

Electrochemical and ^{19}F NMR Detection of Anions, Ion-pairs, and a Zwitterionic Amino Acid with a Ferrocene-based Hetero-ditopic Receptor Bearing *o*-(Carboxamido)trifluoroacetophenone and Crown-ether Ligands

Hidekazu Miyaji,* Dae-Sik Kim, Byoung-Yong Chang, Su-Moon Park,* and Kyo Han Ahn*

Department of Chemistry and Center for Integrated Molecular Systems, POSTECH, Pohang 790-784, Korea

*E-mail: ahn@postech.ac.kr

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Described are the electrochemical and ^{19}F NMR detection of anions, ion-pairs, and zwitterionic L-phenylalanine with the ferrocene-based hetero-ditopic receptor. A cyclic voltammetric study shows that the receptor induces a positive shift in the ferrocene oxidation potential upon binding of a potassium cation, whereas it induces a negative shift upon binding of an acetate anion, both of which can be reversed. Also, the redox potential shifts were dependent on ion-pairing interactions. Furthermore, direct detection of an amino acid in its zwitterionic form is demonstrated by ^{19}F NMR spectroscopy in aqueous media.

Key Words : Electrochemical detection, Anions, Ion-pairs, Zwitterionic amino acid, *o*-(Carboxamido)trifluoroacetophenone

Introduction

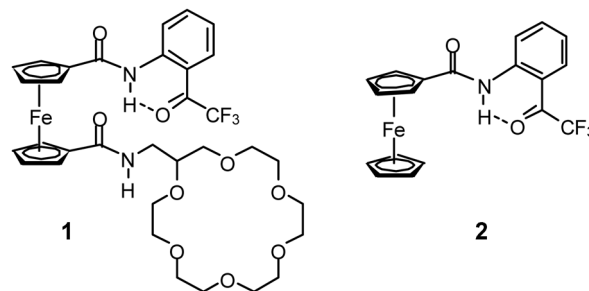
Anions play important functions in chemical and biological systems,¹ and thus much attention has been focussed on devising highly selective anion sensing systems (for phosphate, chloride, fluoride, and cyanide anions).² Many molecular sensing systems are constructed by combining binding motifs and signalling units. As the anion binding motifs, most of known neutral anion receptors use hydrogen bonding donors such as ureas, thioureas, and calixpyrroles that provide NH---anion hydrogen bonding.³ However, such hydrogen bonding motifs generally show weak binding affinity toward anions, particularly in aqueous media or polar solvents, because polar solvent molecules compete with the hydrogen bonding interactions. Exceptional cases are those of receptors with sophisticated molecular structures. For example, 3-dimensionally-preorganized strapped calixpyrroles show very high association constants toward chloride ions and thus detect the anions in aqueous media of a mixed solvent system.⁴ However, synthesis of the strapped calixpyrroles requires many steps. Structurally more simple motifs yet show strong and selective binding properties are in need for the anion recognition in aqueous media.

Trifluoroacetophenone derivatives⁵ have been utilized as unique ionophores for certain anions that form reversible anion-ionophore adducts by attacking at the trifluoroacetyl carbonyl carbon. Recently, we have demonstrated that introduction of a H-bonding donor such as an *o*-carboxamido group to the trifluoroacetophenone can stabilize the anionic adducts and thus significantly enhances receptors' binding affinity toward anions such as carboxylates to a practically useful level.^{6a} This approach of H-bond stabilization has also enabled us to introduce novel fluorescence sensors toward cyanide, carboxylates, and others analytes.^{6b-6f} To further utilize this promising recognition motif in the development

of guest-specific receptors, we have been studying ditopic or hetero-ditopic (hybrid) derivatives of the *o*-(carboxamido)-trifluoroacetophenone (CATFA) system.

Ferrocene was chosen as a platform because (i) it is easy to functionalize at its 1- and 1'-positions (for making a homo- or hetero-ditopic receptor⁷), (ii) its cyclopentadienyl (Cp) units can rotate like a ball-bearing along the vertical axis and thus the two binding sites at the 1- and 1'-positions can adjust readily to form a stable cyclic complex toward a ditopic guest,⁸ and (iii) it can be used as an electro-active probe. In our previous communication,⁹ we reported the synthesis and anion binding properties of a ferrocene-based hetero-ditopic receptor **1** bearing CATFA and crown-ether motifs. The mono-CATFA **2** was used as a reference compound.

