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ORIGINAL ARTICLE

Colorimetric 'naked-eye' sensor for anions based on conformational flexible tripodal receptor

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Abstract A new tripodal receptor for anion sensing based on amide-pyridinium as recognition site and nitro-benzene as signaling unit was designed and successfully synthesized. This receptor showed high selectivity and strong binding affinity toward AcO^- over the investigated anions, especially over $H_2PO_4^-$. Addition of AcO^- induced clear color change of solution from colorless to yellow, realizing the "naked-eye" detection. UV–Vis and ^1H NMR experiments indicated the selectivity might origin from the synergistic effects arising from hydrogen bonding, electrostatic interactions and conformational change.

Keywords Amide-pyridinium · Tripodand · Anion sensing · Conformational change

Introduction

The design and synthesis of receptors capable of selective binding and sensing anions remains challenging and is a current area of active research [1–4]. Besides the well-known roles of various binding motifs play in anion recognition, the overall receptor topology has exhibited a profound effect on anion binding. Comparing with those rigid cyclic systems (it means the preorganized systems such as macrocycles/macrobicycles which are difficult to change their conformation before and after complexation with anions), flexible podands are more intriguing and significant because they are frequently more easily synthesized and undergo conformational change on anion binding offering the induced fit signal transduction. Those properties form the basis of molecular switches and switchable sensing devices. Recently, much excellent work has been done focusing on tripodal anion receptors with a trisubstituted trimethyl or triethylbenzene core [5–8]. The resulting hexasubstituted systems provide some degree of preorganization into a conical conformation (3-up, 3-down) with all three binding and sensing arms orientated in the same direction and thus are able to bind anions more efficiently [7, 8].

As a part of our continuous work on developing new anion receptors [9–12], in this paper, we report a novel conformational flexible tripodand based on amide pyridinium binding motif, which exhibits colorimetric "naked eye" sensing of AcO^- in rather polar organic solvents. In comparison with those well-documented hydrogen donating frameworks such as amide, urea, pyrrole, indole, ammonium, guanidimium and imidazolium, etc. [13–19], amidepyridinium-based anion receptor is relatively less investigated [20–22] in spite of pyridinium-based anion receptors reported by Steed and coworkers exhibited excellent anion binding properties [8, 23]. The main difference between pyridinium and amidepyridinium binding sites is from whether the presence of intramolecular hydrogen bonding or not. As for amidepyridinium binding site, the intramolecular hydrogen bonding was proved to play the positive role to preorganize the conformation of receptor [12]. When interaction with anions, the conformational change will give rise to more efficient anion binding (See Fig. 1).

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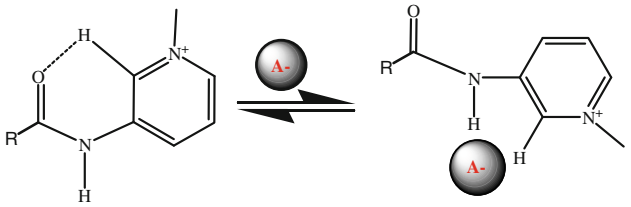


Fig. 1 Intramolecular hydrogen bonding in amidepyrydinium binding site

With this idea in mind, the structure of our designed tripodal receptor is shown in Fig. 2, **L1** comprises trimethylsubstitued benzene as the core to control the direction of the binding arms and nitro-benzene group is introduced as the signal-reporting part. It should be mentioned that the conformation of **L1** would be restricted by the intramolecular hydrogen bonds (IHB) between acidic proton at α-position of pyridinium and carbonyl group, and anion-induced conformational change via disturbing the IHB might realize selective anion sensing, just according with the biologically important induce-fit mechanism [24]. The most interesting point of this mechanism is that only the most suitable anions induce the appropriate conformational change that will result in signal generation even if they have no the strongest bound by the receptor. On the other hand, the electrostatic interaction between electron-positive pyridinium ring and anions will also be expected.

Experimental

Materials and methods

All the anions existed as their tetrabutylammonium salts and were purchased from Alfa-Aesar Chemical Co. Other chemical reagents were used as received without further purification. Unless otherwise specified, all of the UV–vis titration experiments were carried out at 298.2 ± 0.1 K. ^{1}H and ^{13}C NMR spectra were recorded on a AVANCE II400 spectrometer at room temperature using with Me_4Si as an internal standard. HRMS were measured on UPLC/Q-Tof Microa MS apparatus. The UV–Vis titration spectra were measured on a HITACHI U-4100 spectrophotometer.

