Electronic Supplementary Information

Highly cooperative ion-pair recognition of potassium cyanide using a hetero-ditopic ferrocene-based crown ether-trifluoroacetylcarboxanilide receptor

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Synthesis of 1-[(*o*-trifluoroacetylphenyl)amino]carbonyl-1'-chlorocarbonyl-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*-trifluoroacethylaniline (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 ($CHCl_3$/EtOAc = 10/1, R_f = 0.25) to give the product as an orange solid (108 mg, 13%), along with bis[((*o*-trifluoroacetylphenyl)amino)carbonyl]ferrocene (R_f = 0.5, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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), CF_3), 115.2, 74.8, 73.8, 72.7, 70.6; HRMS (MALDI) calc. for $C_{20}H_{13}ClF_3FeNO_3$ 462.9885, found (*m/z*) 428.0213 (M – Cl).

Synthesis of hetero-ditopic receptor 1. 1-[(*o*-Trifluoroacetylphenyl)amino]carbonyl-1'-chlorocarbonylferrocene (50 mg, 0.11 mmol) and 2-(aminomethy)-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 N_2 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: $CHCl_3$/MeOH = 10/1) and then by column chromatography on silica gel (eluent: $CHCl_3$/MeOH = 10/1). The pure product **1** was isolated as an orange viscous solid (58 mg, 73%). ^{1}H NMR

(300 MHz, CD_3CN): 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, OCH_2, 22H), 3.29 (d, J = 3.9 Hz, NCH_2, 2H); ^{13}C NMR (75 MHz, CD_3CN): 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 -CO<u>C</u>F_3 were difficult to determine because of low solubility and weak intensity); ^{19}F NMR (282 MHz, CD_3CN) δ 4.80; HRMS (MALDI) calc. for $C_{33}H_{39}F_3FeN_2O_9$ 720.1957, found (*m/z*) 719.1688 (M – 1).; HRMS (ES+) calc. for $C_{33}H_{39}F_3FeN_2O_9$ 720.1957, found (*m/z*) 721.2225 (M+1).

Synthesis of 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*-trifluoroacethylaniline (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 Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel ($CHCl_3$/EtOAc = 20/1, R_f = 0.5) to give product **2** as an orange solid (387 mg, 52%). ^{1}H NMR (300 MHz, CD_3CN): 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); ^{13}C NMR (75 MHz, CD_3CN): 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 $COCF_3$ were difficult to determine because of low solubility and weak intensity); ^{19}F NMR (282 MHz, CD_3CN) δ 5.33; HRMS (MALDI) calc. for $C_{19}H_{14}F_3FeNO_2$ 401.0326, found (*m/z*) 400.0042 (M – 1). Elemental anal. calc. for $C_{19}H_{14}F_3FeNO_2$: C, 56.89; H, 3.52; N, 3.49. Found: C, 56.72; H, 3.767; N, 3.215.

The isothermal titration calorimetry (ITC) analysis. The binding affinity and thermodynamic data were determined by ITC, using an isothermal titration calorimeter (MicroCal, Inc.).

A typical procedure. To a solution of the receptor (1.5 mL, 0.1 mM, in acetonitrile) in the calorimetry cell, 5.0 μL of guest solution (2.0 mM) was injected 40 times at 303 K. In all titrations, dilution effects were corrected, which were done by carrying out a

separate titration experiment. Thus, the titration result obtained by adding the same guest solution into pure CH_3CN at 303 K was subtracted from the raw titration data to produce the final binding curve. The titration data was analyzed by a curve-fitting software implemented, which gave a number of sites, apparent binding affinity *K*, and the standard enthalpy change ΔH^o.