In this paper, we wish to report details of electrochemical and ^{19}F NMR detection studies on anions, ion-pairs, and an amino acid with the ferrocene-based CATFA receptors. Specifically, cyclic voltammetry (CV) and ^{19}F NMR studies on the recognition/sensing of ion-pairs and a zwitterionic amino acid with the hetero-ditopic receptor **1** are described.



Results and Discussion

We investigated the electrochemical response of receptors

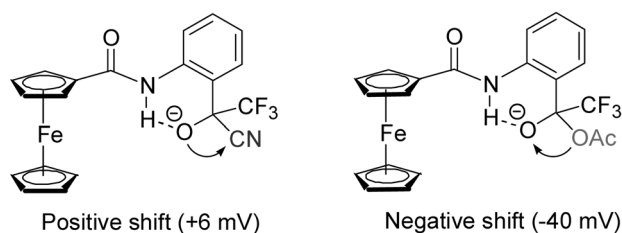


Figure 1. Redox potential changes of **2** upon addition of cyanide or acetate anions.

1 and **2** upon addition of anions by cyclic voltammetry (CV). Receptor **2** itself (1.0 mM in CH₃CN) showed a reversible redox process centered at $E^{0'} = +0.710$ V (vs. Ag/AgCl), where $E^{0'} = (E_{pa} + E_{pc})/2$. The formal oxidation potential ($E^{0'}$) of **2** was shifted upon addition of cyanide, acetate or both (as Bu₄N⁺ salts). When an equimolar amount of the cyanide was added to the solution of **2** in acetonitrile, a small positive shift (+6 mV) in the oxidation potential was observed. ¹H and ¹⁹F NMR studies indicated that almost all of **2** was converted to the cyanide adduct, owing to the strong association constant. Little change was observed in the oxidation potential when additional equivalent of the cyanide was added. However, when two equivalents of the acetate were added to the solution of **2**, a negative shift (-40 mV) in the oxidation potential was observed. At this point, ¹H and ¹⁹F NMR data indicated that almost all of **2** were converted to the corresponding acetate adduct. Thus, the acetate adduct becomes predominant when two equivalents of acetate are added, indicating weaker association compared to the case of cyanide. Further addition of the acetate did not show any change in the oxidation potential. These results suggest that the cyanide adduct influences the ferrocene redox center, making it difficult to be oxidized, probably owing to the electron-withdrawing nature of the cyanide group; whereas, the acetate adduct readily undergoes oxidation, probably owing to the electron-donating nature of the acetate group (Figure 1). Such a redox potential change depending on anions may constitute a unique electrochemical detection method for anions in general. In the present case, the inductive effect by anions added seems to exert the ferrocene redox center through the hydrogen bond as well as through the benzene ring.

Next, we investigated the electrochemical behavior of receptor **1** in the presence of anions (CN⁻ and AcO⁻, as Bu₄N⁺ salts) and cations (K⁺ and Na⁺, as PF₆⁻ salts) by CV in CH₃CN at a receptor concentration of 1.0 mM. The cyclic voltammograms in Figure 2 show that hetero-ditopic receptor **1** undergoes a reversible redox process in the presence of the acetate ion. During the CV study for receptor **1** in the presence of the cyanide, we found that the cathodic peak was not observed although the anodic peak appeared. Also, the anodic peak became smaller during repeated scans. These results suggested that an oxidized species of the cyanide adduct of ferrocene **1** underwent a chemical reaction such as decomposition. Therefore, we investigated CV with the acetate anion. The formal (oxidation) potential for receptor **1** was $E^{0'} = [E_{po} (0.99 \text{ V}) + E_{pc} (0.91 \text{ V})]/2 = +0.95$ V (vs. Ag/

