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ORIGINAL PAPER

Design of Two Pyrazole-Based Sensors with Similar Configuration and Different Fluorescent Response to Anions

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Abstract Two simple fluorescent anion receptors based on 1-phenyl-3-methylpyrozole-5-one-4-one phenylhydrazone (L1) and 1-phenyl-3-methylpyrozole-5-one-4-one *p*-nitrophenylhydrazone (L2) were designed, synthesized and characterized with ^{1}H NMR, COSY spectrum, ^{13}C NMR, ESI-mass and elemental analyse. Interestingly, two receptors with similar configuration exhibited different anion binding behaviors in DMSO solution. The results of Job plots and ESI-mass spectrum indicate that L1 bind anions such as F^-, AcO^-, $H_2PO_4^-$ to form 2:1 host-guest complexation, while L2 bind anions to form 1:1 host-guest complexation in the solution.

Keywords Anion sensor · Pyrazole · Supramolecular chemistry · Fluorescent

Introduction

The design and synthesis of a chemosensor for recognition and sensing of anionic analytes is emerging as a research area of considerable importance [1–4]. Carboxylate anions, for example, are used in diverse industries such as plastic, pharmaceutical, and food. In addition, carboxylate groups are also present in many pesticides and are the active groups in many biological processes [5]. In addition, phosphates can be found in many chemotherapeutic and antiviral drugs, however, it is for sure that phosphate originating from the over use of agricultural fertilizers can also lead to eutrophication in inland waterways [6,7]. As a result of the diversities of anionic species, there is still an urge for design and synthesis of the artificial sensors for such anions.

With a view to anion interacting modes, those are classified basically into electrostatic interactions [8], hydrogen bonding interactions [9,10], interactions with metal centers [8] and chemical reactions with activity centre [11]. Among these interacting modes, the hydrogen bonding interaction is one exploited widely in the development of artificial anion receptors, owing its excellent feature which allows the design of receptors having ability to differentiate between anions with different geometries and hydrogen-bonding requirements. As hydrogen bonding donors, the groups such as ureas/thioureas [12], amines [13], amides [14], thioamides [15], sulfonamides [16], indole [17], pyrroles [18], imidazolium [19] and guanidium cations [20] were widely used; however, the receptor based on the pyrazole derivative was rarely reported in the literature.

With these in mind, we would couple the pyrazole derivative with substituted-phenylhydrazine and obtained two simple and novel anion receptors. Interestingly, the compound 1 displayed a fluorescent enhancement response to anions and the compound 2 exhibited a fluorescent quenching response to anions of interest. In particular, presence of the strong basic anions such as F^- would result

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in configurational changes of the receptors 1 and 2 from the hydrazone form to the azophenol form.

Experimental

Apparatus

^{1}H NMR spectra and ^{13}C NMR spectra were obtained on a Varian UNITY Plus-400 MHz and a Varian UNITY Plus-300 MHz Spectrometer, respectively. ESI-MS was performed with a MARINER apparatus. C, H, N elemental analyses were made on an elementar vario EL. UV-vis spectra were recorded on a Shimadzu UV2450 Spectrophotometer with quartz cuvette (path length=1 cm) and Fluorescent spectra were recorded on a Shimadzu RF-5301PC Spectrophotometer at 298.2±0.1 K and the width of the slits used is 5 nm.

Chemicals

All reagents for synthesis obtained commercially were used without further purification. In the titration experiments, all the anions were added in the form of tetrabutylammonium (TBA) salts, which were purchased from Sigma-Aldrich Chemical, stored in a vacuum desiccator containing self-indicating silica and dried fully before using. DMSO was dried with CaH_2 and then distilled in reduced pressure.

Synthesis

4, 4-dibromo-3-methyl-1-phenyl-pyrazol-5-one (3)

The compounds 1 and 2 were easily obtained in two steps shown in Scheme 1. The intermediate, 4, 4-dibromo-3-methyl-1-phenyl-pyrazol-5-one, was prepare on the basis of a known procedure [21]. To a solution of 3-methyl-1-phenyl-pyrazol-5-one (34.8 g, 0.2 mol) in CH_3COOH (80 ml) was added dropwise a solution of Br_2 (64 g, 0.4 mol) in CH_3COOH (40 ml). The reaction mixture was stirred for 05 h and then was poured into 200 ml water being placed overnight. The precipitate was filtered, washed with water to be neutral, and then recrystallized from ethanol to give 50 g yellow pure product. Yield= 96.5%. ^{1}HNMR (400 MHz, DMSO-d_6, 298 K, TMS): δ 2.50 (3H, s, H-CH_3), 7.17 (2H, t, H-Ar), 7.31 (1H, t, H-Ar), 7.50 (2H, t, H-Ar).

