Preparation of *N,N′*-Bisethoxyethane[12]amideferrocenophane and Its Application in Anion Recognition

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Novel *N,N′*-bisethoxyethane[12]amideferrocenophane has been synthesized by a condensation reaction and characterized by ^{1}H NMR and mass spectrum. The anion recognition properties of the compound are evaluated via ^{1}H NMR, FT-IR, and electrochemical measurement. It is found that *N,N′*-bisethoxyethane[12]-amideferrocenophane exhibits remarkable electrochemical response to $H_2PO_4^-$ anion in CH_2Cl_2 or CH_3CN solution, and response to anions can also be observed in CH_3CN solution containing up to 15% water. Binding constants between the compound and HSO_4^- in different solutions have been determined by UV−vis spectrum titration experiments. The results indicate that the compound shows a selective recognition trend of $H_2PO_4^-$ > HSO_4^- (F^-) > Br^-.

1. Introduction

Anion recognition receives increasing attention because of the various existence and central role of anions in biological systems and chemical processes. Anion receptors that are capable of sensing anions have been extensively studied, and most anion sensing experiments have been carried out in organic solution thus far.[1−5] It is of particular significance to detect the anions in aqueous solution because most anions exist in aqueous medium, such as organisms, pollutants, and so on.[6−9] However, there are relatively fewer examples of detecting anions in aqueous solution, which is yet to be developed.

Chemical groups that can form hydrogen bonding with target anions are widely used when constructing anion receptors. However, anion recognition based solely on hydrogen-bonding interactions usually encounters a serious problem in aqueous solution (i.e., the strong solvent competition). In addition, neutral receptors are mostly soluble in organic solvent rather than in water.[10] A possible solution to these problems is to use positively charged anion receptors. It is believed the strong electrostatic interactions can overcome competing solvation effects and improve the solubility in aqueous systems, but it is also found that the counteranions of the receptors can interfere with the anion sensing process.[10,11] Moutet's group prepared a series of ferrocene-containing 4,4′-bipyridinium-based receptors and studied their anion recognition property.[8] Their study showed that the prepared receptors can selectively detect ATP^{2-}, but the electrochemical response was relatively weak, which limited their application. It is well-established that anion binding using hydrogen bonding is generally better than using electrostatic interactions.[10]

Beer's group demonstrated that polyaza ferrocene macrocyclic ligands can electrochemically recognize anions in aqueous media

SCHEME 1: Synthetic Procedure of Compound 1
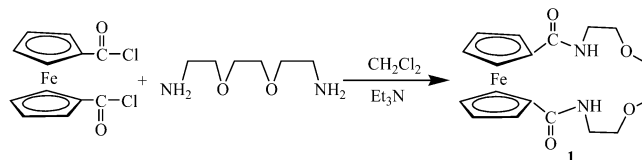
when the receptors are protonated. This recognition process is based on the favorable electrostatic and hydrogen-bonding interactions between the protonated macrocyclic polyamines and the anions.[12,13] We believe that the multifunctional receptor, which combines different kinds of noncovalent interactions to bind anions, can serve as efficient sensor. With this in mind, we designed a novel water-soluble ferrocene-based cyclic amine compound that contains amide functional groups in this study. It is expected that the compound would dimensionally comple-ment and encapsule the anions in its cavity. This interaction, combined with hydrogen bonding, would probably enhance the interaction with the anions in strong polar solution.

2. Experimental Section

2.1. Materials. Dichloromethane, CH_3CN, and triethylene-amine were dried over molecule sieves. 1,1′-Dichlorocarbon-ylferrocene was synthesized according to the literature method.[14]

2.2. Synthesis of *N,N′*-Bisethoxyethane[12]amideferroce-nophane (Compound 1). 1,1′-Dichlorocarbonylferrocene (1.24 g, 4.0 mmol) was dissolved in dry dichloromethane (30 mL), and the solution was added dropwise under argon to a stirred solution of 1,2-bis(aminoethoxy)ethane (0.6 mL, 4.0 mmol) and triethylamine (0.6 mL), also in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 2 h and then refluxed for 20 h. The solution was washed with saturated aqueous solution of Na_2CO_3 and then with distilled water and dried over $MgSO_4$ and filtered. The crude product was purified by column chromatography (silica, CH_2Cl_2/methanol = 20), providing compound **1** as a yellow powder. Yield: 0.231 g (15.2%).