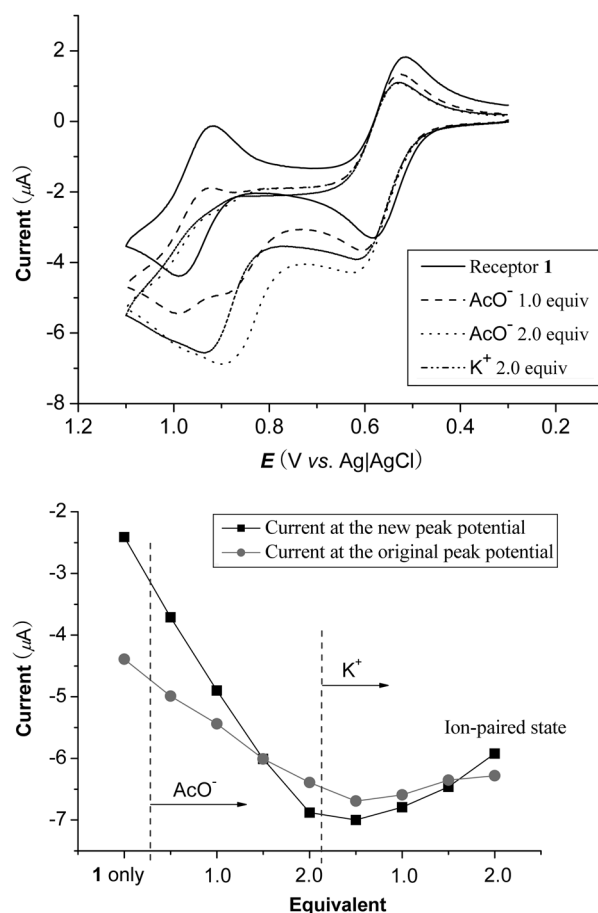


Figure 2. Cyclic voltammograms (up) and the current changes (down) of receptor **1** (1.0 mM in CH₃CN) upon titration with AcO⁻ (as Bu₄N⁺ salt) and K⁺ (as PF₆⁻ salt). Note that the redox peaks at 0.51 V (vs. Ag/AgCl) correspond to the authentic Fc⁻/Fc pair used as an internal reference.

AgCl). After addition of one equivalent of the acetate ion, new cathodic and anodic peaks appeared ($E_{pa} = +0.89$ V, $E_{pc} = +0.81$ V), with a large negative shift in the formal potential (-0.1 V). After addition of two equivalents of the acetate ion, the redox peaks from receptor **1** disappeared and only the new peaks appeared. At this stage, most of receptor **1** seemed to be in the form of the acetate adduct. The peak current of receptor **1** decreased upon addition of the anion guest. When the potassium ion was added to the receptor-acetate adduct solution, a new anodic peak appeared, this time with an increase in the peak current. Figure 2 shows the peak current changes along with the addition of acetate followed by potassium ion. Such peak current changes were not observed in the case of receptor **2** that lacks the crown ether moiety. Also, even in the case of hetero-ditopic receptor **1**, the decrease in the peak current upon addition of acetate was not reversed if Na⁺ instead of K⁺ was used. In other words, the reversal of peak current occurs only when the cation binds to the crown ether ring. The potassium ion bound to the crown ether ring interacts with the anionic acetate adduct through ion-pair interactions, which results in the neutralization of the overall charge of receptor-anion adduct. This charge neutralization seems to modulate the

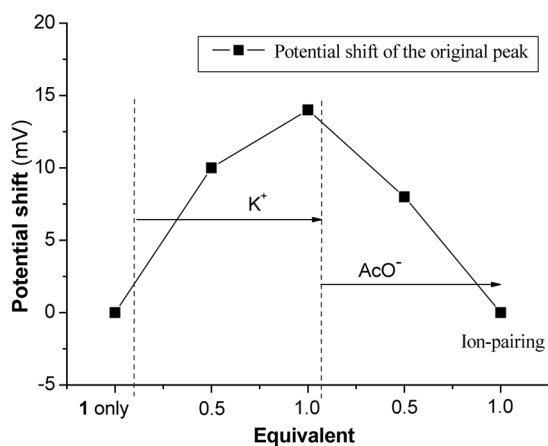
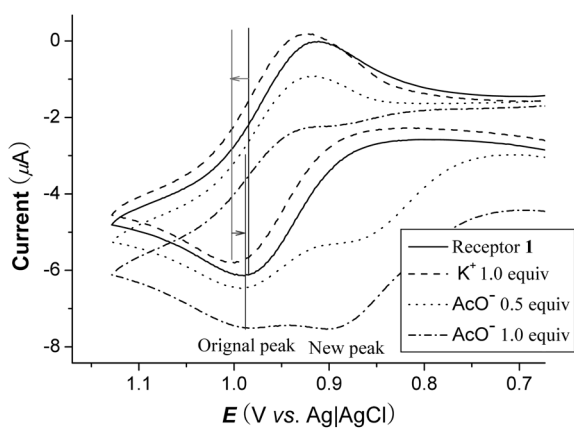


