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Ferrocene-based derivative bearing phenol group recognitive sites: efficient $H_2PO_4^-$ receptor

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Two artificial receptors, bearing ferrocene and phenol groups, were synthesized and their anion-binding properties were evaluated for F^-, Cl^-, Br^-, I^-, AcO^- and $H_2PO_4^-$ by UV–vis, ^1H NMR titration and cyclic voltammetry experiments in order to research the effect of different substituents on anion-recognition properties. Results indicate that the anion binding abilities can be effectively tuned by introducing a nitro group in the *ortho* position of the phenyl ring of the receptors, and the most obvious effect is for $H_2PO_4^-$. Copyright © 2007 John Wiley & Sons, Ltd.

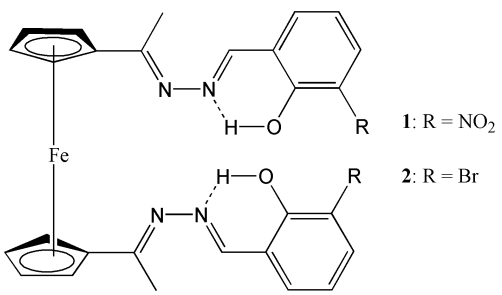
KEYWORDS: phenol group; ferrocene; anion recognition

INTRODUCTION

Artificial anion receptors have attracted considerable attention in the field of host–guest chemistry due to their medicinal and environmental potential.[1–10] The design of these receptors has been focused on having the ability to selectively recognize and sense the biologically important anions. Anions are ubiquitous throughout biological systems. They carry genetic information (DNA is a polyanion), and the majority of enzyme substrates and co-factors are anionic.[5] Phosphate anions are very important anionic species in living organisms. Naturally occurring phosphate-binding protein (PBP) and sulfate-binding protein selectively and strongly bind hydrogen phosphate and sulfate anions, respectively.[11–13] According to reported literature,[14] the ferrocene receptor possesses the intramolecular hydrogen bonding between the amide nitrogen atoms and the hydroxyl groups. The intramolecular hydrogen bonding existing between the donors and the acceptors could enhance the acidity of the hydrogen-bond donors.[15] In the present study, we have synthesized two receptors (Scheme 1) and utilize the intramolecular hydrogen bond as the anion-binding site to reveal the binding–structure relationship by tuning the acidity and the hydrogen-bond donor property of the OH moiety with electron-withdrawing *o*-NO_2 derivative **1** and *o*-Br derivative **2**. The host–guest complexations for binding different anions (F^-, Cl^-, Br^-, I^-, AcO^- and $H_2PO_4^-$) through UV–vis and ^1H NMR measurements were investigated.

RESULTS AND DISCUSSION

The geometries of the two receptors were optimized (Fig. 1) using the HF (Hartree–Fock) method with basis sets LanL2dz for Fe atom and 3-21G for other atoms. The calculation was performed using Gaussian03 program.[16] In receptor **1**, the distances between hydrogen atoms of phenol groups and the nearest nitrogen atoms (N5, N5′) are 1.793 and 1.763 Å;



Scheme 1. Chemical structure of receptors.

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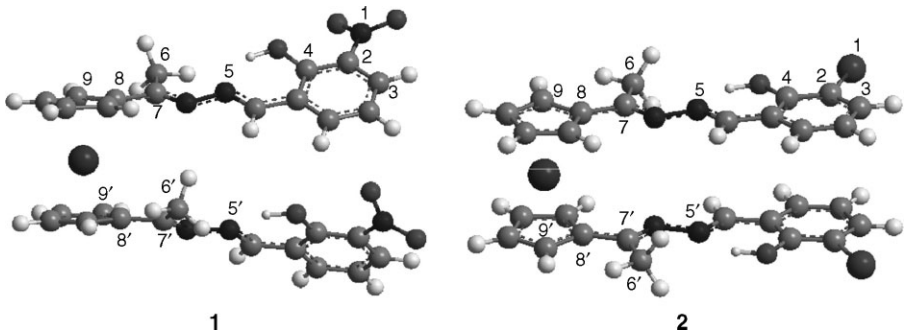

Figure 1. Optimized geometry of receptor **1** and **2**.