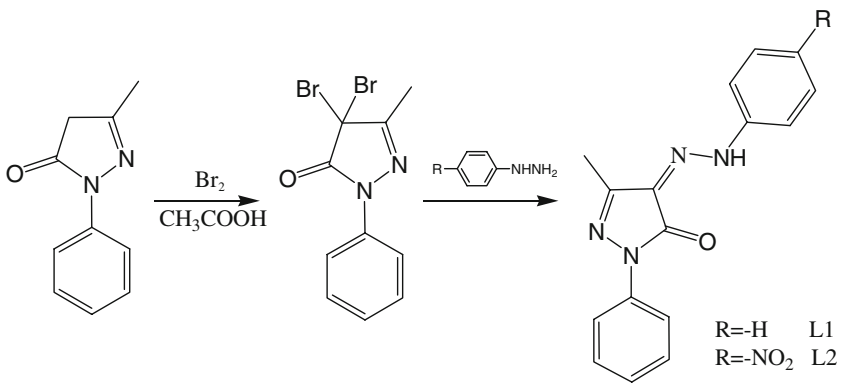
The compounds 1 and 2

4,4-dibromo-3-methyl-1-phenyl-pyrazol-5-one (2) (3.29 g, 0.01 mol) and substituted-phenyl- hydrazine (0.012 mol) were dissolved in ethanol (50 ml) and then reacted at 325–335 K under magnetic stirring for 1 h. Ethanol was removed under reduced pressure and the resulting mixture was neutralized with 5% $NaHCO_3$. The precipitate was filtered and crystallized from methanol to give pure products.

1-phenyl-3-methylpyrozole-5-one-4-one phenylhydrazone (L1): ^{1}H NMR (400 MHz, DMSO-d_6, 298 K, TMS,): δ 2.30 (3H, s, -CH_3), 7.23 (2H, t, H-Ar), 7.46(4H, m, H-Ar), 7.61 (2H, t, H-Ar), 7.92 (2H, d, J=8.4 Hz, H-Ar), 13.27 (1H, s, -NH). ^{13}C NMR (75 MHz, DMSO-d_6, 298 K, TMS): δ: 11.7, 116.2, 117.7, 124.9, 125.8, 127.8, 129.1, 129.7, 138.0, 141.3, 148.6, and 156.6. Elemental analysis calcd for $C_{16}H_{14}N_4O$: C, 69.05; N, 20.13; H, 5.07. Found: C, 69.08; N, 20.07; H, 5.05; EMS—mass m/z calcd. for $C_{16}H_{14}N_4O$ $[M-H]^-$:277.12 and found: 277.66.

1-phenyl-3-methylpyrozole-5-one-4-one *p*-nitrophenylhydrazone (L2): ^{1}HNMR(400 MHz, DMSO-d_6, 298 K, TMS,): δ 2.499 (3H, s, -CH_3), 7.24 (1H, t, H-Ar), 7.47 (2H, t, H-Ar), 7.83 (2H, d, J=9.2 Hz, H-Ar), 7.90 (2H, d, J=8 Hz, H-Ar), 8.30 (2H, d, J=9.2 Hz, H-Ar), 13.23 (s, 1H, -NH). ^{13}CNMR (75 MHz, DMSO-d_6, 298 K, TMS,): δ11.7, 116.2, 117.7, 125.0, 125.4, 129.1, 130.8, 137.7, 143.6, 147.0, 148.9, 155.8. Elemental analysis calcd for $C_{16}H_{13}N_5O_3$: C, 59.44; N, 21.66; H, 4.05. Found: C, 59.43, N, 21.70, H,