Figure 3. Cyclic voltammograms (up) and the potential shift of original oxidation peak (down) of receptor **1** (1.0 mM in CH_3CN) upon titration with K^+ (as PF_6^- salt) and AcO^- (as Bu_4N^+ salt).

diffusion coefficient in such a way to reverse the peak current change.

A similar electrochemical study was carried out by changing the addition sequence. Thus, K^+ (PF_6^- salt) was added first to receptor **1**: A small positive shift in the anodic peak potential was observed (*i.e.*, +14 mV). This positive shift was reversed by subsequent addition of an anion such as acetate or cyanide: E_{pa} changed from +14 mV to 0 mV or from +14 mV to +3 mV, upon addition of one equivalent of the anions, respectively (Figures 3 and 4). Whereas, such a reversal in the anodic peak potential was not observed in the case of receptor **2** and also in the case of hetro-ditopic receptor **1** in which case Na^+ instead of K^+ was used. These results again can be explained by the ion-pairing effect.¹⁰

Oxidation potential change of **1** upon addition of KCN, NaCN, KOAc, and NaOAc (2 equiv each) in 1% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (acetonitrile containing 1% water) was investigated by CV (Figure 5). As we expected, direct addition of KCN into the solution of **1** showed a slight positive shift (+4 mV) of the oxidation potential. When NaCN was added to the solution of **1**, a larger positive shift (+14 mV) of the oxidation potential than that of KCN was observed. These phenomena can be rationalized by ion-pairing effect. The larger positive shift was observed because Na^+ could not be captured by the crown-ether group, and thus cyanide adduct

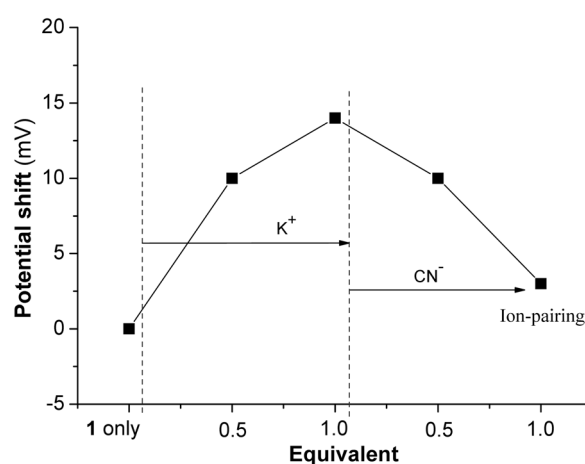
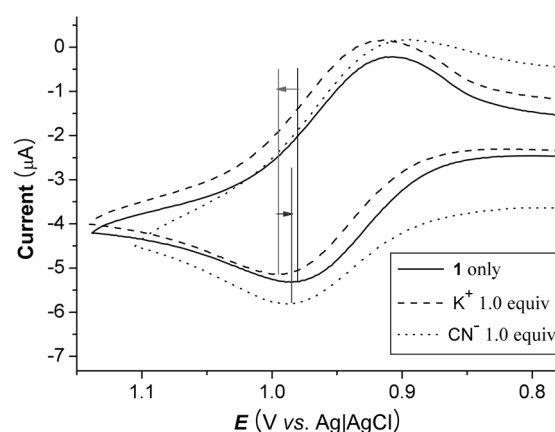