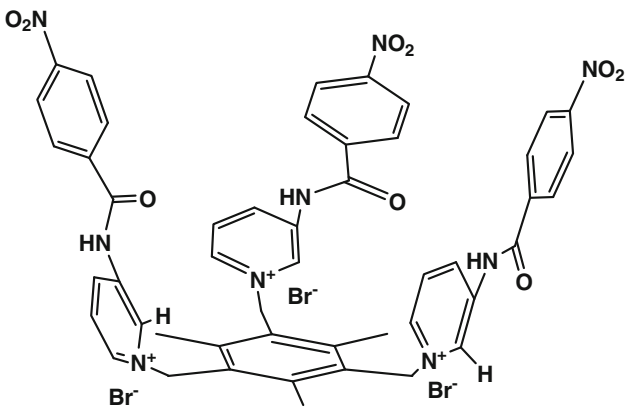
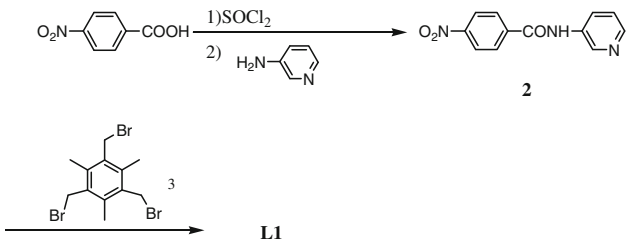


Fig. 2 Structure of tripodal receptor **L1**



Scheme 1 The synthetic route to tripodal receptor **L1**

General experimental procedure for the synthesis of the receptor **L1**

The synthesis of the receptor **L1** is shown in Scheme 1.

Synthesis of intermediate compound **2**

To a solid of 4-nitrobenzoic acid (334 mg, 2 mmol) was added excess of $SOCl_2$ and stirred at 70 °C for about 24 h to give clear solution. The excess of $SOCl_2$ was removed under reduced pressure, and the residue was dried under vacuum for 3 h. The obtained acid chloride was used directly without any further treatment. To a 20 mL of dry THF solution of 3-aminopyridine (190 mg, 2 mmol) was added dropwise a solution of abovementioned acid chloride in 20 ml of dry THF at 0 °C. After the solution was stirred overnight at room temperature, the THF was removed, the solid residue was dissolved in CH_2Cl_2 and the solution was washed with water. The organic layer was separated, dried over $MgSO_4$ and concentrated. The product was purified by silica gel column chromatography (3:1 CH_2Cl_2:AcOEt) to give white solid. The characterized data we showed below are consistence with those reported previously [25].

Yield: 0.784 g (65%), ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 10.75 (s, 1H, NH), 8.92 (s, 1H, Py-H), 8.39–8.36 (d, $J = 11.2$ Hz, 2H, Ph-H), 8.41 (d, $J = 6.0$ Hz, 1H, Py-H), 8.21–8.18 (d, $J = 11.2$ Hz 2H, Ph-H), 8.17 (d, $J = 4.4$ Hz, 1H, Py-H),7.41 (m, 1H, Py-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) 164.8, 149.8, 145.5, 142.2, 140.4, 135.9, 129.8, 128.0, 124.1. HRMS (ESI$^+$) m/z: 244.0731; calcd 244.0722.

*Synthesis of target tripodal receptor **L1***

A mixture of **2**(263 mg, 1.07 mmol) and **3** [26] (160 mg, 0.357 mmol) in dry 15 mL CH_3CN was refluxed for 3.5 h, and gradually white precipitate was formed. After cooling

to room temperature, the precipitate was filtered and washed several times with cold CH_3CN to give pure compound **L1** with bromide as counter ion.