Scheme 1 The synthesis of the compounds 1 and 2



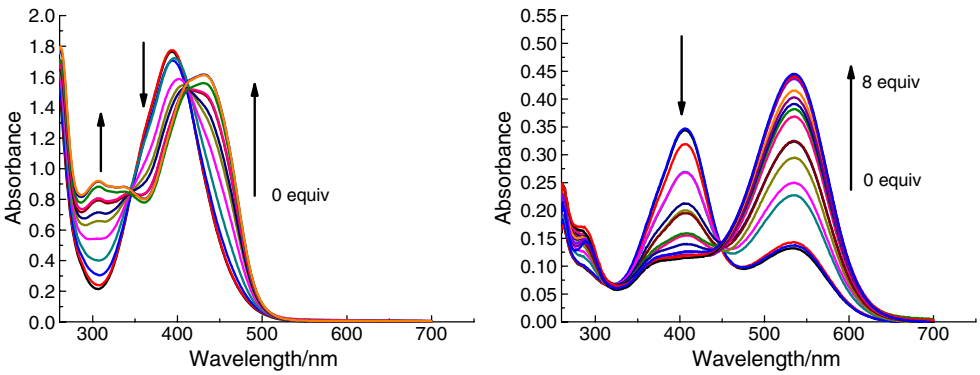


Fig. 1 Changes in the UV-vis spectra for the receptors 1 (left) and 2 (right) (1×10^{-5}M) in the absence and presence of F^- in DMSO solution

4.02. ESI-mass m/z calcd. for $C_{16}H_{13}N_5O_3$ $[M-H]^-$: 323.1 and found 322.82.

Results and discussion

UV-vis titrations

The anion binding ability of the receptors L1and L2 was evaluated through UV-vis titrations by adding a standard solution of the tetrabutylammonium salt of anions to a dry DMSO solution of the sensors at 298.2±0.1 K. Obviously, the free L1 exhibited a main absorption band centered at 394 nm and there was a significant decrease in the absorption of 394 nm and appearance of two new absorption peaks at 306 nm and 431 nm, respectively upon the addition of fluoride ions (Fig. 1a). In addition, two isosbestic points at 346 nm and 410 nm and these results indicated that the stable complex was obtained with a certain stoichiometric ratio between L1 and F^- [22]. The presence of AcO^- and $H_2PO_4^-$ ions induced similar spectral changes with those resulting from addition of F^- and no obvious spectral changes were observed on the addition of excess equiv of Cl^-, Br^- and I^- ions (Fig. 2).

In the case of L2, there were two absorption bands at 407 nm and 537 nm (Fig. 1b), and there a great decrease in the absorption band at 407 nm and an obvious increase in the absorption of 537 nm upon addition of F^- accompanying with naked-eye color changes from red to purple.

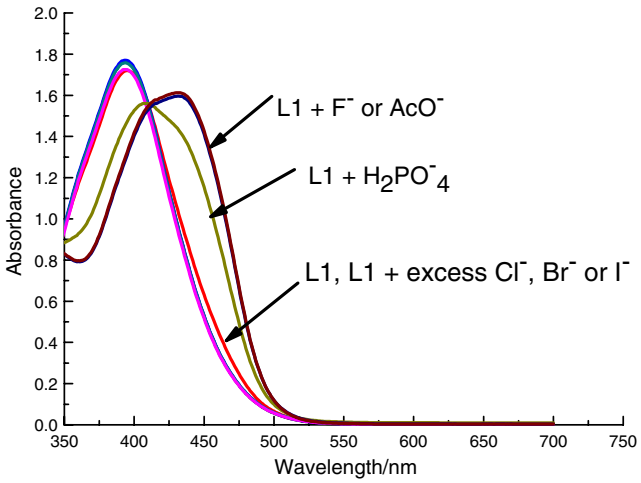


Fig. 2 Spectral changes of L1 (1×10^{-5}M) induced by addition of different anions in DMSO