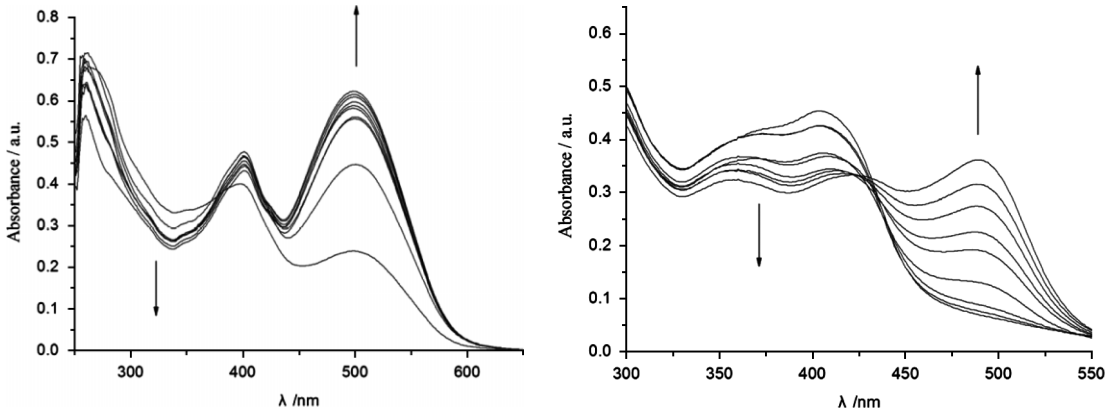

Figure 2. UV–vis spectral changes of receptor **1** and **2** upon the addition of $TBAH_2PO_4$; [**1**] = [**2**] = 2.0×10^{-5} M [$TBAH_2PO_4$] = 0–160×10^{-5} M. Arrows indicate the direction of increasing anion concentration.

the distances are both 1.814 Å in receptor **2**. This proves the speculation that there exists an intramolecular hydrogen bond between OH and nitrogen atom and a six-member ring is formed in receptors **1** and **2**. The bond angle N1 –C2 –C3, N1 –C2 –C4 is 116.4° and 121.9°, while the bond angle Br1 –C2 –C3, Br1 –C2 –C4 is 119.6° and 118.7°. The dihedral angle C6 –C7 –C8 –C9, C6′–C7′–C8′–C9′ is 12.2° and 158.2° in receptor **1**; the dihedral angle C6 –C7 –C8 –C9, C6′–C7′–C8′–C9′ is −4.6° and −179.2° in receptor **2**. In addition, the two arms of the optimized geometry **2** are parallel, while the two arms of receptor **1** are 'V' shape. The reason may be that the oxygen atom of NO_2 is inclined to form hydrogen bonds with hydrogen atoms of opposite phenyl ring (the distance O ···H is 2.570 and 2.432 Å).

The interactions of receptors with a variety of anions were investigated through UV–vis spectral titrations in dry DMSO by the addition of a standard solution of the tetrabutyl ammonium (TBA) salt of the investigated anion to a solution of receptors. Figure 2 shows the UV–vis spectral changes of **1** and **2** during the titration with $H_2PO_4^-$ anion. Upon the addition of $H_2PO_4^-$, the intensity of receptor **1** at about 400 and 500 nm increases, while the intensity at about 330 nm decreases. The yellow color of the receptor **1** solution turns orange-red at the same time. The isosbestic point is at 380 nm.

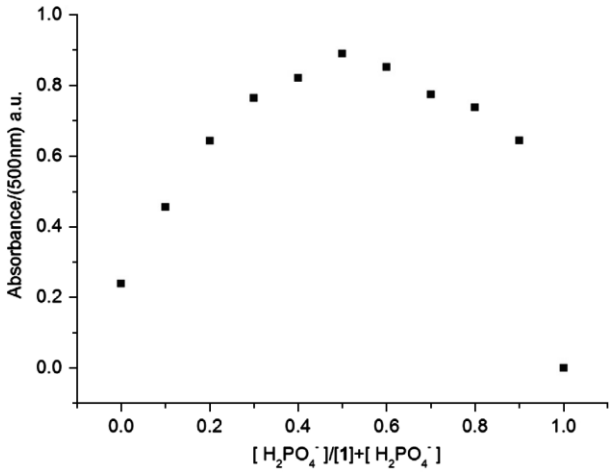

Figure 3. A Job plot for complexation of receptor **1** with $H_2PO_4^-$ determined by UV–vis in DMSO at 298 K; [**1**] + [$H_2PO_4^-$] = 2.0×10^{-4} mol l^{-1}.