Yield: 0.338 g (80%), ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 11.37 (s, 2H, NH), 9.36 (s, 2H, Py-H), 8.90 (d, $J = 6.0$ Hz,2H, Py-H), 8.68 (d, $J = 8.4$ Hz, 2H, Py-H), 8.30–8.27 (d, $J = 8.4$ Hz, 4H, Ph-H), 8.18 (m, 2H, Py-H), 8.01–7.99 (d, $J = 8.4$ Hz,4H, Ph-H), 6.21 (s, 4H, –CH_2–), 2.45 (s, 9H, MePh); ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) 164.4, 149.5, 144.1, 139.5, 139.1, 137.9, 135.4, 1346, 129.5, 128.9, 128.3, 123.5, 58.9, 17.1; ESI–MS (m/z): found [M-Br$^-$]: 1048.1.

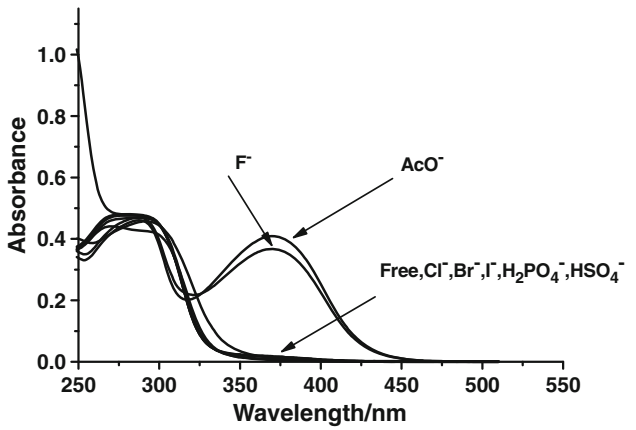


Fig. 3 The absorption spectra of **L1** (10^{-5} M) after the addition of 5 equivalent of representative anions

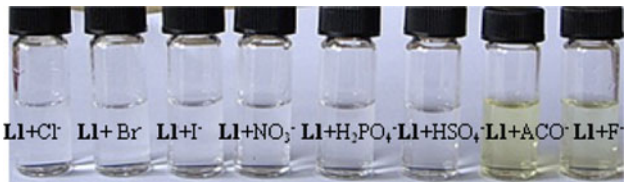


Fig. 4 The visible color changes of the receptor **L1** in CH_3CN (10^{-5} M) upon additions of 5 equivalent of different anions

Results and discussion

UV–vis spectroscopic studies

In order to investigate the anion sensing properties of **L1**, we carried out the UV–vis titration experiments by adding a standard solution of the tetrabutylammonium salt of anions, such as F^-, Cl^-, Br^-, I^-, HSO_4^-, AcO^-, NO_3^- and $H_2PO_4^-$, to a dry CH_3CN solution of the **L1** (1×10^{-5} mol/L) at 298 ± 0.1 K (Fig. 3). As shown in Fig. 3, free **L1** displayed a broad absorption band centered about at 275 nm coming from substituted phenyl group. Among the anions tested, only addition of AcO^- and F^- resulted in a new peak centered about at 375 nm. Other anions, even $H_2PO_4^-$, did not induce any spectral response even added in abundance. Upon addition of AcO^- and F^-, the maximum absorption peak of **L1** was shifted from UV to visible region, which rationalized the corresponding color change of the solution from colorless to yellow-green, realizing a "naked-eye" detection of AcO^- and F^- in solution (Fig. 4). The significant bathochromic shift could be explained on the basis of the intramolecular charge transfer (ICT) from electron-rich anion binding amide pyridinium unit to relative electron-deficient nitro-benzene fragment.

In addition, 1:1 stoichiometry of the receptor **L1** with AcO^- was confirmed by the Job plot analysis, and the binding constant of **L1** toward AcO^- was calculated to be $(1.00 \pm 0.05) \times 10^5$ M^{-1} from the nonlinear curve fitting based on the detailed titration of **L1** (Fig. 5). On the other hand, the Job plot curve of the complex with F^- was not conventional as usual, which might be due to the larger electro negativity and stronger basicity of F^-, which