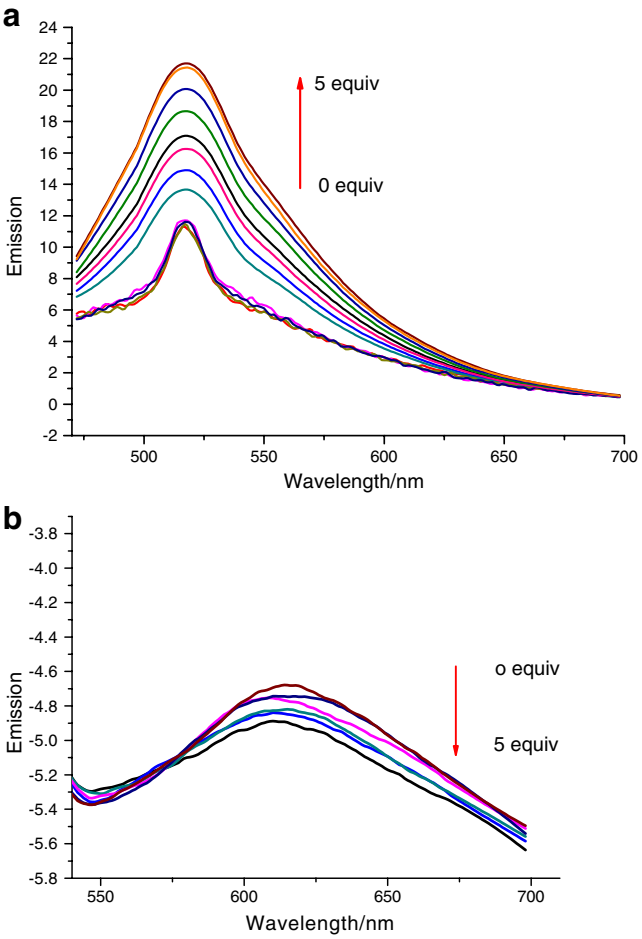


Fig. 3 Changes in the fluorescent emission spectra for the receptors 1 (λ_{Ex}=415 nm) (A) and 2 (B) (1×10^{-5}M) in DMSO in the absence and presence of F^- (Excitation at 450 nm and slit width is 5)

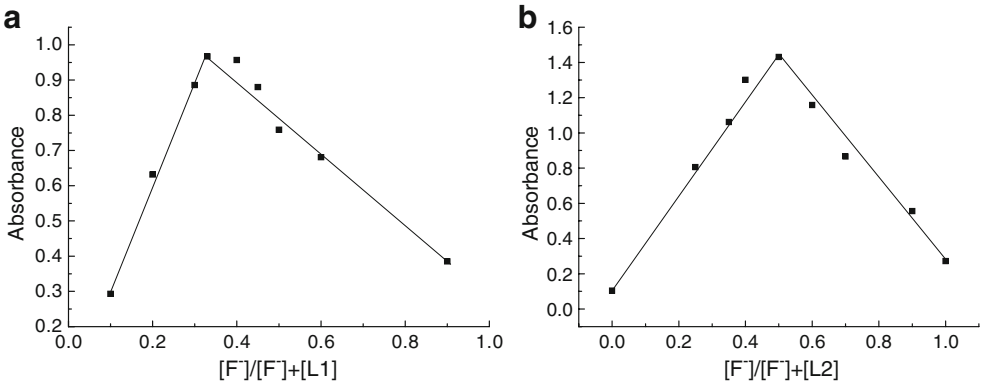


Fig. 4 Job plots of the receptors 1 (**a**) and 2 (**b**) with fluoride

Similarly, there was a well-defined isosbestic point demonstrating formation of the stable complex. The receptor 2 exhibited a similar spectral response to the strong basic anions such as AcO^- and $H_2PO_4^-$ and was insensitive to addition of excess equiv weak basic anions such as Cl^-, Br^- and I^- (see Supporting information). The results of the spectral changes of L1 and L2 could be rationalized on the basis of the fact as follow. Actually, L1 and L2 displayed a tautomeric equilibrium between the hydrazone form and the azophenol form just as reported by G. Kaupp [23], where the hydrazone form dominated in the solution. Upon addition of the strong basic anions, the hydrazone form would be transferred to the azophenol form, which interacted with anionic analytes and was responsible for the spectral changes and naked-eye color changes, which would be further discussed in detail in the ^{1}H NMR titration experiment.

Fluorescent titrations

Interestingly, the receptors L1 and L2 showed positive and negative fluorescent responses to anions, respectively, although two receptors had similar chemical configuration. Just as Fig. 3 showed, upon excitation at 397 nm, L1 showed a weak emission at 415 nm and the visible fluorescent enhancement was observed with addition of the strong basic anions such as F^-. However, L2 exhibited a fluorescent emission band centered at 667 nm when was excitated (λ_{Ex}=450 nm) and such emission would be gradually quenched upon addition of fluoride ions (Fig. 3b). The possible explanation for this result might be that the receptors L1 and L2 employed two different signaling transduction mechanisms for anion binding. Upon complexation with anions, the configuration of L1 was rigidified, resulting in inhibiting vibrational and rotational relaxation modes of nonradiative decay [24], and thus the fluorescent enhancement of L1 was observed. In the case of L2, an electron-withdrawing substituent ($-NO_2$) was introduced into L2 and accordingly there would be a photoinduced electronic transfer (PET) [25] from the pyrazole unit (a fluorophore) to the electron-withdrawing