Figure 4. Cyclic voltammograms (up) and potential shifts of the oxidation peak (down) of receptor **1** (1.0 mM in CH_3CN), upon titration with K^+ (as PF_6^- salt) and CN^- (as Bu_4N^+ salt).

caused a positive shift. Whereas, K^+ can be captured by the crown-ether and the resultant ion-pairing interactions reduce the positive shift through the charge neutralization. This ion-pairing effect was effectively observed in the case of NaOAc. The addition of KOAc (2 equiv) into the solution of **1** in 1% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ did not show any shifts in the oxidation potential, even with excess amounts of KOAc, whereas NaOAc (2 equiv) showed a negative shift (−6 mV). Further addition of NaOAc (10 equiv, saturated concentration) caused more negative shift (−10 mV). Addition of an excess amount of NaOAc to **1** in 3% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ caused further negative shift (−43 mV, 3% H_2O added to increase the solubility of NaOAc). These negative shifts seem to be caused by the acetate adduct of **1**, in which the counteranion cannot participate in the ion-pairing interactions.

During this study, we realized that TFA-based hetero-ditopic receptor **1** is a useful reagent for the detection of anions by ^{19}F -NMR spectroscopy: The chemical shift change of the fluorine atoms in receptor **1** can be used for probing different anions. For example, receptor **1** with anions provide unique chemical shifts for CN^- (−5.56 ppm) and AcO^- (−9.28 ppm) in the mixed solvent system. Instead of D_2O , a mixed solvent containing H_2O was also found to provide similar chemical shifts. Furthermore, detection of

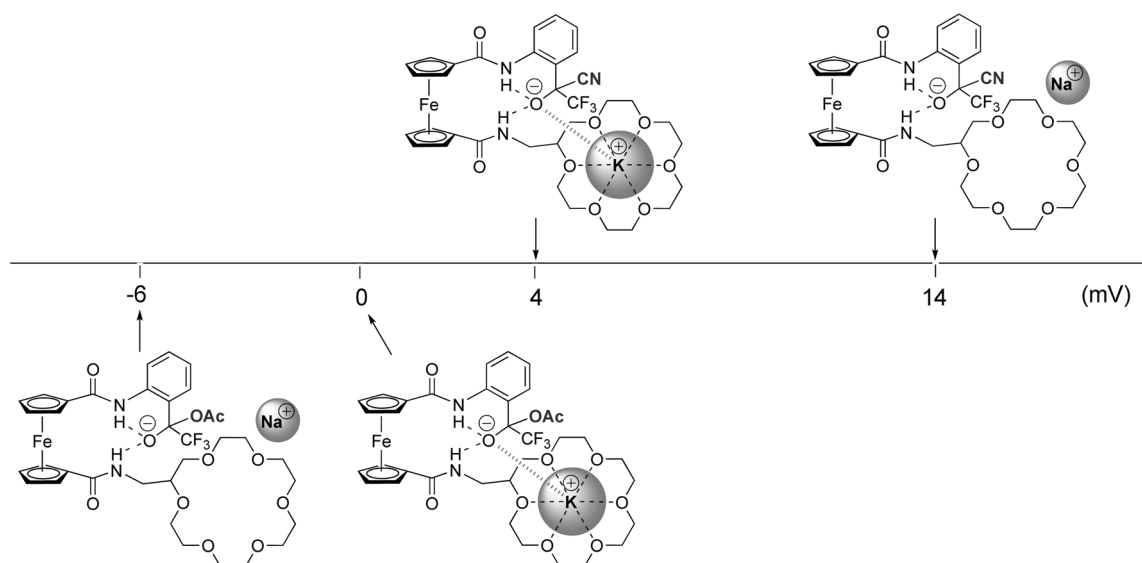


Figure 5. Oxidation potential changes of **1** upon addition of KCN, NaCN, KOAc, and NaOAc (2.0 equiv, each) respectively, in 1% H₂O/CH₃CN.