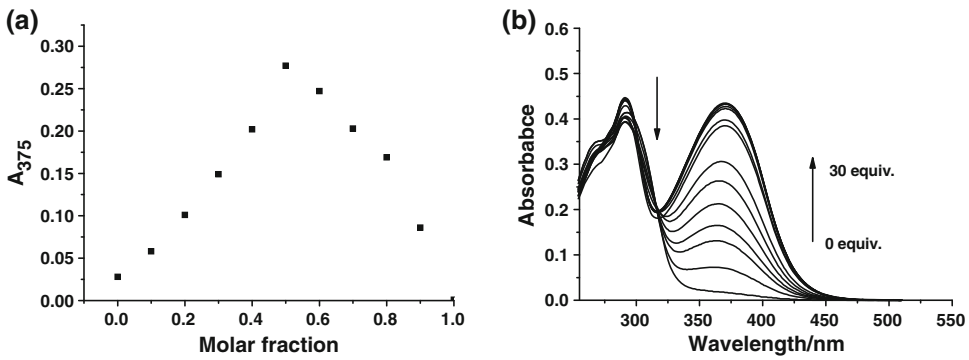


Fig. 5 **a** Job plot for the complex formation [L1] + [AcO^-] = 2×10^{-5} mol L^{-1} at 298.2 ± 0.1 K. **b** The UV–vis spectra of the receptor L1 (10^{-5} mol L^{-1}) in CH_3CN solution during the titration with 0, 0.2, 0.4, 0.7, 0.9, 1.0, 1.2, 1.5, 2.0, 2.5, 3.0, 5.0, 10, 15, 20, and 30 equivalent of AcO^-

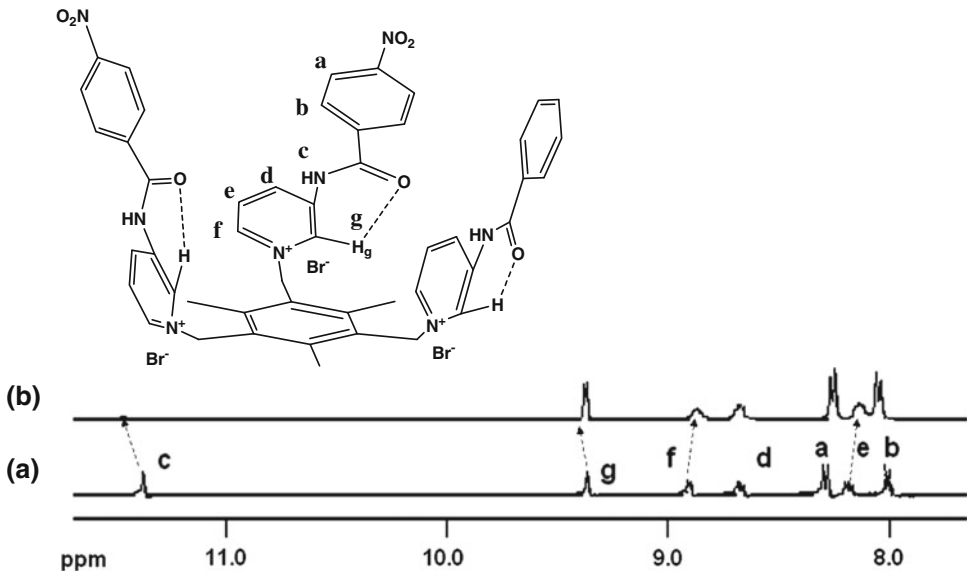


Fig. 6 Partial ^{1}H NMR spectra of **a** receptor **L1** only and **b** in the presence of 1.0 equivalent of AcO^{-} in DMSO-d_6

resulted in complicated binding manner between **L1** and F^{-} (see supporting information).

NMR spectroscopic studies

To further investigate the nature of the receptor–anion interactions, ^{1}H NMR experiment was performed. As shown in Fig. 6, apparently, the amide proton (from 11.37 to 11.50 ppm) and hydrogen proton at the α-position of pyridinium ring (from 9.36 to 9.38 ppm) displayed a remarkable downfield shift upon addition of 1.0 equivalent of AcO^{-} indicating that acidic proton H_g at α-position of pyridinium and carbonyl group participated in hydrogen-bonding interactions with AcO^{-}. On the other hand, other hydrogen protons at the pyridinium ring shifted to upfield implying the participation of electrostatic interaction of charged pyridinium ring in binding AcO^{-} [12].