Table 1 The association constants logK_{ass} of the receptors (L1 and L2) with anions in DMSO at 298.2±0.1 K

Anions[a]	L1 logK_{ass}	L2 logK_{ass}
F^-	5.35	5.45
AcO^-	5.07	5.40
$H_2PO_4^-$	4.97	4.15
Cl^-	–[b]	–
Br^-	–	–
I^-	–	–

[a] All the anions were added in the form of tetra-n-butylammonium (TBA) salts

[b] Very weak complexation. The association constant could not be determined

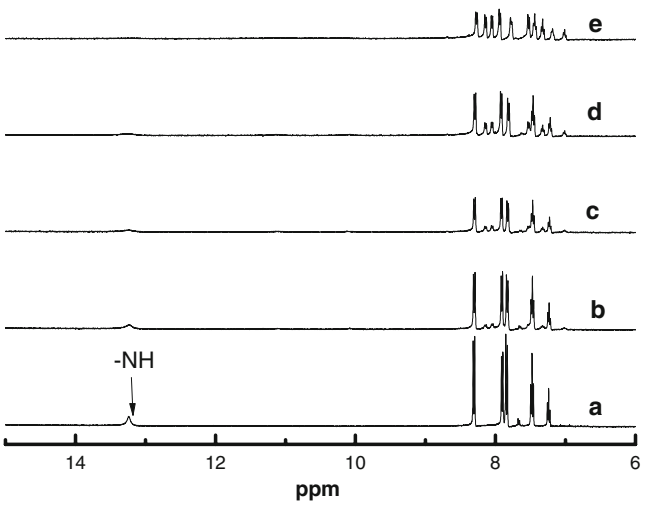


Fig. 5 Changes in the ^{1}HNMR spectra of L2 with gradual addition of F^- in DMSO-d_6, a) L2 only, b) 0.2 equiv F^-, c) 0.4 equiv F^-, d) 0.6 equiv F^-, e) 2 equiv F^- (the figure magnified is shown in S9 in Supporting information)

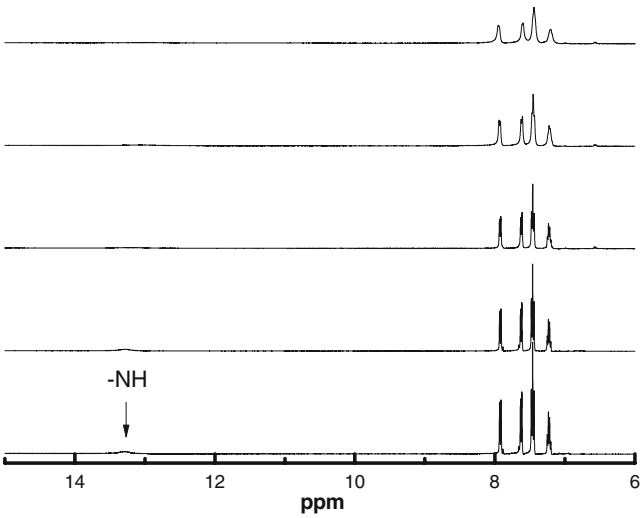


Fig. 6 Changes in the ^{1}HNMR spectra of L1 with gradual addition of F^- in DMSO-d_6, a) L1 only, b) 0.5equiv F^-, c) 5 equiv F^-, d) 10 equiv F^-, e) 15 equiv F^- (the figure magnified is shown in S10 in Supporting information)

substituent (-NO_2) and as a result the fluorescent emission would be gradually quenched upon addition of fluoride ions.

Determination of the association constants

To determine the certain stoichiometric ratio between two receptors and anions tested, the Job plots experiments and ESI-mass of supramolecular systems were carried out. Figure 4 showed the Job plots of two receptors with fluoride, indicating L1 bind $F^-$to form 2:1 host-guest complexation, while L2 bind F^- to form 1:1 host-guest complexation in the solution. The results of Job plots could be further validated by ESI-mass spectra of supramolecular systems. As an example, the signal of the 2:1 complex (2 L1+F^-) was calculated to be 577.24 and found to be 577.86 (see S1 in Supporting information). Such different anion binding behaviors of L1 and L2 were possibly due to that electron withdrawing/donating group of the receptor triggered different binding events during the recognition. Consequently, the association constants of L1 and L2 with anions, which were shown in Table 1, were determined according to the Eqs. (1) and (2) [26], respectively.