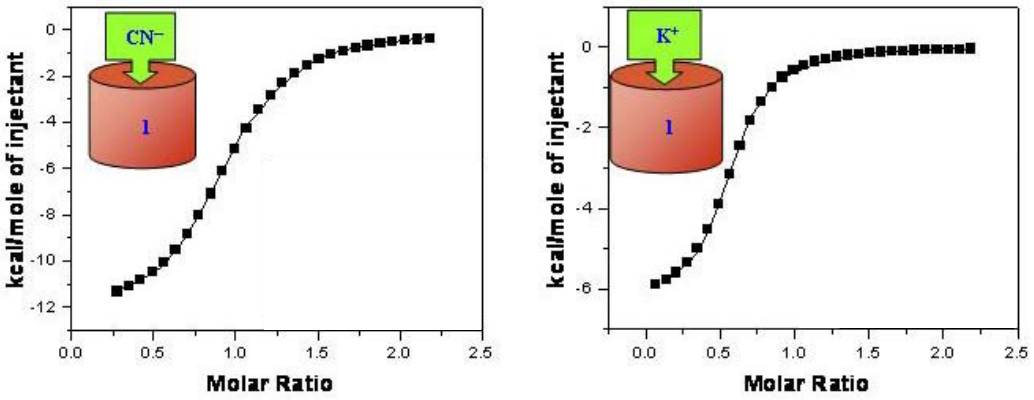


Figure S1. ITC titration data of receptor **1** (1.0×10^{-4} M in CH_3CN) with Bu_4NCN (left) and KPF_6 (right) in CH_3CN at 303 K.

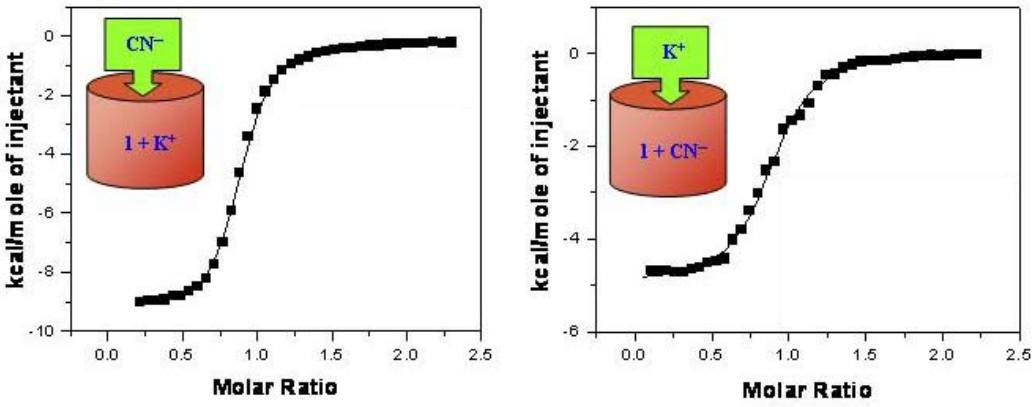


Figure S2. ITC titration data of an equimolar mixture of **1** and KPF_6 (1.0×10^{-4} M, each in CH_3CN) with Bu_4NCN (left), and for an equimolar mixture of receptor **1** and Bu_4NCN (1.0×10^{-4} M, each in CH_3CN) with KPF_6 (right), in CH_3CN at 303 K.