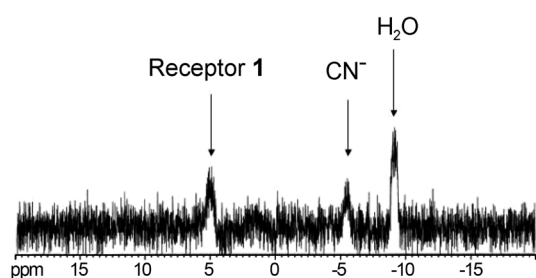


Figure 6. ¹⁹F NMR spectrum for a mixture of receptor **1** (0.5 mM), KCN (1.0 mM), KCl (1.0 mM), KBr (1.0 mM), KOAc (1.0 mM) and K₂SO₄ (1.0 mM), taken in 1% H₂O/CD₃CN.

cyanide from multi-anionic species in aqueous media was tested in a H₂O/CD₃CN mixed solvent system. Figure 6 shows ¹⁹F NMR spectrum of **1** (0.5 mM) in 1% H₂O/CD₃CN containing KCN (1.0 mM), KCl (1.0 mM), KBr (1.0 mM), KOAc (1.0 mM) and K₂SO₄ (1.0 mM). Specifically, heteroditopic receptor **1** was dissolved in 495 μL of CD₃CN and 5 μL of H₂O solution containing KCN (100 mM), KCl (100 mM), KBr (100 mM), KOAc (100 mM), as K₂SO₄ (100 mM). The cyanide ion was detected at -5.6 ppm (acetate was overlapped with the hydrate signal near -9.2 ppm).

As receptor **1** recognizes ion pairs, it may also recognizes zwitterions such as amino acids. A molecular modeling study showed that receptor **1** can recognize α-amino acids as their zwitterionic forms. Therefore, we examined the recognition of L-phenylalanine (L-Phe), an α-amino acid,¹¹ in its zwitterionic form with receptor **1** by NMR spectroscopy. Although it was difficult to dissolve the zwitterionic amino acid in acetonitrile, we were able to measure NMR spectra for **1**-Phe complexes at a sub-mM-level concentration in acetonitrile containing 1-25% of water. The ¹⁹F NMR spectrum taken in 1% D₂O/CD₃CN showed a distinct chemical shift for a 1:1 complex of L-Phe and receptor **1** (-9.63 ppm), along with those of receptor (+4.80 ppm) and its hydrated

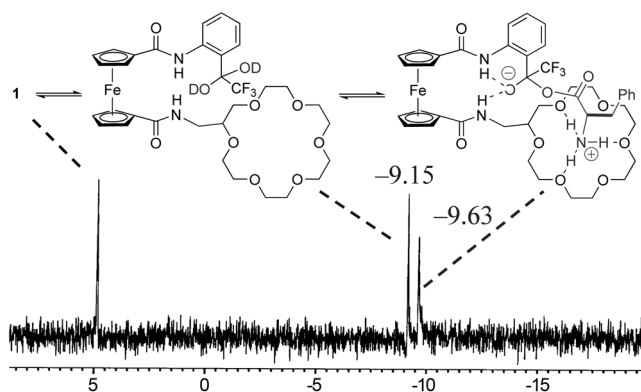


Figure 7. ¹⁹F NMR spectrum for a mixture of receptor **1** (1.0 mM) and L-Phe (excess), taken in 1% D₂O/CD₃CN.

form (-9.15 ppm), respectively (Figure 7). The ¹H NMR spectrum also supported the presence of the three species. In a solvent system of higher water content, such as 25% D₂O/CD₃CN, most of receptor **1** existed as its hydrated form; however, still its amino acid adduct was observable upon addition of about 30 equivalents of L-Phe. The complex formation between receptor **1** and L-Phe was further confirmed by electrospray ionization mass spectrometry (ESI-MS), which was carried out in acetonitrile containing 25% water. A molecular ion peak corresponding to the receptor-substrate complex was observed at *m/z* = 886.2717 [M + 1], where M = 885.2747 is the exact molecular mass of the receptor-substrate complex. Furthermore, direct addition of L-Phe (2 equiv) into a solution of **1** in 1% H₂O/CH₃CN caused a slight negative shift (-6 mV) in the oxidation potential. This indicates that the carboxylate-adduct part influences the ferrocene redox center slightly stronger than the bound ammonium cation does. Unfortunately, the poor solubility of zwitterionic forms of other α-amino acids precluded us from examining them further. However, the result described here clearly demonstrates that receptor **1** and its

derivatives can recognize α -amino acids in their zwitterionic forms.