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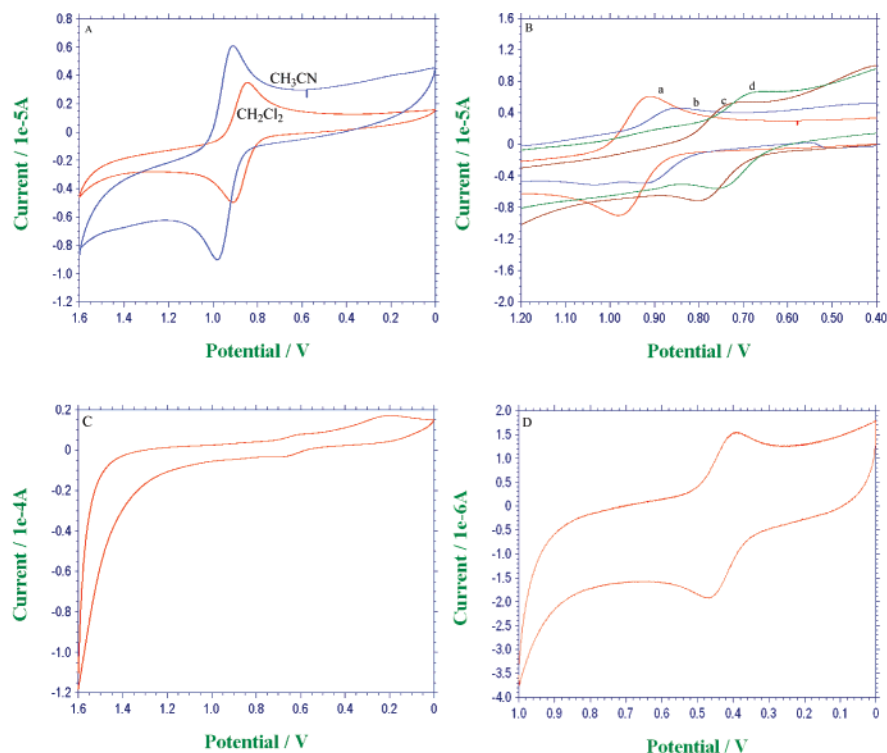
Figure 1. CVs of compound **1** in (A) CH₂Cl₂ solution and CH₃CN solution; (B) H₂O/CH₃CN mixture solution with different water content (v%): (a) 0, (b) 5, (c) 10, and (d) 15; (C) H₂O/CH₃CN mixture solution with 25% water content; and (D) water solution (supporting electrolyte: KNO₃, 0.1 M). Scan rate: 0.1 V/s.

2.3. Instruments and Measurements. ^{1}H NMR spectra were recorded with an AVANCE DMX-400 NMR spectrometer by using tetramethylsilane as internal standard at room temperature. The mass spectrum was recorded with an esquireplus mass spectrometer. Infrared (IR) spectra were recorded on a Nicolet 5700 infrared spectrophotometer, and the receptor and receptor/anion solution were coated on the KBr crystal wafer for the measurement. UV−vis spectra were recorded with an HP8453 UV−vis spectrometer. The CV measurements were carried out with a CHI-630A electrochemical analyzer (CH Instruments,