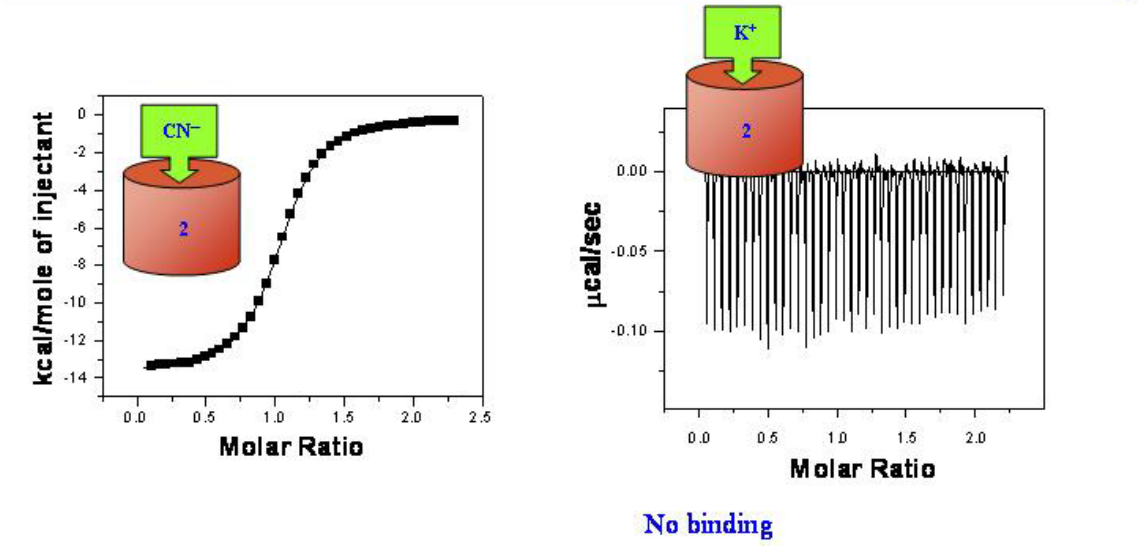


Figure S3. ITC titration data of receptor **2** (2.0×10^{-4} M in CH_3CN) with Bu_4NCN (left) and KPF_6 (right) in CH_3CN at 303 K.

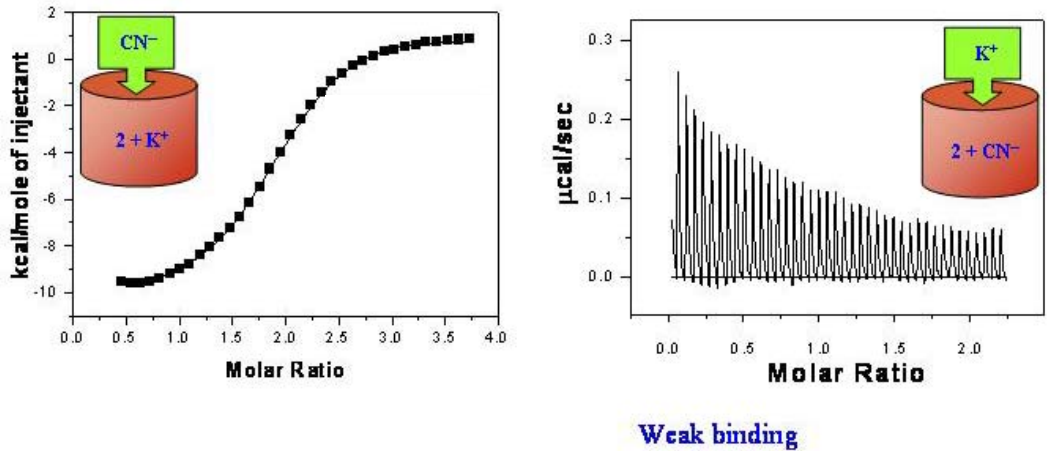


Figure S4. ITC titration data of an equimolar mixture of receptor **2** and KPF_6 (2.0×10^{-4} M, each in CH_3CN) with Bu_4NCN (left), and for an equimolar mixture of **2** and Bu_4NCN (2.0×10^{-4} M, each in CH_3CN) with KPF_6 (right), in CH_3CN at 303 K.