Conclusions

We have achieved cooperative recognitions of ion pairs such as potassium cyanide and zwitter ionic L-phenylalanine by the ferrocene-based hetero-ditopic receptor **1**. The cyclic voltammetric study shows that receptor **1** induces a positive shift in the ferrocene oxidation potential upon binding a potassium cation, whereas it induces a negative shift upon binding an acetate anion, both of which can be reversed by ion-pairing process. Furthermore, receptor **1** can be used to detect potassium cyanide and an α -amino acid in aqueous media simply by ¹⁹F NMR spectroscopy. Thus, receptor **1** represents a new class of ion-pair receptor molecule of which binding and electrochemical properties can be controlled by both cation and anion recognition events.

Experimental Section

General. All chemicals were of reagent grade and used without further purification. ¹H and ¹⁹F NMR measurements were carried out on a FT-300 MHz Bruker 300 NMR spectrometer. Trifluoroacetic acid in D₂O was used as a standard (δ 0.0 ppm) for ¹⁹F NMR measurements.

Electrochemistry. Cyclic voltammograms were obtained at 298 K using a three-electrode cell connected to a potentiostat. The cell contained a nitrogen-purged acetonitrile solution of receptor (1.0 mM) and Bu₄N⁺ClO₄⁻ as supporting electrolyte (0.1 M). Ag/AgCl (3.0 M NaCl) was used as the reference electrode, with glassy carbon as the working electrode, and Pt as the counter electrode. The scan rate was 250 mVs⁻¹. Ferrocene (*ca.* 1 mM) was added as an internal reference in each case (Fc⁺/Fc: $E^0 = 0.51$ V vs Ag/AgCl).

Synthesis

1-[(*o*-Trifluoroacetylphenyl)amino]carbonyl-1-chloro-carbonyl-ferrocene: To a suspension of 1,1'-ferrocenedicarboxylic acid (500 mg, 1.83 mmol) in dry dichloromethane (30 mL), was added oxalyl chloride (3.2 mL) dropwise, and the resulting mixture was stirred overnight at room temperature and then refluxed for 2 h. The solvent was evaporated and the residue was dried *in vacuo* to give a crude 1,1'-di(chlorocarbonyl)ferrocene, which was dissolved in dry THF (10 mL) and transferred to a solution of *o*-trifluoroacetylphenylamine (350 mg, 1.83 mmol) and triethylamine (1.3 mL) in dry THF (10 mL). The reaction mixture was stirred at room temperature overnight. After evaporation of THF, the residue was dried *in vacuo* and purified by column chromatography on silica gel (CHCl₃/EtOAc = 10/1) to give the product as an orange solid (108 mg, 13%), along with more polar bis{[(*o*-trifluoroacetylphenyl)amino]carbonyl}-ferrocene (30%). ¹H NMR (300 MHz, CDCl₃): δ 11.43 (s, NH, 1H), 8.89 (d, $J = 8.6$ Hz, 1H), 7.98 (d, $J = 6.2$ Hz, 1H), 7.68 (q, $J = 7.3$ Hz, 1H), 7.20 (q, $J = 7.3$ Hz, 1H), 5.08 (m, Cp-H, 2H), 4.94 (m, Cp-H, 2H), 4.68 (m, Cp-H, 2H), 4.58 (m, Cp-H, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 183.5 (q, $J =$

34.6 Hz (coupled with F), CO), 168.7, 166.4, 143.9, 138.1, 132.2, 132.1, 127.0, 125.0, 122.7, 121.2, 120.7 (q, $J = 279.7$ Hz (coupled with F), CF₃), 115.2, 74.8, 73.8, 72.7, 70.6; HRMS (MALDI) calc. for C₂₀H₁₃ClF₃FeNO₃ 462.9885, found (m/z) 428.0213 (M - Cl).