Inc.) in an undivided three-electrode cell. All electrodes were from CH Instruments. The counter electrode and reference electrode were a platinum wire and Ag/AgCl (3 M), respectively. The working electrode is a Teflon-shrouded platinum disk electrode (Φ = 2 mm, geometric area = 0.0314 cm^2), which was polished to a mirror finish with 0.05-μm Al₂O₃ paste on felt and cleaned by ultrasonication successively in 0.1 M NaOH, 1:1 HNO₃/anhydrous ethyl alcohol, and double-distilled water. Cyclic voltammograms were obtained by using a solution containing [n-Bu₄N][BF₄] (0.1 M) as the supporting electrolyte
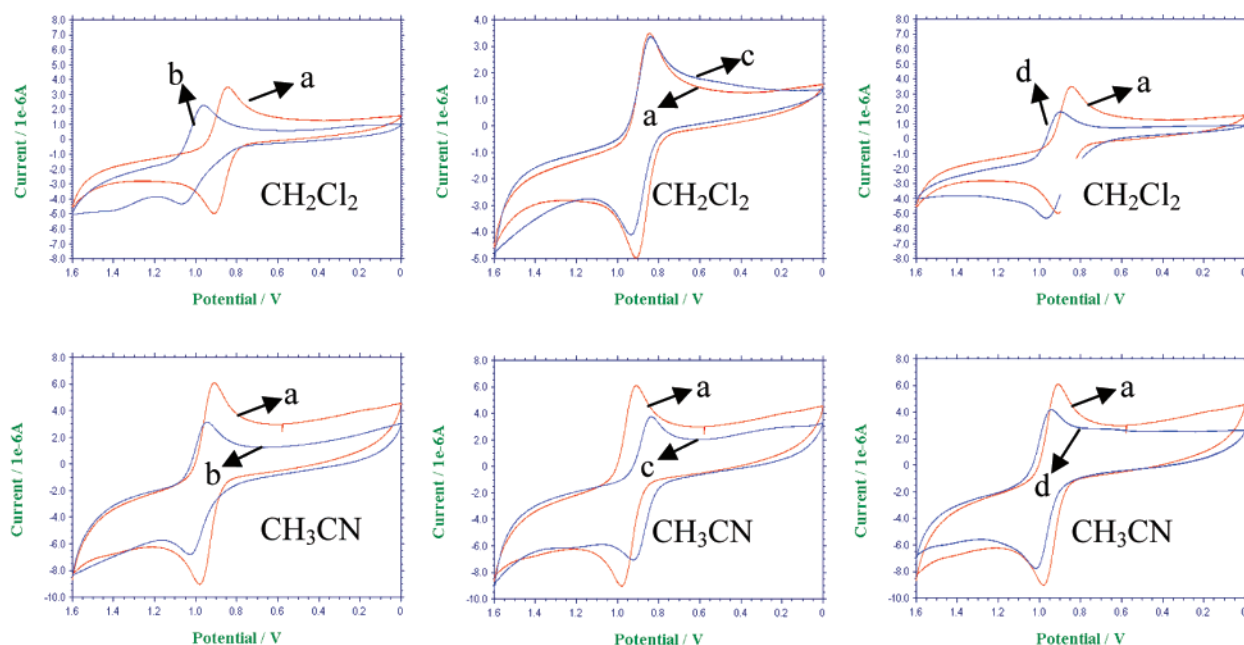
Figure 2. CVs of receptor **1** before (a) and after adding H₂PO₄⁻ (b), HSO₄⁻ (c), and F⁻ (d) in CH₂Cl₂ and CH₃CN solution, respectively. [Fe] = 0.5 mM, scan rate: 0.1 V/s.
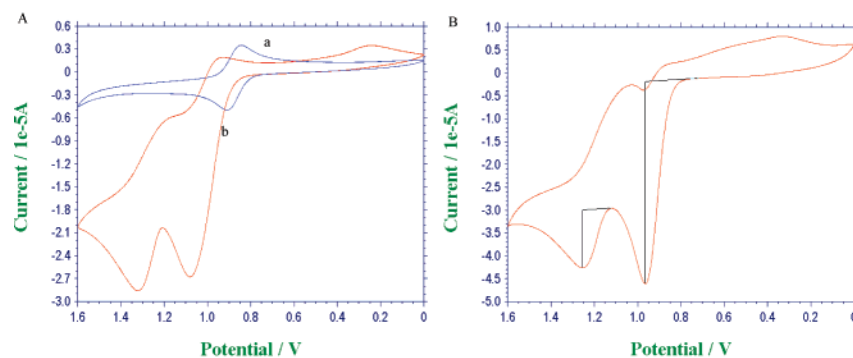
Figure 3. (A) CVs of receptor **1** before (a) and after (b) adding Br$^-$. (B) CV of the Br$^-$ alone. Solvent: CH$_2$Cl$_2$, [Fe] = 0.5 mM, scan rate: 0.1 V/s.
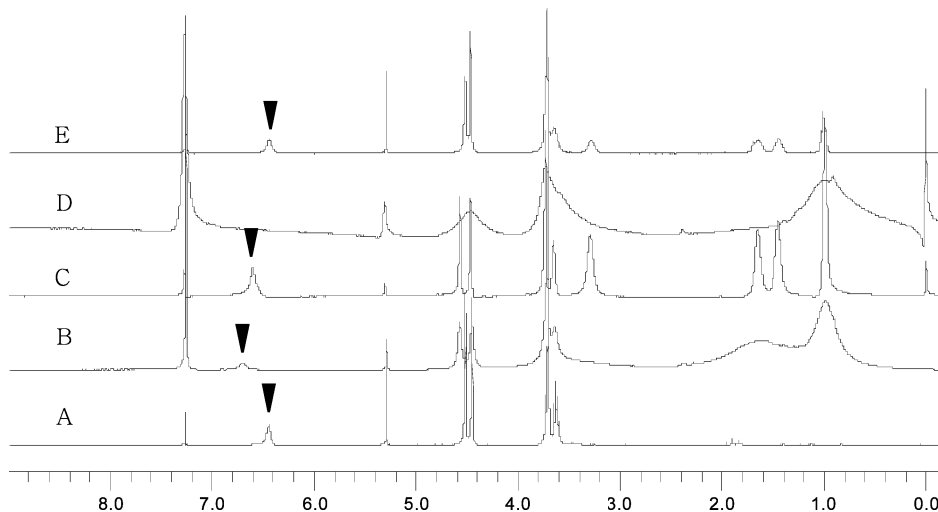
Figure 4. ^{1}H NMR spectra of compound **1** in CDCl$_3$ before (A) and after adding 2 equiv of H$_2$PO$_4^-$ (B), HSO$_4^-$ (C), F$^-$ (D), and Br$^-$ (E). The peaks attributed to the NH proton are marked with ▼.