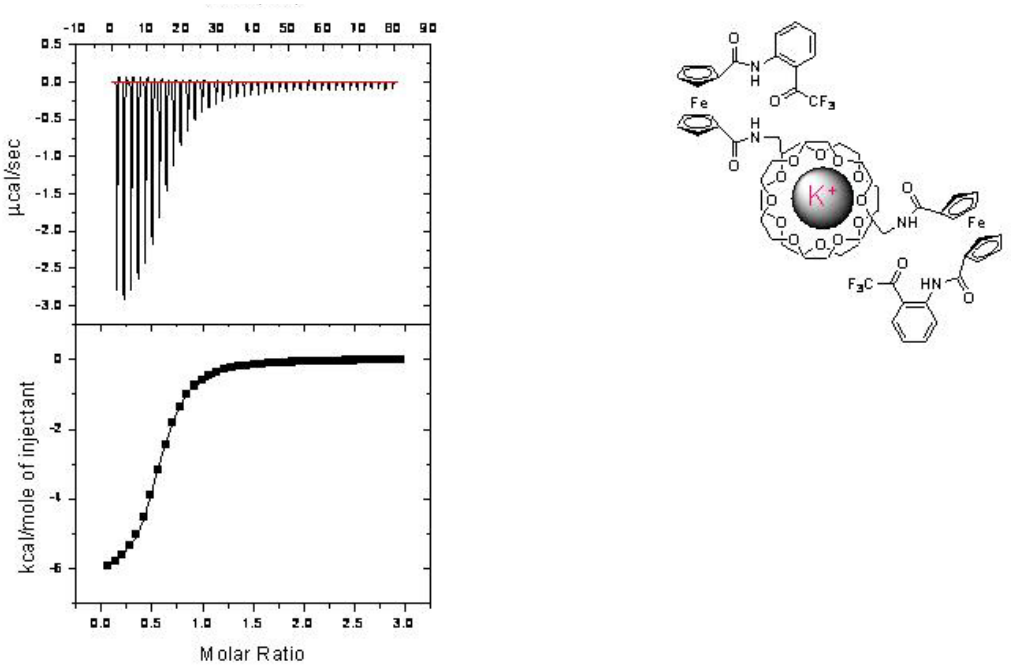


Figure S5. ITC titration data of receptor **1** (1.0×10^{-4} M in CH_3CN) with KPF_6 in CH_3CN at 303 K (left), and a structure of a (2 : 1)-(receptor **1**: K^+) complex (right).

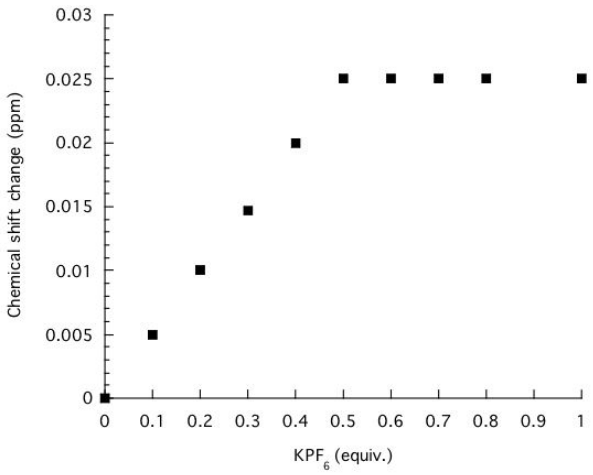
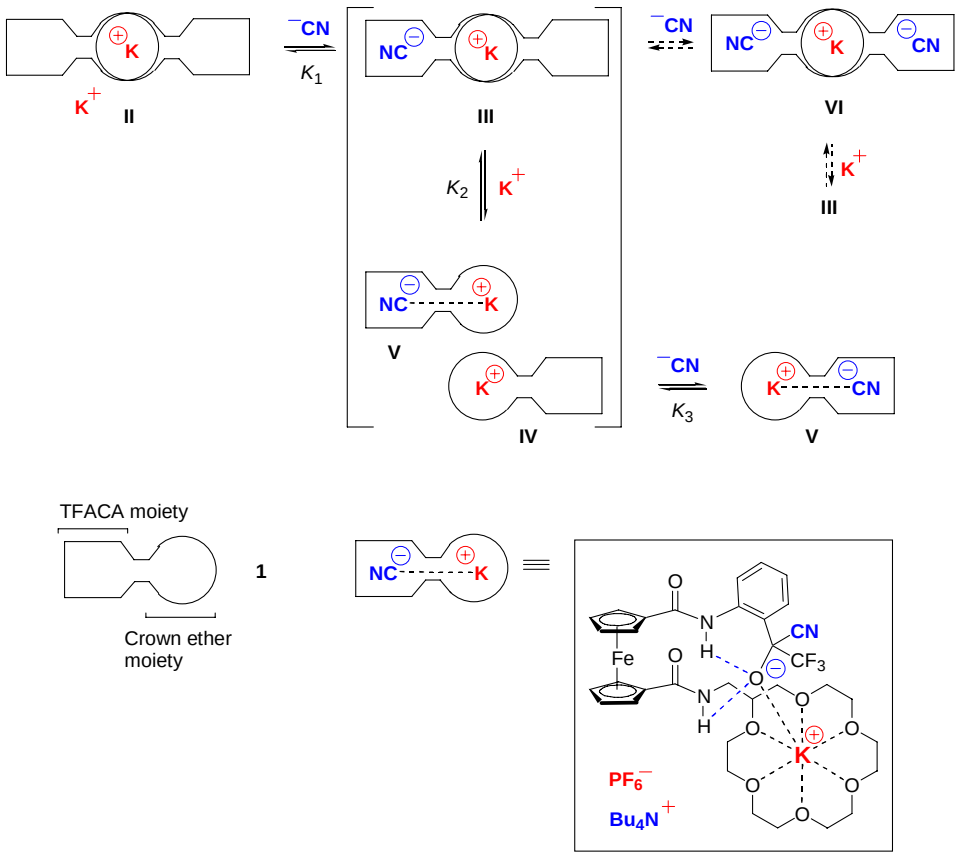


