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Fluorescent Receptor Bearing Two 2-Aminobenzimidazole Moieties for Dicarboxylates

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A new neutral receptor containing 2-aminobenzimidazole moieties was synthesized. The binding properties of the host 1 toward dicarboxylates and mono anions have been examined by using fluorescence spectrometry. The host 1 effectively recognized malonate, succinate, glutarate, adipate, and pimelate with 1:1 binding through hydrogen bonding interactions, and it also recognized acetate with 1:1 binding.

Keywords: Anions; Host-guest systems; Hydrogen bonds; Neutral receptor; Dicarboxylates

INTRODUCTION

Selective chemosensors for anions have been drawing much attention because anions play an important role in biology, medicine, and environmental chemistry [1–5]. Chemosensors based on anion-induced changes in optical signals are particularly attractive. Among them, fluorescent chemosensors are an invaluable tool for detecting anions due to their simplicity, high sensitivity, and low detection limit [6–29]. Careful design of the fluorescent chemosensors may produce a perceptible signal when the desired anion is selectively bound.

Dicarboxylates are one of the most attractive sensing molecules since several carboxylate functional groups exist in a variety of biomolecules such as amino acids and proteins. Dicarboxylates also play a major role in the regulation of metabolic processes including the citric acid and glyoxylate cycles [30].

Several sensors for recognition of dicarboxylates have been reported over the last few years [30–40], but neutral fluorescent dicarboxylate sensors are still rare [41–49]. Although some neutral anion receptors containing amides, urea/thiourea, and pyrrole units have been reported previously [41–49], the neutral receptors for recognition of dicarboxylates employing 2-aminobenzimidazole as binding sites have never been reported to the best of our knowledge. Interested in the development of easy-to-make fluorescent dicarboxylate sensors where the anion recognition takes place at neutral binding units, we synthesized and analyzed binding properties of host **1** bearing two 2-aminobenzimidazole moieties as a fluorescent chemosensor for dicarboxylates. The anion recognition of this compound was investigated by using fluorescent emission spectrometry.

RESULTS AND DISCUSSION

9,10-Bis-chloromethyl anthracene (**2**) was used as the starting material for the synthesis of the host **1**. 9,10-Anthracenedicarboxaldehyde (**3**) was synthesized by oxidation of **2** [50]. The synthesis of **1** was carried out by condensing 9,10-anthracenedicarboxaldehyde with 2-aminobenzimidazole in the prescence of toluenesulfonic acid, which was followed by reduction with $NaBH_4$ in MeOH (Scheme 1). The reaction mixture was poured into water, and the solid precipitated was chromatographed on silica gel (CH_2Cl_2:MeOH, 19:1) giving the host **1** in 58% yield. IR, ^1H, ^{13}C NMR, and EA were consistent with the structure of **1**.

The recognition properties of the host **1** with a series of anions such as malonate, succinate, glutarate, adipate, acetate, and halogen anions

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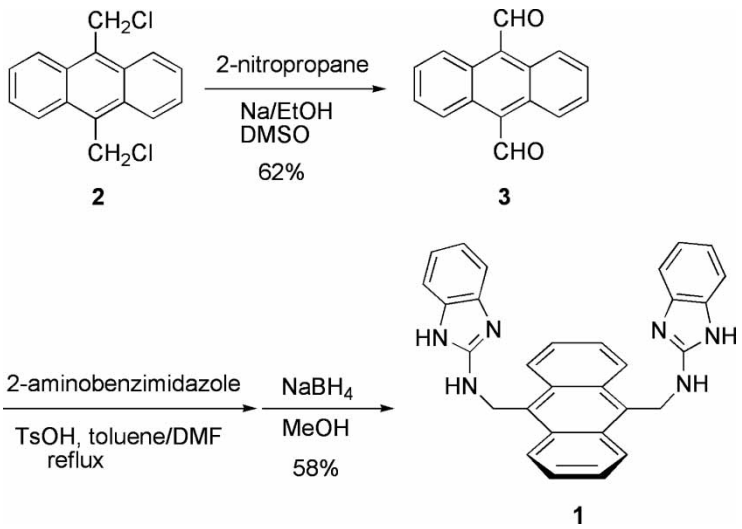

SCHEME 1 Synthesis of the host **1**.