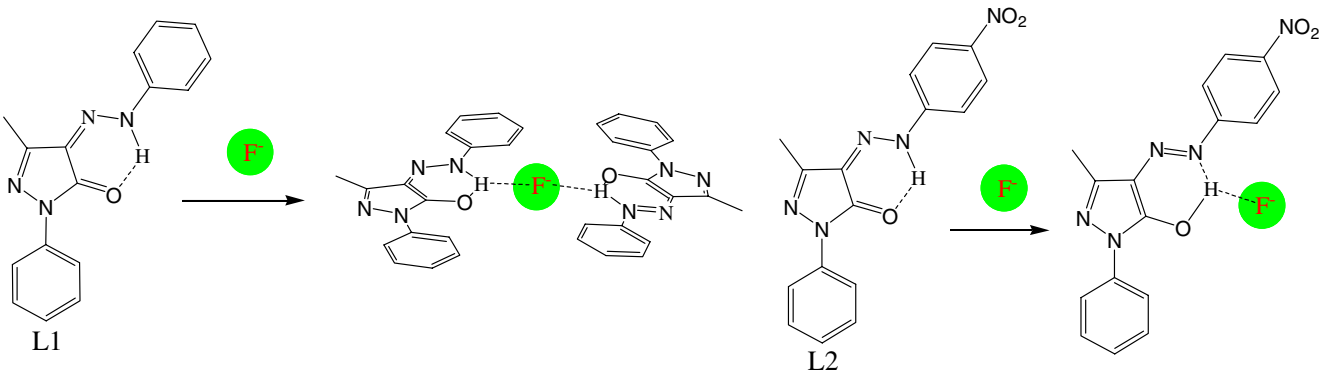
$$\frac{A_o}{A-A_o}=\left(\frac{\varepsilon_o}{\varepsilon_o-\varepsilon}\right)^2\left(\frac{1}{K_B[\text{substrate}]^2}+1\right) \quad (1)$$

$$\frac{A_o}{A-A_o}=\left(\frac{\varepsilon_o}{\varepsilon_o-\varepsilon}\right)\left(\frac{1}{K_B[\text{substrate}]}+1\right) \quad (2)$$

A_O and A are the absorbance of the receptor in the absence and presence of the anion analytes respectively; ε_0 and ε are the corresponding molar absorption coefficients of the receptor in the absence and presence of the anion analytes, respectively. [substrate] is the concentration of the titrants and K_B represents the association constant of host–guest complexation.

^{1}H NMR titrations

To examine the nature of the interactions between anions and the receptors, ^{1}H NMR spectral changes were investigated with addition of F^- as their tetrabutylammonium salts to the DMSO-d_6 solution of the receptors (5×10^{-3}mol L^{-1}). For example, Fig. 5 (or the magnified figure in Supporting information, S9) demonstrated ^{1}H NMR spectral changes of L2 induced by presence of F^-. The free L2 had a proton signal at 13.23 ppm, being ascribed to –NH moiety. Upon addition of 0.2 equiv of F^-, a new proton signal appeared at 9.90 ppm, which was attributed to –OH…F^- moiety of the azophenol form. In addition, the signal of –NH moiety of the hydrazone form was splitted into two signals at 13.23 ppm and 10.10 ppm, indicating that the –NH moiety of the hydrazone form interacting with F^- ions had an upfield shift to 10.10 ppm and the signal of the free –NH moiety did not shift. In other words, the signals at 13.23 ppm, 10.10 ppm and 9.90 ppm could be ascribed to



Scheme 2 The proposed anion binding modes of the receptors L1 and L2 in solution

the free –NH of the hydrazne form, the –NH of the hydrazne form binding F^- and the –OH of the azophenol form binding F^-, respectively. The ^1H NMR spectral changes of L1 were similar with those of L2, which were shown in Fig. 6 (or the magnified figure in Supporting information, S10). According to the results of UV-vis spectral, fluorescent and ^1H NMR titrations, the anion binding modes of the receptors L1 and L2 were shown in Scheme 2.

Conclusions

In summary, we have successfully showed two fluorescent anion receptors based on the pyrazole derivative. The receptor L1 exhibited a fluorescent enhancement (OFF-ON) response to anions and the receptor L2 displayed a fluorescent quenching response (ON-OFF) to anions in DMSO solution. L1 with absence of electron withdrawing groups employed a signaling transduction mechanism based on anion-induced rigidity of the host and L2 with presence of electron withdrawing groups ($-NO_2$) exploited a PET signaling transduction mechanism upon binding anions.

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