In Fig. 3, Job's plot of receptor **1** and $H_2PO_4^-$ anion in DMSO shows the maximum at a molar fraction of 0.5. This result indicates that the receptor **1** binds the $H_2PO_4^-$ anion guest

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with a 1:1 ratio. Analogous investigations were carried out on a variety of anions such as F^-, Cl^-, Br^-, I^- and AcO^-. The F^- and AcO^- anions induced some spectral changes, but the spectral responses were not as sensitive as $H_2PO_4^-$ with the increase in anion concentration. Compared with receptor **1**, the intensity of receptor **2** centered at 400 nm decreased and a new peak at 500 nm appeared upon the addition of $H_2PO_4^-$. The F^- and AcO^- anions induced significant spectral changes, and the spectral responses were more sensitive than $H_2PO_4^-$ with the increase of anion concentration. Other anions such as Cl^-, Br^- and I^- did not induce any spectral response.

Very recently, a number of fluorogenic and/or chromogenic anion sensors comprising recognition moieties such as urea, thiourea or amide have been reported to undergo an anion-induced deprotonation.[17–19] According to these reports, one new triplet resonance appears at about 16.0 ppm, the characteristic resonance of bifluoride (F–H–F) and the chemical shifts of non-interacted sites' proton signals occur up-field in the ^{1}H NMR spectrum. To investigate the anion-binding properties of receptors, ^{1}H NMR spectral changes upon the addition of F^- as its TBA^+ salt to the DMSO-d_6 solution of the receptor **1** are measured (Fig. 4). Upon the addition of F^-, the OH proton resonance at about 13.56 ppm disappears, indicating either the formation of O–H···F^- hydrogen bonding or the deprotonation of receptor **1**.[20] Detailed analysis reveals no significant shifts of almost all the proton signals in the ligand, except the phenyl proton, which exhibits a upfield shift from 6.9 to 6.6 ppm, indicating the formation of O–H···F^- hydrogen bonding and the breaking of intramolecular hydrogen bonding due to the solvation of DMSO (Scheme 2).[21]

The affinity constants of receptors **1** and **2** with various anions obtained by the method of non-linear least square fitting are summarized in Table 1.[22,23] The electron-withdrawing ability of nitro group is stronger than that of bromine upon theory, so the binding ability of receptor **1** should be stronger than that of receptor **2** and affinity constants can prove this. It is noteworthy that the affinity constant of $H_2PO_4^-$ with receptor **1** is almost 181-fold greater than that with receptor **2**. For F^- and AcO^-, the former is almost 10- and 2-fold greater than the latter, respectively. Obviously, the change in *ortho* substituent is the most effective for $H_2PO_4^-$ among studied anions; the second most effective is for F^-.

Commonly, electrochemical anion sensing has been achieved potentiometrically by ferrocenyl species or other organometallic derivatives.[24–28] To explore further **1** and **2** as electrochemical anion sensors, cyclic voltammetry (CV) studies were performed in dry DMSO (Fig. 5). The addition