unless stated, and the concentration of the ferrocenyl compound was 0.5 mM ferrocene unit. IR compensation was applied to all voltammogram measurements.

3. Results and Discussion

3.1. Synthesis and Characterization. The water-soluble ferrocene derivative was synthesized by a [1 + 1] condensation reaction (Scheme 1). It is suggested that the synthesis be carried out at high dilution to minimize the polymer byproduct. The synthetic compound was characterized by ^{1}H NMR and mass spectrum. Figure 4A shows the ^{1}H NMR spectrum of the compound. The peak at 6.4 ppm can be assigned to the amide group, and the double peaks around 4.5 ppm are attributed to the protons of the Cp ring, whereas the multiple peaks around 3.5 ppm correspond to the CH$_2$ groups of the molecule. This indicates that the objective molecule has been successfully synthesized. This structure was further confirmed by mass spectrum.

3.2. Electrochemical Behavior. In our previous articles, the electrochemical behavior of poly(ferrocenylsilanes) was intensively studied.[15−19] In this study, we also begin with properties of compound **1** with its electrochemical property, which is essential to determine suitable testing conditions for electrochemical anion recognition testing. Figure 1 shows the CVs of compound **1** in different solutions. Single reversible redox waves at $E_{1/2}$ = 0.875 and 0.975 V versus Ag/Ag$^+$ were observed in CH$_2$Cl$_2$ and CH$_3$CN solution, respectively. The electrochemical behavior in aqueous solution is irreversible with a potential separation of 77 mV, indicating a slow electron-transfer rate.

Electrochemical behavior of CH$_3$CN/H$_2$O mixture solutions has also been investigated. It is found that compound **1** exhibits a "water recognition" process, namely the increasing water content causes the redox couple to shift to more negative potentials, and the redox wave becomes inconspicuous when the water content is higher than 20%. This is presumably due to the existence of hydrogen bonds between compound **1** and water, which is similar to the interaction between receptor and anions.

3.3. Electrochemical Response to Anions. Electrochemical methods are among the most widely employed ways to detect anions because of their convenient accomplishment. The complexation with the anion effectively stabilizes the positive charge of the ferrocinium, which causes the redox couple shift to a smaller potential, and the potential shift ($\Delta E°$) values disclose the different binding strengths.[1−5,20] We studied the anion recognition property of compound **1** by the CV method. Figure 2A shows the CVs of compound **1** before and after adding different anions. Upon addition of H$_2$PO$_4^-$ anions, the initial redox couple shifted to more positive potentials, along with a decrease of its intensity, indicating the formation of complex between the receptor and H$_2$PO$_4^-$. While adding HSO$_4^-$ anions, we observed hardly any perturbation for the redox couple. Anion sensing experiment carried out in the CH$_3$CN solution shows a behavior similar to that in CH$_2$Cl$_2$, and the potential shifts induced by the anions in different solutions are listed in Table 1.