(Cl^- and Br^-) were investigated by observing the fluorescence changes of the host **1** in CH_3CN upon anion titration. Tetrabutylammonium (TBA) salts of anions were used as anion sources. Fig. 1 shows the fluorescence changes of the host **1** (1 μM) with different concentrations of malonate. The strong fluorescence emission spectra at 423 nm attributed to the anthracene group was appeared when excited at 375 nm. As the concentration of malonate was increased, the intensity of emission spectra decreased, which implies the formation of the host-anion complex. No other spectral changes were observed in the emission spectra, indicating that there was no evidence of either exciplex or excimer emissions. Upon titration of the malonate, no changes were observed in UV/Vis spectrum of the host **1**. This indicates that the fluorescence response is not a function of changes in the ground state. The changes in the fluorescence emission spectra are due to an enhanced rate of photoinduced electron transfer (PET) from the anion bound receptors to the excited state of the fluorophore [42]. It is known that in a system where a fluorophore and a binding site are separated by a methylene spacer, only interaction between the two moieties is *via* electron transfer. Hence, the intensity of fluorescence is varied only upon anion sensing.

Titration of the host **1** with succinate, glutarate, adipate, and pimelate resulted in similar specta. The titration data and Job's plot [51] for malonate, succinate, glutarate, adipate, and pimelate were consistent with a 1:1 (host/guest) complex (Fig. 2). Association constants between the host **1** and dicarboxylates were calculated with Benesi–Hildebrand plots [52] by using the fluorescent intensity changes at 423 nm. The association constants of the host **1** with malonate, succinate, glutarate, adipate, and pimelate were calculated to be 33500, 28800, 21000, 16300, and 9600 M^{-1} (errors $< 10\%$), respectively. The binding affinities strongly depended on the chain length of dicarboxylates. The order of binding affinities showed the importance

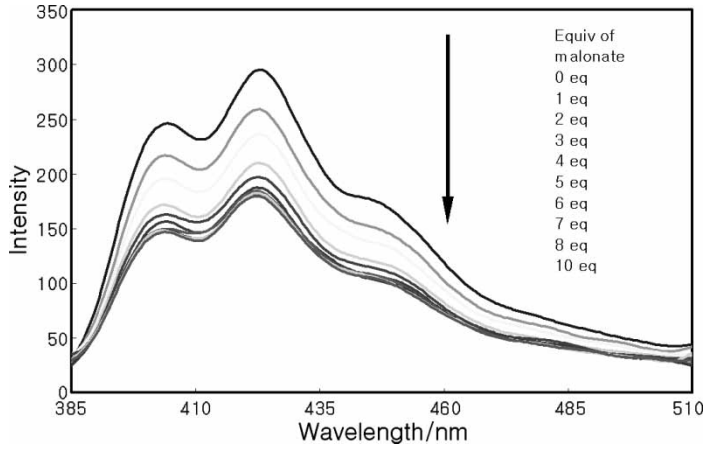

FIGURE 1 The change of fluorescence spectra of **1** (1 μM) in CH_3CN at 25°C excited at 375 nm upon addition of Bu_4N (malonate).

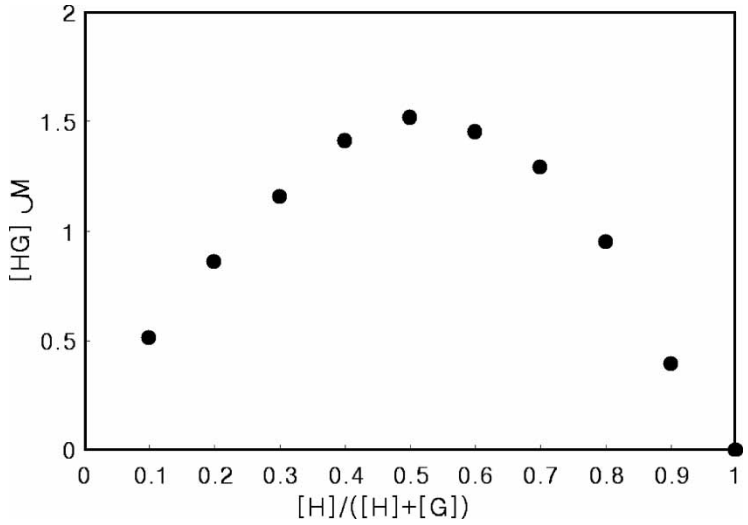

FIGURE 2 Job's pot between **1** and malonate at 25°C in CH_3CN, [G] + [H] = 10 μM.

of the match between the chain length of dicarboxylates and the distance between the two binding sites in the host **1**. Of the dicarboxylates tested, malonate had the highest affinity to the host **1**. The association constant of the host **1** with malonate was approximately 3.5 times larger than that with pimelate. As shown in Fig. 3, the host **1** selectively recognized malonate over longer dicarboxylate anions.