Figure S6. ^{1}H NMR chemical shift changes (300 MHz) for the titration of receptor **1** with KPF_6 in CD_3CN (the diagnostic peak at 4.75 ppm was used in this plot).

Binding modes. Scheme S1 shows a tentative explanation for the sequential binding mode (Entry 3 in Table 1). We may assume that the 1:1 mixture of receptor **1** and potassium ion in a titration "cell" exists mostly as the sandwich-type K^+-complex **II**, considering the large association constant observed (Entry 2, Table 1). The first binding process (**II** → **III**) involves the addition of cyanide to one of the trifluoacetyl groups in

the sandwich-type complex **II**. The alkoxide moiety in complex **III** seems to be stabilized by intramolecular H-bonding with the two carboxamide NH protons, as discussed in the following NMR studies. An ionic interaction between the alkoxide and crown ether-bound potassium ion may not be significant in the intermediate **III** because the potassium ion is buried between the two crown ether rings. Subsequently, the unbound potassium ion may interact with one of the sandwich-type crown ethers, which constitutes the second binding process (**III** → **IV** + **V**). The second process thus involves the dissociation of the sandwich-type complex, which may represent both the large favorable entropy change and unfavorable enthalpy change. Such an opposite effect seems to result in the smaller association constant. Finally, the third process (**IV** → **V**), addition of cyanide to the K^+-bound species **IV**, would result in the very strong binding due to an ion-pairing interaction, which is apparently entropically unfavorable as observed. The formation of intermediate species **VI** would be less probable than **III** at the early stage of titration where the concentration of cyanide is low. Once species **III** is formed, it reacts with the unbound potassium ion and follows the major route described.



Scheme S1. A suggested binding process for the entry 3 in Table 1 (The dotted line

between cyanide and potassium ions implies the existence of ion-pair interactions).

We have estimated the cooperative ion-pair interaction in the following way. The data in the entry 3 represents the molecular interactions between the sandwich-type K^+-adduct of **1** and CN^-, which is suggested to involve the three-stage binding processes. The largest association constant ($K_3 = 1.9 \times 10^7\ M^{-1}$) is assigned to the binding process between CN^- and the proposed intermediate **IV**. This binding should comprise the known molecular interaction between **1** and CN^- ($K_{ass} = 1.9 \times 10^5\ M^{-1}$, entry 1) and the positive cooperative ion-paring between the cyanide adduct and the bound K^+, which thus amounts to $\Delta K_{ass} = 1.0 \times 10^2\ M^{-1}$ ($\Delta\Delta G = 2.9$ kcal·mol^{-1}), two-order of magnitude enhancement in the binding affinity.

We also can estimate the association constant (K_{IV}) for the formation of intermediate **IV** from **1** and K^+ as follows. The data in the entry 4 represents the binding process between the cyanide adduct of **1** (**1** $\supset CN^-$) and K^+, giving $K_{ass} = 4.2 \times 10^5\ M^{-1}$. This binding process similarly should involve the same amount of cooperative ion-pairing as in the entry 3, along with the binding affinity (K_{IV}) between K^+ and the crown-ether moiety that forms the proposed intermediate **IV**. If we subtract the ion-pairing amount ($\Delta K_{ass} = 10^2\ M^{-1}$) from the overall association constant, we can estimate the association constant K_{IV}, which cannot be determined directly, to be $4.2 \times 10^3\ M^{-1}$. This is reasonable magnitude if we think that the sandwich-type complex forms between **1** and K^+, which is more stable ($K_{ass} = 2.5 \times 10^5\ M^{-1}$).