It is quite a challenge to detect the anions in polar solution, particularly in water. According to Kubic,[21] in solvent mixtures that contain water, the free energy for anion binding becomes larger with increasing content of water, and we would expect
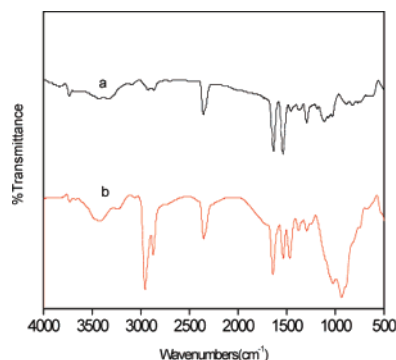
Figure 5. FT-IR spectra of **1** in CH_2Cl_2 before (a) and after (b) adding 2 equiv of $H_2PO_4^-$.

TABLE 1: Potential Shift $\Delta E_{1/2}$ (mV) Observed in the $Fe^{\alpha/\beta}$ Redox System upon Addition of Various n-Bu_4N^+ Salts[a]

| solvent	$H_2PO_4^-$	HSO_4^-	F^-
CH_2Cl_2	139	0	57
CH_3CN	41	67	33
CH_3CN/H_2O (19:1)	149[b]	a	83[b]
CH_3CN/H_2O (9:1)	95	a	a
CH_3CN/H_2O (85:15)	162	14	32

[a] Unable to be determined because of the inconspicuous redox wave. [b] Recorded with respect to the oxidation peak.

an 11-fold drop in affinity upon increasing the mole fraction of water from 49 to 80%. Our initial study shows that redox behavior of compound **1** in pure aqueous solution can only be observed using KNO_3 as supporting electrolytes (Figure 1D); however, this prevents further electrochemical measurements for anion recognition because the influence of anions (NO_3^-) of supporting electrolytes on anion binding behavior of the receptor is unclear for our system. But stable and reproducible cyclic voltammograms of the receptor could be recorded in CH_3-CN containing up to 20% (v/v) of water as described above. Anion recognition experiments show that compound **1** can recognize anions in CH_3CN containing up to 15% (v/v) of water by displaying clear electrochemical response. The potential shifts induced by different anions are also listed in Table 1. The results reported here are remarkable because voltammetric sensing of the $H_2PO_4^-$ anion takes place in a relatively polar solvent (mixture solvent of acetonitrile and water), where hydrogen-bonding interactions between the amide functional groups and the anion are usually weakened by competing solvent molecules, such as water.

Selectivity of compound **1** to anions has been studied by recording the CVs upon addition of different anions. It was noticed that the potential shifts induced by HSO_4^- and F^- are smaller than those induced by $H_2PO_4^-$. These results indicate that compound **1** displays the selectivity trend $H_2PO_4^- > HSO_4^-(F^-)$, which is consistent with the basicity of the anions. According to Watanabe,[22] the free energy of hydration of the anions reflects the ability of the guest anions to form hydrogen bonds to the amide ligands. The preference for $H_2PO_4^-$ over other anions indicates that the hydrogen bond interaction between NH and oxygen atoms of the anions or dimensional complement between host and guest significantly contributes to the anion recognition.

The electrochemical behavior by adding Br^- (Figure 3) was totally different from the case of $H_2PO_4^-$. Two oxidation peaks at more positive potential have been observed by adding Br^-. This may be because of the redox of Br^- anions. We further surveyed the electrochemical property of Br^- alone. Figure 3B shows the CV recorded in CH_2Cl_2 solution. It is quite similar
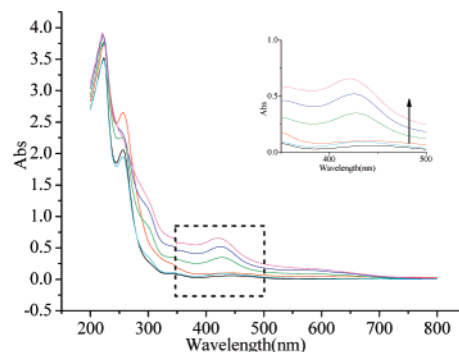
Figure 6. UV−vis spectra of **1** in CH_3CN solution (concentration [**1**] = 0.5 mM) by adding 0, 1, 5, 10, 20, and 40 equiv of $H_2PO_4^-$ anions. (Inset) Magnification of the spectra in the region 350−500 nm. The arrow shows the increasing addition of anions.

