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Diamidonaphthalenodipyrrole-derived fluorescent sensors for anions

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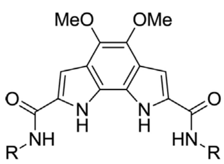
ABSTRACT

We describe the synthesis and properties of bisamide derivatives of naphthalenedipyrrole, which represent a convenient platform for the construction of fluorescent anion sensors. As we show, the spectroscopic properties of such sensors can be fine-tuned through small modifications of the structure at the sensor periphery. The strong fluorescence of these compounds is perturbed through the binding of anionic species in the binding pocket through four hydrogen bonds. Importantly, these effects depend on the nature of the anionic guest, its concentration, and the specific structure of the receptor host. For instance, in the case of one derivative (**2a**) the fluorescence is selectively quenched upon addition of $PhCO_2^-$, while other anions do not have an effect on its spectral properties. In another case (**2b**), only $H_2PO_4^-$ triggers a spectacular enhancement of fluorescence (more than five times higher intensity), while other anions do not change its spectral properties. Such selective responses are related to the selectivity of the anionic species binding, which can be controlled with the structure of the binding pocket. Overall, the study demonstrates that a diamidonaphthalenedipyrrole platform can be used to construct selective sensors for anions that allow for fast and efficient identification of the desired anion present in the analytical samples.

1. Introduction

Fluorescent sensors for anions that respond selectively to the presence of desired anionic species are attractive for the development of fast and efficient analytical methods, suitable for high-throughput applications, such as: monitoring against environmental pollution, controlling industrial processes, as well as, medical diagnostic methods [1]. While myriads of highly selective anion receptors have been reported [2], there is only a limited number of fluorescent sensors, which properties change upon anion binding, hence offering limited potential for such applications [3]. The common issue is the separation of the binding site from the reporting site – the fluorescent moiety, which results in weak responses of the sensor upon anion binding [4]. We envisioned that the construction of sensors with the fluorescent moiety incorporated directly into the binding site would allow to overcome such limitations.

Pyrrole and benzopyrroles bearing amide functions have been used to construct effective anion receptors [5]. For instance, diamide derivatives of benzodipyrrole (**1**) can bind hydrogenpyrophosphate in aqueous solution (acetone with 5% water), as reported by Curiel et al. [6]. Inspired by these results and taking into account the absorption-emission properties of the naphthalene moiety, we designed the diamidonaphthalenodipyrrole platform that combines the fluorescent unit with the binding pocket. We synthesized receptors, equipped with two amide groups and both *n*-butyl (**2a**) or phenyl (**2b**) residue. Here we report the synthesis and properties of these compounds as the sensors for anions.



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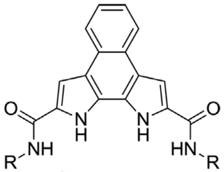

2a: R=n-Bu
2b: R= Ph

2. Material and methods

Fluorescence measurements were conducted in DMSO dried over molecular sieves (4 Å). Solutions of 6×10^{-6} M of ligands were

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used. The slit width was 0.5 μm/0.3 μm (ex/em). Compounds **2a** and **2b** were excited by 320 and 350 nm, respectively, spectra were registered with 1 nm interval and 0.5 s acquisition time.

NMR titration experiments were conducted in DMSO-d_6 (with 0.5% H_2O). In a typical, experiment 0.55 ml of receptor solution (12–17 mM) was titrated with TBA salt dissolved in a receptor solution (to avoid receptor dilution). 12–16 titration points were taken. K_a's were calculated using HypNMR software [7], taking all N—H protons into account. In most cases, 1:1 stoichiometry allowed good refinement. In case of **2b**:$H_2PO_4^-$ complex sequential binding model was used in refinement.

Mass spectra were recorded using EI BE sector mass spectrometer.

All measurements of crystals were performed on a KM4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation. The crystal was positioned at 65 mm from the CCD camera. 1500 frames were measured at 0.5° intervals with a counting time of 12 s. The data was corrected for Lorentz and polarization effects. Empirical correction for absorption was applied [8]. Data reduction and analysis were carried out with the Oxford Diffraction programs [9].

The structure was solved by direct methods [10] and refined using SHELXL [11]. The refinement was based on F^2 for all reflections except those with very negative F^2. Weighted R factors and all goodness-of-fit S values are based on F^2. Conventional R factors are based on F with F set to zero for negative F^2. The $F_o^2 > 2\sigma(F_o^2)$ criterion was used only for calculating R factors and is not relevant to the choice of reflections for the refinement. The R factors based on F^2 are about twice as large as those based on F. All hydrogen atoms were located geometrically and their position and temperature factors were not refined. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2 in Ref. [12].

2.1. *Diethyl 2,2′-(2,2′-(naphthalene-2,3-diyl)bis(hydrazin-2-yl-1-ylidene))dipropanoate*
5

Double-necked flask, equipped with funnel, was charged with Na_2SO_3 (60 g) and dissolved in boiling water. H_2SO_4 (40 ml) was dropped into the solution. Evolved SO_2 (15 g) was cold-trapped, and cooled hydrazine monohydrate (55 ml) was slowly added. The mixture was diluted with ethanol (35 ml) and 2,3-dihydroxynaphtalene (170 mmol, 27 g) was added. It was then refluxed for 6 h and left for 12 h to cool down. Resulting precipitate was filtered off, washed with ethanol (250 ml), affording 21 g (65%) of **4** which was subjected to next reaction step without further purification. Methyl pyruvate (22 ml) was added into vigorously stirred solution of hydrazine **4** (11 g, 58 mmol) in ethanol (15 ml). After a few minutes a yellow solid precipitated. Stirring was continued for 2 h, and the precipitate was filtered off and washed with cold ethanol (250 ml). After recrystallization from ethanol yellow crystals of **5** (13.4 g, 70%) were obtained.

mp. 123–124° C (lit [13]. 123−125° C);

^{1}**H NMR** (200 MHz, $CDCl_3$) δ = 9.18 (bs, 2H), 7.64 (m, 2H), 7.60 (s, 2H), 7.28 (m, 2H), 4.32 (q, 4H, J_1 = 7 Hz), 2.18 (s, 6H), 1.37 (t, 6H, J_1 = 7 Hz).