A competition experiment to verify the selectivity of the host **1** for malonate over Cl^- was carried out. Whereas the fluorescence intensity of a solution of the host **1** with 1 equiv of Cl^- was the same as that of the host **1** only solution, the intensity of fluorescence was quenched upon addition of malonate clearly showing that the host **1** was selectively binding malonate over Cl^-. The binding ability of the host **1** with malonate in DMSO which was known as a highly competitive solvent to hydrogen bonding was also examined. The association constant of 20,000 M^{-1} as high as that in CH_3CN was obtained providing the evidence for the formation of the hydrogen-bonded complex even in DMSO.

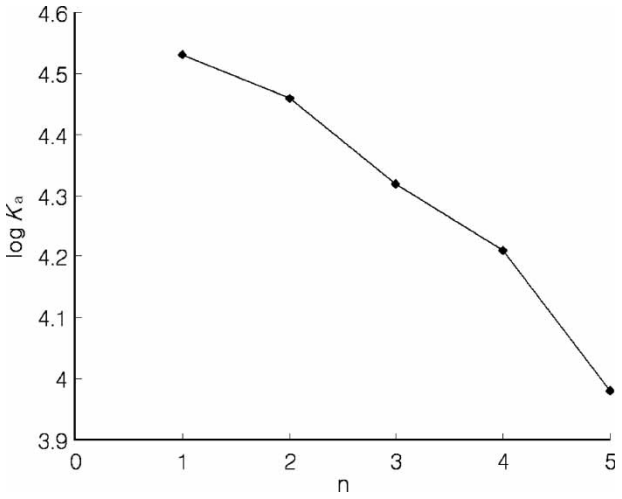

FIGURE 3 Graphic representation of log K_a of the host **1** with dicarboxylates against the number of methylenes between two $-CO_2^-$ groups.

Thiourea-based sensors reported by Gunnlaugsson and co-workers selectively recognized glutarate [42]. Diarboxylates anion receptors bearing amide and thiourea binding sites synthesized by He and co-workers showed the selectivity for adipate over other dicarboxylates [46]. However, the receptor **1** selectively binded a shorter dicarboxylate such as malonate with a high association constant.

We also examined the binding properties of the host **1** with acetate. The fluorescence intensities of the host **1** were gradually decreased when acetate was added to confirm the formation of a host-anion complex with the association constant of 31644 M^{-1}. Job's plot using fluorescence showed that the host **1** recognized acetate with 1:1 binding. Spherical anions such as Cl^- and Br^- did not give any changes in emission spectra.

To get a clear picture of the nature of the interaction between the host **1** and dicarboxylates, we carried out a ^1H NMR titration on the host **1** using malonate. Addition of 1 equiv of malonate to the host **1** (1 mM) in DMSO-d_6 caused the position of benzylic N–H to move downfield from 7.05 to 7.17 ppm ($\Delta\delta = 0.12$ ppm), and the N–H protons in imidazole rings disappered. The protons at benzylic positions shifted a little upfield from 5.56 to 5.49 ppm ($\Delta\delta = 0.07$ ppm). These results show that the host **1** and dicarboxylates form a 1:1 stoichiometry complex through a hydrogen bonding interaction of N–H at benzylic and imidazole ring positions with dicarboxylates.

Comparison of the binding constants for dicarboxylates showed the importance of the distance between two carboxylate anions. Docking studies

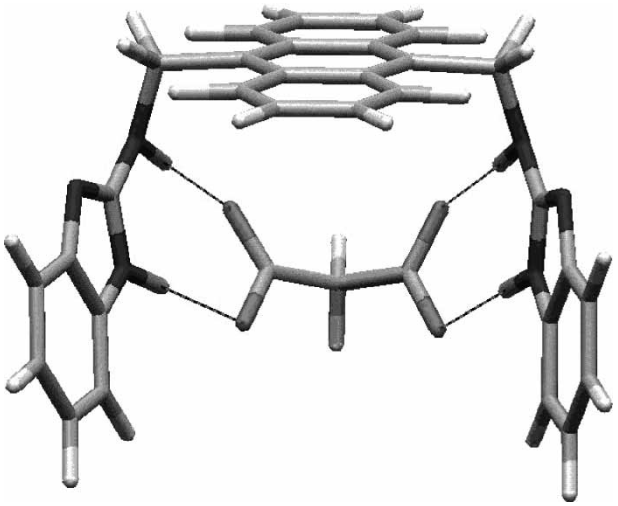

FIGURE 4 Energy-minimized structure of the complexes of **1** with malonate obtained by MacroModel calculation.

by using MacroModel v. 7.1 using MM2* force field [53] gave the most stable structures in which the host **1** was not large enough to accommodate the dicarboxylates thoroughly within its cavity when four hydrogen bonds were applied (Fig. 4). Modeling calculation showed the distance between hydrogen in the N–H and oxygen in malonate fell in the range of 1.84–1.92 Å.