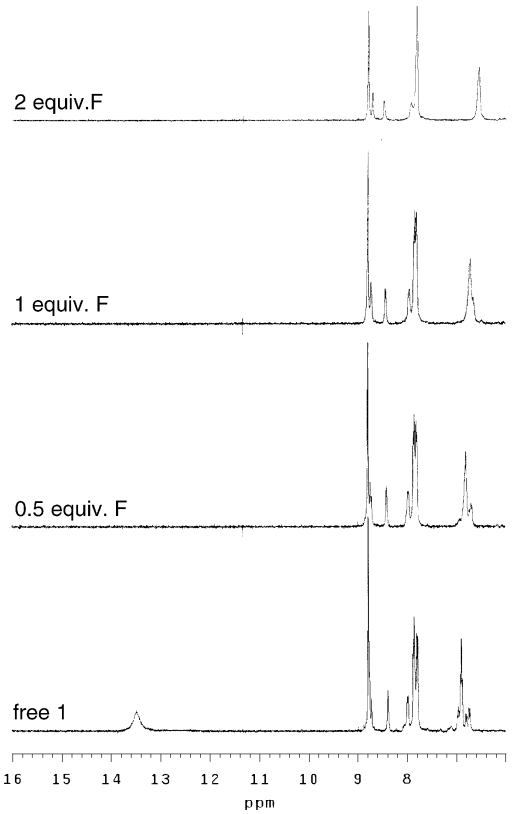
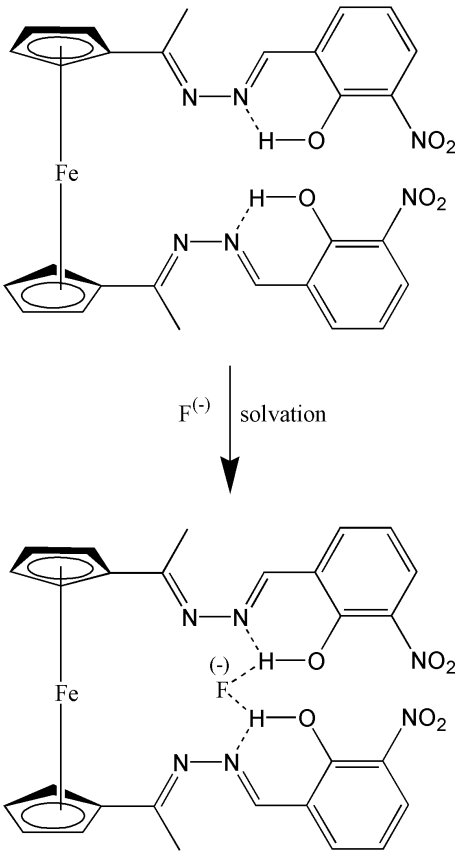


Figure 4. Partial ^{1}H NMR (400 MHz) spectra of receptor **1** in DMSO-d_6 upon addition of TBAF.



Scheme 2. The proposed binding mode.

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Table 1. Affinity constants of receptor **1** and **2** with various anions

Anion	K_s (l)	K_s (2)(M^{-1})
$H_2PO_4^-$	$(2.66 \pm 0.21) \times 10^4$	146.9 ± 16.4
AcO^-	$(5.28 \pm 0.39) \times 10^3$	$(2.74 \pm 0.04) \times 10^3$
F^-	$(1.40 \pm 0.24) \times 10^4$	$(1.44 \pm 0.04) \times 10^3$
Cl^-	<10	ND
Br^-	<10	ND
I^-	<10	ND

ND, cannot be determined.