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** (1.0 mM) and $Bu_4N^+ClO_4^-$ as supporting electrolyte (0.1 M). Ag/AgCl (3M NaCl) was used as the reference electrode, a gold disk (0.025 cm^{-2}) 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).

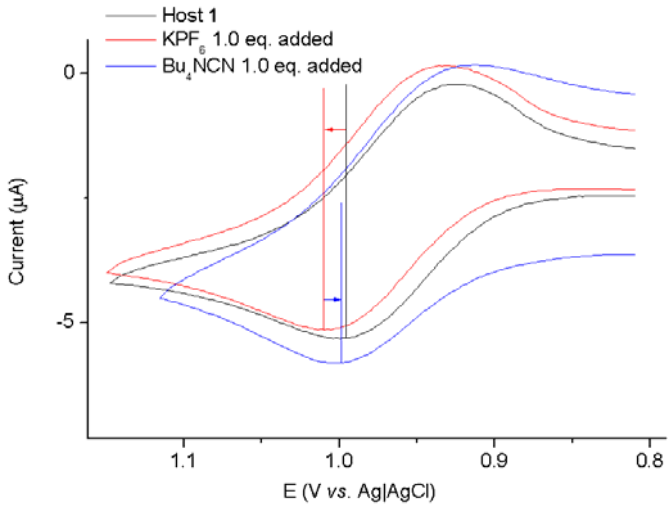


Figure S7. Cyclic voltammograms showing the potential shifts of oxidation peak of receptor **1** (1.0 mM in CH_3CN) upon addition of $K^+(PF_6^-)$ and then addition of CN^- (Bu_4N^+).

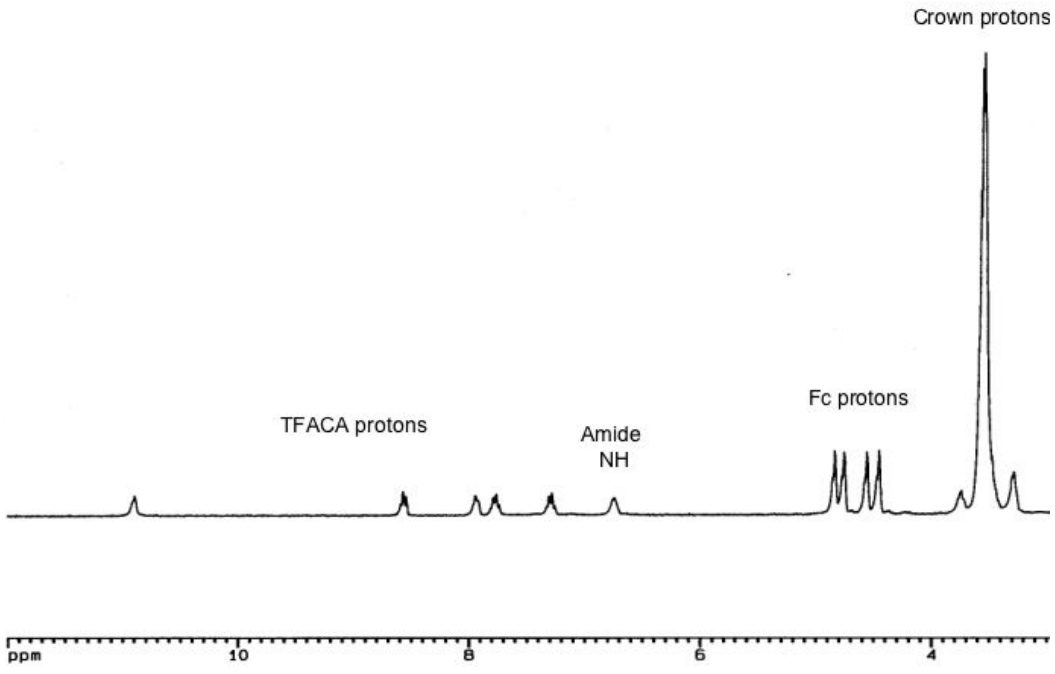


Figure S8. ^{1}H-NMR spectrum of receptor **1** (1.0×10^{-3} M) in CD_3CN (FT-300 MHz).