Receptor 1: 1-[(*o*-Trifluoroacetylphenyl)amino]carbonyl-1'-chlorocarbonylferrocene (50 mg, 0.11 mmol) and 2-(aminomethyl)-18-crown-6 (Aldrich, 32 mg, 0.11 mmol) were mixed together in dry THF (10 mL) containing triethylamine (11 mg, 0.11 mmol) and DMAP (1 mg). The solution was stirred under N₂ for 2 h and then concentrated *in vacuo* to give crude product, which was first purified by short column chromatography on neutral alumina (Activity II, eluent: CHCl₃/MeOH = 10/1), and purified again by column chromatography on silica gel (CHCl₃/MeOH = 10/1). The pure product **1** was isolated as an orange viscous solid (58 mg, 73%). ¹H NMR (300 MHz, CD₃CN): δ 10.89 (s, NH, 1H), 8.57 (d, $J = 8.2$ Hz, 1H), 7.94 (t, $J = 6.1$ Hz, 1H), 7.76 (q, $J = 8.1$ Hz, 1H), 7.28 (q, $J = 8.1$ Hz, 1H), 6.74 (s, NH, 1H), 4.84 (m, Cp-H, 2H), 4.75 (m, Cp-H, 2H), 4.55 (m, Cp-H, 2H), 4.45 (m, Cp-H, 2H), 3.74 (s, OCH, 1H), 3.55 (m, OCH₂, 2H), 3.29 (d, $J = 3.9$ Hz, NCH₂, 2H); ¹³C NMR (75 MHz, CD₃CN): δ 171.9, 170.1, 142.8, 137.8, 131.7, 124.3, 122.6, 79.8, 78.9, 78.6, 74.0-62.3 (11 carbon signals), 62.3, 40.7, 40.4 (Signals for COCF₃ were difficult to determine because of low solubility and weak intensity.); ¹⁹F NMR (282 MHz, CD₃CN) δ 4.80; HRMS (MALDI) calc. for C₃₃H₃₉F₃FeN₂O₉ 720.1957, found (m/z) 719.1688 (M-1); HRMS (ES⁺) calc. for C₃₃H₃₉F₃FeN₂O₉ 720.1957, found (m/z) 721.2225 (M+1).

Receptor 2: To a suspension of ferrocenecarboxylic acid (500 mg, 2.17 mmol) in dry dichloromethane (30 mL), was added oxalyl chloride (1.5 mL) dropwise, and the resulting mixture was stirred overnight at room temperature and then refluxed for 2 h. The solvent was evaporated and the residue was dried *in vacuo* to give a crude chlorocarbonylferrocene, which was dissolved in dry THF (10 mL) and transferred to a solution of *o*-(trifluoroacetyl)aniline (400 mg, 2.12 mmol) and triethylamine (1.3 mL) dissolved in dry THF (10 mL). The reaction mixture was stirred at room temperature overnight. After evaporation of THF, the residue was dissolved in chloroform and washed with water. The organic phase was dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography on silica gel (CHCl₃/EtOAc = 20/1) to give product **2** as an orange solid (387 mg, 52%). $R_f = 0.5$; ¹H NMR (300 MHz, CD₃CN): δ 10.95 (s, NH, 1H), 8.69 (d, $J = 8.1$ Hz, 1H), 7.99 (d, $J = 6.1$ Hz, 1H), 7.77 (t, $J = 8.5$ Hz, 1H), 7.26 (t, $J = 7.2$ Hz, 1H), 4.87 (t, $J = 1.9$ Hz, Cp-H, 2H), 4.54 (t, $J = 1.9$ Hz, Cp-H, 2H), 4.28 (s, Cp-H, 5H); ¹³C NMR (75 MHz, CD₃CN): δ 171.1, 144.2, 141.1, 138.5, 132.5, 123.9, 122.1, 77.2, 73.0, 71.3, 69.9 (Signals for COCF₃ were difficult to determine because of low solubility and weak intensity.); ¹⁹F NMR (282 MHz, CD₃CN) δ 5.33; HRMS (MALDI) calc. for C₁₉H₁₄F₃FeNO₂ 401.0326, found (m/z) 400.0042 (M - 1). Elemental anal. calc. for C₁₉H₁₄F₃FeNO₂: C, 56.89; H, 3.52; N, 3.49. Found: C, 56.72; H, 3.767; N, 3.215.

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