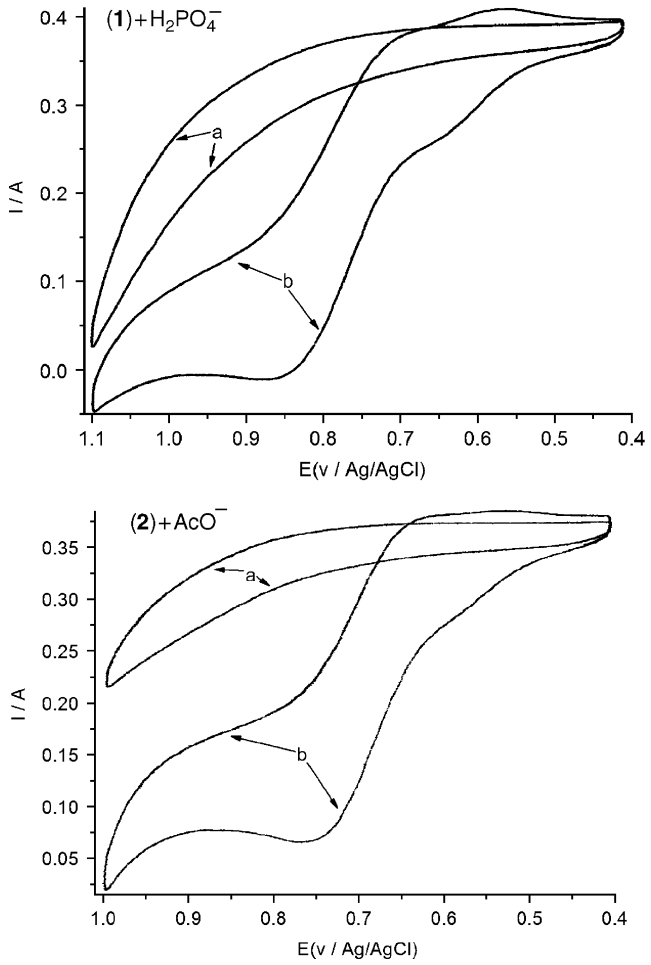

Figure 5. Cyclic voltammetry of receptor **1** (1×10^{-2} mol l^{-1}) and **2** (1×10^{-2} mol l^{-1}) recorded in the presence of $H_2PO_4^-$ or AcO^- in dry DMSO at 298 K, (a) receptor and amounts of anions; (b) free receptor, supporting electrolyte: $NaClO_4$ (0.1 mol l^{-1}), working electrode: glassy carbon (diameter = 3.8 mm), reference electrode: Ag/AgCl, auxiliary electrode: Pt, scan rate: 100 mV s^{-1}.

of amounts of $H_2PO_4^-$ to the solution of **1** led to a complete disappearance of the redox signals. These changes were interpreted in terms of the complex formation between **1** and $H_2PO_4^-$. The similar phenomenon exists in receptor **2** when the AcO^- anion is added.

CONCLUSION

In summary, we have demonstrated two ferrocene derivatives bearing phenol groups for anion-binding ability in DMSO. The anion-binding properties of these receptors are ascribed to hydrogen-bond formation. By changing the electron properties of substituents on the phenyl *ortho* position, the receptor–anion interaction ability can be finely tuned. The anion binding ability is related to the electron properties of substituents on the phenyl *ortho* position. The change in *ortho* substituent is the most effective for $H_2PO_4^-$ among the studied anions; the second most effective is for F^-. However, the receptor **1** for $H_2PO_4^-$ cannot distinguish it from F^-. The excellent selectivity of receptors for a certain anion is attributed to the fitness in the acidity of interacted sites' proton. The correlation between the electron properties of the substituent and the binding ability will be a very useful clue to design stronger receptors to bind a certain anion. The studies on this line are in progress. We believe that the results presented will be useful for the design of more sophisticated receptors for phosphate derivatives, such as co-enzymes.

EXPERIMENTAL

Most of the starting materials were obtained commercially and all reagents and solvents used were of analytical grade. All anions, in the form of tetrabutylammonium salts, were purchased from Sigma-Aldrich Chemical Co., stored in a desiccator under vacuum containing self-indicating silica, and used without any further purification. Dimethyl sulfoxide (DMSO) was distilled *in vacuo* after drying with CaH_2. Tetra-*n*-butylammonium salts [such as $(n-C_4H_9)_4NF$, $(n-C_4H_9)_4NCl$, $(n-C_4H_9)_4NBr$, $(n-C_4H_9)_4NI$, $(n-C_4H_9)_4NAcO$ and $(n-C_4H_9)_4NH_2PO_4$] were dried for 24 h in vacuum with P_2O_5 at 333 K before use. C, H, N elemental analysis was carried out on a Vanio-EL. ^1H NMR spectra were recorded on a Varian Unity Plus-400 MHz Spectrometer. ESI-MS was performed with a Mariner apparatus. UV–vis spectroscopy titrations were made on a Shimadzu UV2450 Spectrophotometer at 298 K. The affinity constants K_s were obtained by non-linear least square calculation method for data fitting. Electrochemical measurements were performed using a CH-Instruments-430 potentiostat interfaced with Pentium PC. A platinum wire was used as an auxiliary electrode, an Ag/AgCl reference electrode was used and the working electrode was a glassy carbon electrode (diameter = 3.8 mm). $NaClO_4$ (0.1 mol l^{-1}) was present as the supporting electrolyte. The scan rate was

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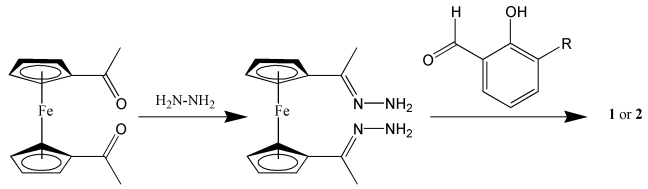

Scheme 3. Synthesis of receptor **1** and **2**.