^{19}F-NMR study. ^{19}F NMR measurements were carried out on a FT-300 MHz Bruker Aspect 300 NMR spectrometer. Trifluoroacetic acid in D_2O was used as a reference for the spectra.

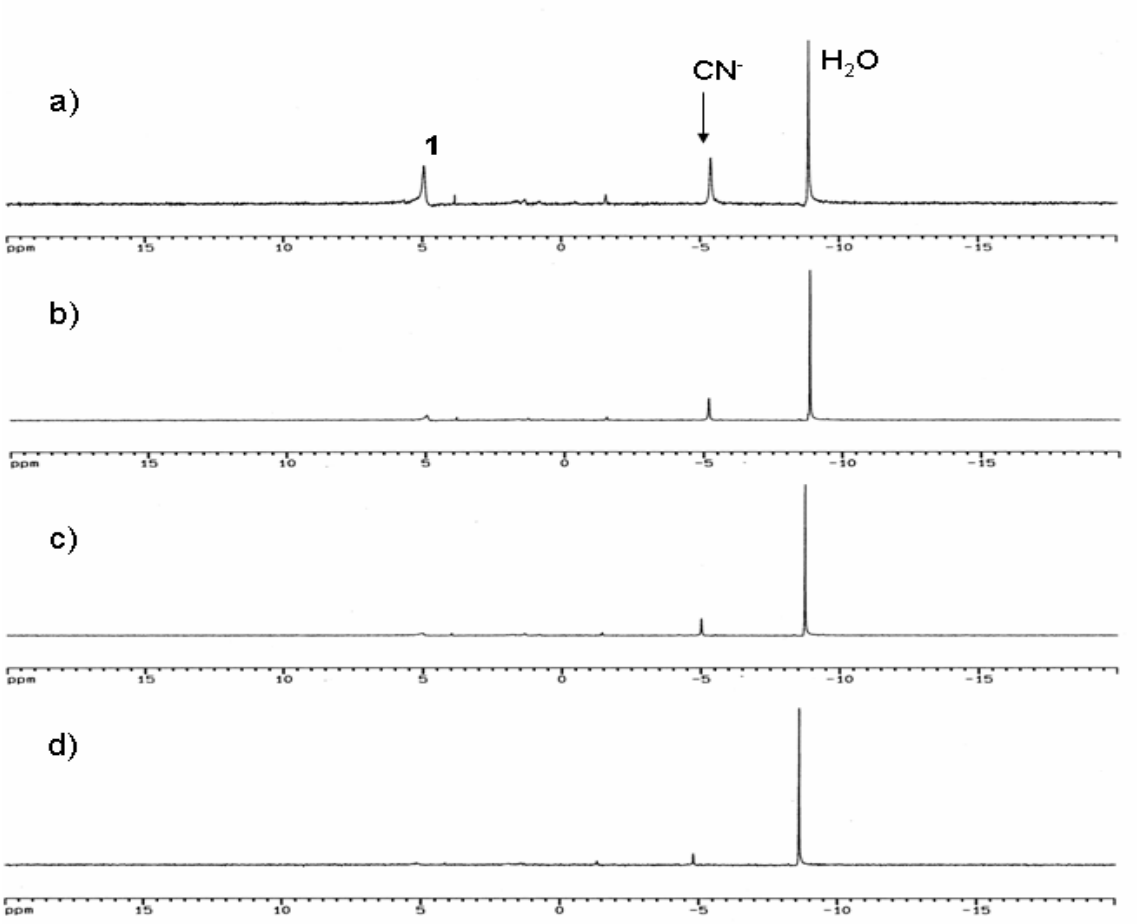


Figure S9. ^{19}F-NMR spectra of receptor **1** (5×10^{-4} M) upon the addition of KCN (1.0×10^{-3} M): a) in 2% H_2O/CD_3CN, b) in 10% H_2O/CD_3CN, c) in 25% H_2O/CD_3CN, and d) in 50% H_2O/CD_3CN.