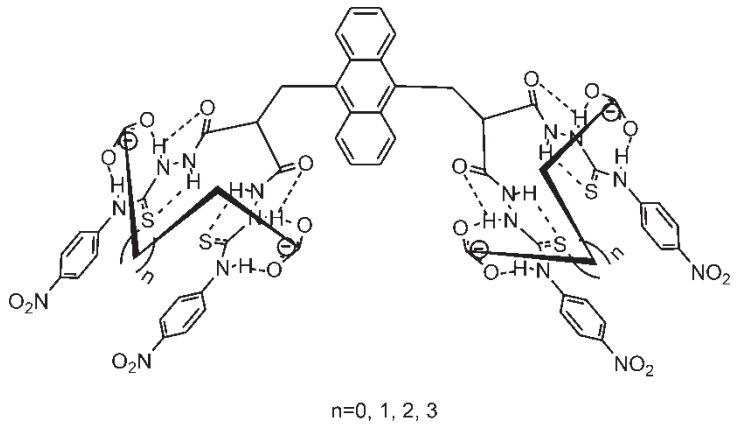
The —NHNH— component in receptor **1** was rigid for the repulsion of the nonpaired electrons on neighboring nitrogen atoms and the preferential Z-conformation of the secondary amide; therefore, two five-membered ring intramolecular hydrogen bonds were formed in the most stable conformation by AM1 calculations [32]. The intramolecular hydrogen-bond network of two five-membered rings would enhance the stability of complexes between host and guest, and facilitate the excited-state communication of the receptor unit with the signaling unit via hydrogen bonds to make fluorescent sensing possible (Scheme 2).

The anion-induced fluorescence enhancement might be due to the efficient fluorescent retrieval upon interaction between anion guest and the receptor unit of **1**. In the absence of anion, the fluorescent intensity of receptor **1** was quenched to some extent by a photoinduced electron transfer (PET) process. However, when the anion was introduced into the solution of receptor **1**, the interaction between the receptor unit and the anion might diminish the efficiency of the PET process to introduce the "switch on" action based on the fluorescent retrieval of the anthracene units [33].

Because the associate constants of receptor **1** with the α,ω-dicarboxylate anion species were too large to be calculated precisely by the UV–vis spectral study, the fluorescence titration method was a better choice for higher sensitivity [30]. The following equation was easily deduced while anion guests were in excess [34–36]:

$$\log[(F - F_0)/(F_\infty - F)] = n \log[G] + \log K_{ass}$$

where F is the fluorescent intensity of the solution, F_0 and F_∞ are the limiting values of F at zero anion concentration and saturating anion concentration, respectively, n is the number of anion guest



SCHEME 2 Hypothetic binding mode of receptor **1** with dicarboxylate anions.

molecules bound by a host molecule, and K_{ass} is the apparent association constant. The values of n and $\log K_{ass}$ are summarized in Table I. This illustrates that receptor **1** forms 1:2 complexes with α,ω-dicarboxylate anions. From the UV–vis and fluorescence spectra titration studies, the interactions between the halogen anion (Cl^-, Br^- or I^-) and the host were found to be too weak to calculate their association constants. The data in Table I show that the sensitivity for recognition of dicarboxylate depended strongly on the chain length of these dicarboxylate anions. Receptor **1** binds the anions in the order adipate > glutarate > succinate > malonate ⩾ halogen (Cl^-, Br^-, I^-). Receptor **1** has four branched chains to recognize the anions, and each chain has three hydrogen-bonding sites. The recognition ability of **1** depends on whether the chain length of the dicarboxylate anions matches the distance between two adjacent chains in receptor **1**.

Large changes in the chemical shifts were observed for the amide or thiourea NH protons of receptor **1** upon the addition of dicarboxylate. Receptor **1** showed three signal peaks at 9.55 (amide NH), 10.18 and 10.75 ppm (thiourea NH). Addition of the adipate anion (1:1) shifted the peaks downfield with broadening to 11.02, 11.90 and 13.50 ppm, respectively. The results illustrate that the recognition of receptor **1** for dicarboxylate anions was by multiple hydrogen-bonding interactions.

TABLE I n and $\log K_{ass}$ of receptor **1** with anions* in DMSO

Anion	n	$\log K_{ass}$
Malonate	1.73 ± 0.12	7.90 ± 0.40
Succinate	1.77 ± 0.21	8.35 ± 0.11
Glutarate	2.12 ± 0.13	8.98 ± 0.39
Adipate	1.98 ± 0.11	9.93 ± 0.49

* Anions were used as their tetrabutylammonium salts.

In summary, the multi-armed neutral anion receptor **1** bearing multiple amide and thiourea binding sites was synthesized. The sensitivity for recognition of dicarboxylates depends strongly on the chain length of the dicarboxylate anions. Receptor **1** forms 1:2 complexes with dicarboxylate anions by multiple hydrogen-bonding interactions, with considerable change in the absorbance and fluorescence spectra and a visible color change. This indicates a promising use as optical chemosensors for the dicarboxylate anions.

MATERIALS AND METHODS

Ethanol, DMF were dried and distilled before using according to standard procedures. All other commercially available reagents were used without further purification. The anions were used as their tetrabutylammonium salts. 9,10-Bis(chloromethyl)-anthracene was synthesized according to the literature [23].