100 mV s^{-1}. Receptors **1** and **2** were synthesized according to the route shown in Scheme 3.

1,1′-Diacetylferrocene[29]

Ferrocene (30 g, 0.102 mol), dissolved in 100 ml of dry methylene chloride, was added over a period of 15 min to a stirred mixture of aluminum chloride (53 g, 0.40 mol) and acetyl chloride (32 ml, 0.45 mol) in 200 ml of dry methylene chloride. The mixture was stirred at room temperature for 2 h, then cooled, decomposed with ice and extracted several times with chloroform. The solvent was evaporated under reduced pressure and the red solid was recrystalized from 95% ethanol; red needle crystals were obtained. Yield: 89%; m.p. 127–128 °C.

1,1′-Diacetylferrocenedihydrazone[30]

To a solution of 1,1′-diacetylferrocene (0.5 g, 1.89 mmol) and concentrated hydrochloric acid (0.05 ml) in ethanol (30 ml) at 80 °C, hydrazine hydrate (5 ml) in ethanol (10 ml) was added slowly. After 12 h under reflux the solvent was concentrated to about 5 ml under reduced pressure and the orange-red product was filtered and dried in a vacuum. Yield: 76%; m.p. 150–152 °C. Elemental analysis: calcd for $C_{14}H_{18}FeN_4$, C, 56.39; H, 6.08; N, 18.79; found, C, 56.21; H, 6.04; N, 18.72.

Di[5-(2′-hydroxyl-3′-nitro-phenyl)-2,4-dien-3,4-diazapentanyl-2]-ferrocene (1)

Di[5-(2′-hydroxyl-3′-nitro-phenyl)-2,4-dien-3,4-di-azapentanyl-2]-ferrocene (**1**) was prepared by boiling under reflux a mixture of 1,1′-diacetylferrocenedihydrazone (300 mg, 1 mmol) and 2-hydroxyl-3-nitro-benzaldehyde (334 mg, 2 mmol) in dry ethanol (40 ml) for 12 h. The solid was filtered and dried in vacuum. Yield: 91%. ^{1}H NMR(400 MHz, DMSO-d_6, 298 K) $\delta = 13.56$ (s, 2H), 8.58 (s, 2H), 7.83 (d, 4H), 7.56 (d, 2H), 4.84 (s, 4H), 4.55 (s, 4H), 2.32 (s, 6H) Elemental analysis: calcd for $C_{28}H_{24}FeN_6O_6$, C, 56.39; H, 4.06; N, 14.09; found, C, 56.05; H, 4.45; N, 13.91. ESI-MS (m/z): 594.96 $(M - H)^-$.

Di[5-(2′-hydroxyl-3′-bromine-phenyl)-2,4-dien-3,4-diazapentanyl-2]-ferrocene (2)

Di[5-(2′-hydroxyl-3′-bromine-phenyl)-2,4-dien-3,4-di-azapentanyl-2]-ferrocene (**2**) was prepared by a procedure similar to that above. ^{1}H NMR(400 MHz, DMSO-d_6, 298 K) $\delta = 11.94$ (s, 2H), 8.65 (s, 2H), 7.49 (d, 4H), 6.70 (d, 2H), 4.84 (s, 4H), 4.52 (s, 4H), 2.31 (s, 6H). Elemental analysis: calcd for $C_{28}H_{24}FeBr_2N_4O_2$, C, 50.63; H, 3.64; N, 8.44; found, C, 50.97; H 3.87; N, 8.49. ESI-MS (m/z): 663.14 $(M + H)^+$.

Acknowledgments

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