As mentioned before, it is interesting that the receptor **L1** showed high selectivity for AcO^{-} over $H_2PO_4^{-}$ and the conformational change might play a positive role to explain this superiority. In this case, the conformational analyses were carried out by using 2D-COSY NMR spectra. It is well known that, **L1** might adopt "3-up or 3-down" conformation due to the steric effect of the methyl groups on benzene core. In addition, as shown in Fig. 7a, before addition of AcO^{-}, there is clear correlation between methylene proton H_h and protons on pyrydinium ring, such as H_d, H_g and H_f respectively, which indicated that the pyridinium ring might face to the center of cavity taking the twisted conformation. On the other hand, there is no coupling between H_c with H_g indicating the long distance between them due to the presence of intramolecular hydrogen bond of proton H_g with

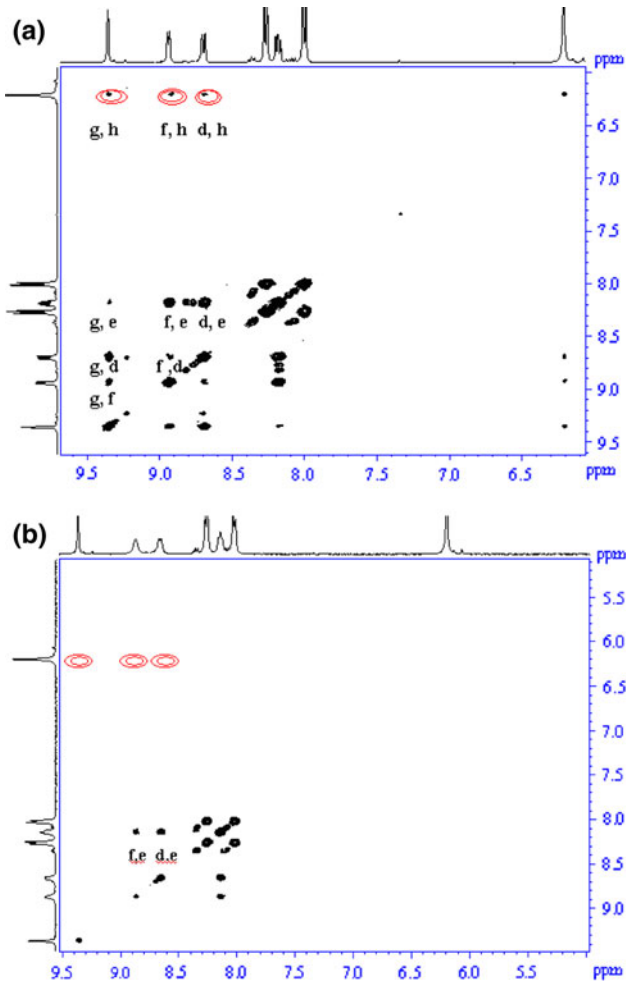


Fig. 7 Partial 2D-COSY NMR spectra of **a** free **L1** and **b** **L1** upon addition of 1.0 equivalent of AcO^{-} in DMSO-d_6

oxygen atom of carbonyl group. As a result, **L1** could form a cavity and the conformation was affected by the intramolecular hydrogen bonds. The conformational flexibility of **L1** would allow for a change in geometry to bind the appropriate guests to realize higher selectivity.

The 2D-COSY spectrum of **L1** upon addition of 1.0 equivalent of AcO^- was recorded in Fig. 7b. Clearly, the coupling of acidic proton H_g with H_f, H_d, and H_e disappeared, which suggested that the hydrogen bonds between H_g and oxygen atom of carbonyl group was broken by fitting AcO^- into the cavity of **L1** to form a new stable conformation. Accordingly, the higher selectivity of **L1** toward AcO^- over $H_2PO_4^-$ was ascribed to the synergistic effects, including hydrogen bonding, electrostatic interaction and conformational change process. We have to say, the binding process was also influenced by the anion basicity, F^- resulted in the similar change compared to AcO^-.

Conclusions

In conclusions, a new tripodal colorimetric chemosensor **L1** based on amidepyridinium binding motif was developed, which only showed a distinct color change of the solution when treated with F^- and AcO^- among anions tested. The higher selectivity for AcO^-over $H_2PO_4^-$ can be attributed to the cooperation of multi-effects, such as hydrogen bonding, electrostatic interactions, as well as the dynamic conformational change, which provide a new idea for designing efficient anion sensing agents.

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