SCHEME 2: Proposed Binding Mode between Receptor 1 and $H_2PO_4^-$ Anion
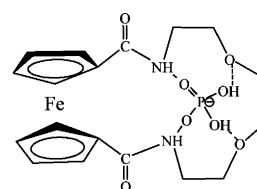
to the CV in the presence of receptor. These results indicate that the interaction between the receptor and Br^- anion is so weak that it cannot influence the electrochemical property of Br^-. This also indicates a selective binding trend of $H_2PO_4^- > HSO_4^-(F^-) > Br^-$.

3.4. Anion Recognition Detected by ^1H NMR. To get insight views of the anion binding property of the receptor, ^1H NMR experiment was carried out in $CDCl_3$ solution. Amide NH protons are commonly observed to be broad peaks in $CDCl_3$ solution, because of intramolecular or intermolecular hydrogen bonding.[10,23−26] However, this still allows us to study the anion recognition property by ^1H NMR technique. We studied the binding ability of the receptor with the monovalent anions as their tetrabutylammonium salts. Figure 4 shows the ^1H NMR spectra of the receptor by adding different anions. The NH protons of the unequivalent amide groups in the compound were monitored, and they were found to exhibit one broad single peak around 6.4 ppm. Upon addition of $H_2PO_4^-$, notable downfield shift of the NH peak was observed. The broad single peak at 6.4 ppm shifted downfield to 6.7 ppm in the presence of 2 equiv of $H_2PO_4^-$. As expected, the signals for other protons exhibited hardly any shift upon anion addition. HSO_4^- anion also caused the NH peak to shift downfield, with a change of chemical shift $\Delta\delta$ 0.2 ppm. The NH signals were not affected upon addition of Br^- or F^-, suggesting that compound **1** does not interact significantly with Br^- or F^- anion. These observations indicate that the host **1** has essentially no affinity with Br^- and F^-, but is much stronger with $H_2PO_4^-$ and HSO_4^- through hydrogen bonds or dimensional interaction.[15] These data are in agreement with the electrochemical measurements.

3.5. Anion Recognition Detected by FT-IR and UV−Vis Spectrum. The strong affinity between the receptor and $H_2PO_4^-$ anions was further confirmed from FT-IR spectroscopy (Figure 5). The FT-IR spectrum of the receptor in CH_2Cl_2 solution displays characteristic bands at 1636, 1539, and 3332 for the amine group. It is noticed that the relative absorbance strength between the C=O group and NH group changed upon addition of $H_2PO_4^-$ anions (i.e., the stronger absorbance peak attributed to the NH group becomes weaker after adding $H_2PO_4^-$ to the

solution of receptor). This again verifies that receptor **1** can bind with $H_2PO_4^-$ and that the interaction between NH and oxygen atoms is the dominant factor (Scheme 2).

Anion recognition property was further characterized by the UV−vis spectrum. Typical spectra of compound **1** by adding different amounts of anion are shown in Figure 6. As can be seen, the absorbance at 421 nm increases with increasing addition of the $H_2PO_4^-$ anion, which suggests the strong interaction between $H_2PO_4^-$ and receptor **1**. On the basis of these absorbance changes and the Benesi−Hildebrand equation, the binding constants between the receptor and $H_2PO_4^-$ in different solvents have been determined. It was found that the binding strength decreases with increasing polarity of the solvent.

4. Conclusions

A water-soluble ferrocene-based anion receptor was prepared. The receptor shows reversible electrochemical behavior in CH_2Cl_2 and CH_3CN solutions. The anion recognition properties of the receptor were evaluated via ^1H NMR, electrochemical, and FT-IR measurements. A selective binding trend for $H_2PO_4^-$ over HSO_4^-, F^-, and Br^- was observed. The largest potential shift induced by $H_2PO_4^-$ in acetonitrile containing 15% (v/v) of water is about 162 mV. ^1H NMR and FT-IR measurements indicate that the main interaction is the hydrogen bonds formed between the NH group of the receptor and oxygen atoms of the anion. This synthetic receptor represents a novel candidate for electrochemical sensor in organic solution and has potential application in anion sensing in aqueous solution.

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