Melting points were measured on a Reichert 7905 melting-point apparatus (uncorrected). The infrared spectra were recorded on a Nicolet 670 FT-IR spectrophotometer, and the mass spectra on a Finnigan LCQ advantage spectrometer. Elemental analyses were determined by using a Perkin-Elmer 204B elemental autoanalyzer. ^{1}H NMR spectra were recorded on a Varian Mercury VX-300 MHz spectrometer, and UV–vis spectra on a TU-1901 spectrometer. Fluorescence spectra were obtained on a Shimadzu RF-5301 spectrometer.

Synthesis

Compound 2

A solution of sodium ethoxide in anhydrous ethanol (0.26 g, 11.3 mmol of Na in 20 ml of ethanol) was added to a solution of diethyl malonate (1.76 g, 11.0 mmol) in ethanol (10 ml). After refluxing for 2 h,

the solvent was removed under reduced pressure. Then 9,10-bis(chloromethyl)anthracene (1.5 g, 5.5 mmol) and anhydrous DMF (100 ml) were added and the mixture refluxed for 24 h. Most of the DMF was evaporated under reduced pressure. A large amount of water (150 ml) was added to the residue, the precipitate was filtrated and dried under vacuum, and then this initial product was recrystallized from toluene to obtain 1.2 g (42% yield) of **2** as a pale yellow solid: mp 162–163°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.04 (12H, t, $J = 8$ Hz, CH_3), 3.82 (2H, t, $J = 7$ Hz, CH), 4.02 (8H, q, $J = 8$ Hz, $COOCH_2$), 4.28 (4H, d, $J = 7$ Hz, $ArCH_2$), 7.49 (4H, dd, $J_o = 7$ Hz, $J_m = 3$ Hz, ArH), 8.28 (4H, dd, $J_o = 7$ Hz, $J_m = 3$ Hz, ArH); IR (KBr pellet) ν (cm^{-1}) 1737 (CO), 757 (Ar); elemental analysis calcd (%) for $C_{30}H_{34}O_8$: C 68.95, H 6.56; found: C 69.03, H 6.63.

Compound 3

Compound **2** (0.26 g, 0.5 mmol) and hydrazine hydrate (2 ml) were heated at reflux in ethanol (20 ml) for 40 h. The precipitate was collected and washed in $CHCl_3$ and ethanol, and the solid was dried under vacuum to obtain 0.2 g (86% yield) of **3** as a pale yellow solid: mp 256–257°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ3.37 (2H, t, $J = 6$ Hz, CH), 4.07 (4H, d, $J = 6$ Hz, $ArCH_2$), 4.30 (8H, br, NH_2), 7.52 (4H, dd, $J_o = 7$ Hz, $J_m = 3$ Hz, ArH), 8.31 (4H, dd, $J_o = 7$ Hz, $J_m = 3$ Hz, ArH), 8.79 (4H, br, CONH); IR (KBr pellet) ν (cm^{-1}) 1667 (CONH), 756 (Ar); elemental analysis calcd (%) for $C_{22}H_{26}N_8O_4$: C 56.64, H 5.62, N 24.02; found: C 56.74, H 5.58, N 23.97.

Receptor 1

Compound **3** (0.1 g, 0.215 mmol) and *p*-nitrophenyl isothiocyanate (0.16 g, 0.88 mmol) were stirred in anhydrous DMF (20 ml) at room temperature for 10 h. A large amount of water (80 ml) was poured into the solution. The collected precipitate was washed in $CHCl_3$ and ethanol, and the solid was dried under vacuum to obtain 0.23 g (91% yield) of **1** as a pale yellow solid: mp 207–208°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ3.93 (2H, t, $J = 7$ Hz, CH), 4.24 (4H, d, $J = 7$ Hz, $ArCH_2$), 7.55 (4H, dd, $J_o = 7$ Hz, $J_m = 3$ Hz, ArH), 7.84 (8H, d, $J = 9$ Hz, PhH), 8.16 (8H, d, $J = 9$ Hz, PhH), 8.41 (4H, dd, $J_o = 7$ Hz, $J_m = 3$ Hz, ArH), 9.55 (4H, br, CONH), 10.18 (4H, br, CONHN*H*), 10.75 (4H, br, PhNH). IR (KBr pellet) ν (cm^{-1}) 1701 (CONH), 1508 (NO_2), 1336 (N—CS—N), 851 (Ph), 749 (Ar); ESI-MS: m/z 1185 ($M^+ - 1$), 1186 (M^+) and 1187 ($M^+ + 1$); elemental analysis calcd (%) for $C_{50}H_{42}N_{16}O_{12}S_4$: C 50.58, H 3.57, N 18.88; found: C 50.44, H 3.59, N 18.80.

Binding Studies

The studies on the binding properties of **1** were carried out in DMSO or DMSO-d_6. The UV–vis spectral study was carried out with a series of 2.5×10^{-5} mol l^{-1} solutions of receptor **1** containing different amounts of anion. The fluorescence titration was performed with a series of 5×10^{-6} mol l^{-1} solutions of receptor **1** containing different amounts of anion (the excitation wavelength was 361 nm, the excitation and emission slit widths were both 5 nm). A Job plot study was performed on a total concentration of 0.1 mM. ^{1}H NMR spectra were recorded on adding equivalent amounts of anion to the receptor (10^{-2} mol l^{-1}).

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