CONCLUSIONS

We synthesized an easy-to-make neutral fluorescent anion sensor using 2-aminobenzimidazole moiety and investigated the stoichiometry and binding strengh of the complex. The host **1** effectively recognized malonate, succinate, glutarate, adipate, and pimelate with 1:1 binding. The sensitivity of the host **1** for recognition of dicarboxylates depended strongly on the chain length between two anions. Among the dicarboxylates, the host **1** particularly showed strong binding to malonate. The host **1** recognized acetate with 1:1 binding.

EXPERIMENTAL

Melting points were determined with a Stuart Scientific melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 NMR spectrometer. Mass spectra were recorded with a 5973 GC/MSD (Agilent Technologies). UV–Vis spectra were recorded using a Perkin Elmer Lambda 25 UV/Vis spectrometer. Fluorescence spectra were obtained on a Perkin Elmer LS55 Luminescence spectrometer. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (Merck, Kieselgel 60F-254). Column chromatography was performed on silica gel (Merck, Kieselgel 60, 230–400 mesh). Solvents were used either as purchased or dried and purified by standard methodology under argon. Starting materials were purchased from Aldrich Chemical Co.

9,10-Anthracenedicarboxaldehyde (3)

9,10-Bis-(chloromethyl)anthracene (**2**) (1.0 g, 3.63 mmol) was dissolved in DMSO (20 mL). To this solution was added a solution of 2-nitropropan (1.3 mL, 14.5 mmol) and Na (332 mg, 14.5 mmol) in absolute EtOH (12 mL). The solution was stirred for 5 h at room temperature. The mixture was poured into cold water and extracted with CH_2Cl_2 twice. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was recrystallised from toluene affording 526 mg (62%) of the compound **3**. The experimental results were accordance with the literature [50]. Mp 243–246°C (lit. [50] 241–244°C); IR (KBr): $\tilde{\nu} = 3034, 2852, 2778, 1765, 1443, 1349, 889, 745\,cm^{-1}$; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.68–7.72$ (dd, $J = 6.9$, 3.3 Hz, 4H), 8.72–8.75 (dd, $J = 6.9$, 3.3 Hz, 4H), 11.48 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 123.7$ 127.9 129.5 131.2 193.9 ppm. EI-MS: m/z (%) = 234 (100) [M^+], 205 (80), 176 (77), 151 (20), 126 (3), 98 (5), 88 (19), 76 (9).

9,10-Bis-(2-aminobenzimidazolylmethyl) anthracene (1)

A solution of antharacenedicarboxaldehyde (**3**) (100 mg, 0.43 mmol), 2-aminobenzimidazole (125 mg, 0.94 mmol), and a catalytic amount of *p*-toluenesulfonic acid in toluene was heated to reflux with a Dean-Stark trap for 36 h. To the solution was added $NaBH_4$ (64 mg, 1.67 mmol) in MeOH (10 mL) after cooling down to 0°C. After stirring for 3 h, the mixture was poured into cold water. The resulting precipitate was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 19:1) to give 115 mg (58%) of the title compound **1**. Mp 248–250°C; IR (KBr): $\tilde{\nu} = 3394, 3046, 1591, 1463, 1263, 877, 742\,cm^{-1}$. ^{1}H NMR (DMSO-$d_6$, 300 MHz): $\delta = 5.54$ (d, $J = 4.2$ Hz, 4H), 6.91–6.94 (m, 4H), 7.05 (s, 2H), 7.22–7.25 (m, 4H), 7.59–7.62 (dd, $J = 6.6$, 3.0 Hz, 4H), 8.53–8.57 (dd, $J = 6.6$, 3.0 Hz, 4H), 10.41 (br, 2H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 64.9, 119.3, 125.2, 125.4, 125.9, 129.6, 129.9, 130.9, 155.1$ ppm. $C_{30}H_{24}N_6$: calcd. C 76.90, H 5.16, N 17.94; found C 76.75, H 5.10, N 17.79.

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