^{13}**C NMR** (50 MHz, $CDCl_3$) δ = 164.8, 133.9, 131.6, 129.9, 126.5, 124.7, 112.6, 61.2, 14.4, 10.8.

2.2. *Diethyl 1,10-dihydrobenzo[e]pyrrolo[3,2-g]indole-2,9-dicarboxylate 6*

P_2O_5 (142 g, 1 mol) was dissolved in diethyl ether (300 ml) and chloroform (150 ml) and refluxed for 4 d under Ar. Resulting solution was decanted from a yellowish precipitate. The clear solution was concentrated and the residual solvents were evaporated under vacuum in 40° C for 2 d. Hydrazide **5** (8.8 g, 23 mmol) and PPE (100 g) was stirred for 1 h in 100° C. The mixture was then poured into water (500 ml), and the resulting precipitate was filtered off and washed with water (500 ml) until the filtrate became neutral. The crude product has been recrystallized twice from ethyl acetate, resulting in 6.4 g (80%) of crystals of ester **6**.

mp > 280° C (lit [13]. 315° C);

^{1}**H NMR** (200 MHz, DMSO) δ = 11.87 (d, 2H, J_1 = 1.8 Hz), 8.34–8.29 (m, 2H), 7.82 (d, 2H, J_1 = 2.2 Hz), 7.48–7.44 (m, 2H), 4.38 (q, 4H, J_1 = 7.2 Hz), 1.38 (t, 6H, J_1 = 7.2 Hz);

^{13}**C NMR** (50 MHz, DMSO) δ = 161.6, 126.1, 125.5, 124.8, 124.4, 122.2, 109.7, 61.1, 15.1;

LR ESI calcd for $C_{20}H_{18}N_2O_4$ [M+H]$^+$: 351.13, found: 351.16.

2.3. *1,10-Dihydrobenzo[e]pyrrolo[3,2-g]indole-2,9-dicarbonyl dichloride 7*

Ester **6** (1.5 g, 4.4 mmol) was dissolved in *i*-PrOH (8 ml) and KOH (6 g, solution in 50 ml of water) was added and the mixture was refluxed for 8 h. Active charcoal was added, refluxed for a few minutes and subsequently filtered on Celite. The filtrate was acidified and the precipitate was filtered off, washed with water (200 ml) and air-dried. The crude product was then dissolved in THF, triturated with hexanes, yielding 1 g (80%) of diacid (colorless crystals). Diacid (0.7 g, 2.4 mmol) was suspended in CH_2Cl_2 (20 ml) and thionyl chloride (1.7 ml, 24 mmol) was added. After addition of two drops of DMF the mixture was refluxed under Ar. During reflux $SOCl_2$ (0.85 ml, 12 mmol, in 10 ml of CH_2Cl_2) was added after 8 and 16 h. After 30 h of continuous reflux mixture was cooled down to rt and green precipitate of dichloride **7** was filtered off, washed with CH_2Cl_2, and dried under vacuum, yielding 0.75 g (94%) of green crystals which were used without further purification.

Mp. 238–240° C (lit [13]. 240–241° C).

2.4. *N^2,N^9-Dibutyl-1,10-dihydrobenzo[e]pyrrolo[3,2-g]indole-2,9-dicarboxamide*
2a

Ester **6** (0.6 g, 1.6 mmol) and butylamine (4 ml) were placed in a dry vial, sealed and heated at 70° C for 12 h. The mixture was then diluted with EtOAc (50 ml) and washed with 2 M HCl (3 × 30 ml) and brine (20 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was crystalized from EtOAc (20 ml) with a few drops of THF, yielding 0.52 g (80%) of colorless crystals of amide **2a**.

Mp. > 280° C.

^{1}**H NMR** (200 MHz, DMSO) δ = 11.73 (d, 2H, J_1 = 1.6 Hz), 8.48 (t, 2H, J_1 = 5.7 Hz), 8.13–8.08 (m, 2H), 7.74 (d, 2H, J_1 = 2.0 Hz), 7.48–7.44 (m, 2H), 3.34 (dt, 4H, J_1 = 6.2 Hz, J_2 = 6.4 Hz), 1.56 (m, 4H), 1.35 (m, 4H), 0.93 (t, 6H, J_1 = 7.3 Hz);

^{13}**C NMR** (50 MHz, DMSO) δ = 161.2, 128.8, 125.9, 124.6, 123.5, 123.0, 120.8, 103.6, 38.9, 32.0, 20.2, 14.3;

HR EI calcd for $C_{24}H_{28}N_4O_2$ M$^+$: 404.22123, found: 404.22256;

Elemental analysis calcd $C_{24}H_{28}N_4O_2$: C 71.26, H 6.98, N 13.85, found: C 69.66, H 6.86, N 13.19.

2.5. *N^2,N^9-Diphenyl-1,10-dihydrobenzo[e]pyrrolo[3,2-g]indole-2,9-dicarboxamide*
2b

Dichloride **7** (0.74 g, 2.2 mmol) was dissolved in THF (60 ml) and aniline (6 ml, 66 mmol) was added. A white solid precipitated. The mixture was stirred for 6 h and then filtered. The filtrate was poured slowly into HCl solution (3 ml of concentrated acid in 80 ml of water). The precipitate was filtered off, washed with water,