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'Cleft-form' electrochemical anion chemosensor with amide and triazole donor groups

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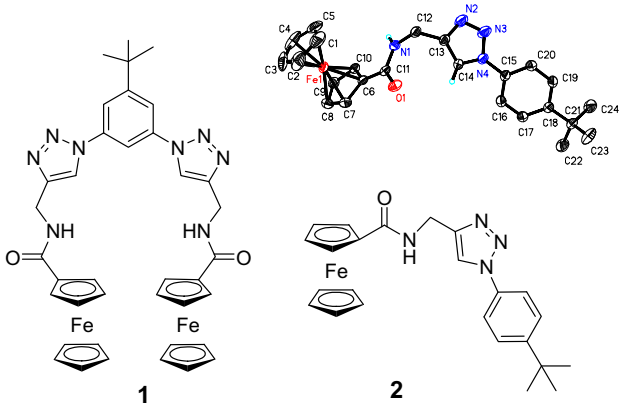
ABSTRACT

A novel 'cleft-form' electrochemical anion receptor bearing amide and triazole donor groups, **1**, has been synthesized and characterized. Among various anions, **1** shows a significant anodic shift response for $H_2PO_4^-$ and F^-, with its multiple N–H···anion and C–H···anion interactions, which is supported by theoretical calculation and NMR titration results.

There has been growing interest in anion recognition because anions play important chemical and biological roles.[1] Over the past decade, various examples of N–H···anion hydrogen bonding donors (e.g., urea, thiourea, amine, amide, pyrrole) moieties have been shown to be particularly effective anion receptors in organic solvents.[2] In addition, the $(C–H)^+$···anion hydrogen bonding donors (e.g., imidazolium[3] and triazolium[4]) moieties are often incorporated in these systems. More generally, however, neutral C–H···anion hydrogen bonding donors are less commonly recognized on account of their weakness, even though the CH unit is present in the majority (97%) of chemical compounds.[5]

Recently, the disubstituted aryl-1,2,3-triazoles have been employed in anion recognition, because the 1,2,3-triazole ring shows large polarity (dipolemoment ~5D), and that of the C5-H bond creates an electropositive site that can function as an effective C–H···anions interaction.[6] Some triazole-based receptors including macrocycles,[7] foldamers,[8] and short flexible oligomers[9] have been prepared. Macrocycle [3_4] triazolophane has unexpectedly large halide binding constants, because it takes an advantage of macrocyclic preorganization to direct four triazole C–H donors and four phenylene C–H donors into the central cavity.[7a] In addition, the anion binding capacity can be enhanced by incorporating more traditional NH donors, such as pyrrole, into these systems.[10]

We are interested in ferrocene-based receptors for anion/cation recognition,[11] since ferrocene is a good electrochemical response element due to its strong π-donating ability and good reversibility when it displays an one-electron oxidation at a desirable range. Some ferrocene-based receptors for cations and anions have been reported to reveal large shift in the redox potential of the ferrocene/ferrocenium redox couple upon the addition of target ions.[12] Recently, we reported a ferrocene-appended aryl–triazole receptor that can electrochemically respond to phosphate anions selectively with a large cathodic shift due to pure C–H···O interactions.[11c] However, the binding constant of this receptor to anions is poor. We envision that incorporating traditional NH donor amide into this system may increase its binding ability. Therefore, we designed here a 'cleft-form' ferrocene-based anion receptor with



Scheme 1. Compounds **1** and **2** with crystal structure of **2**.

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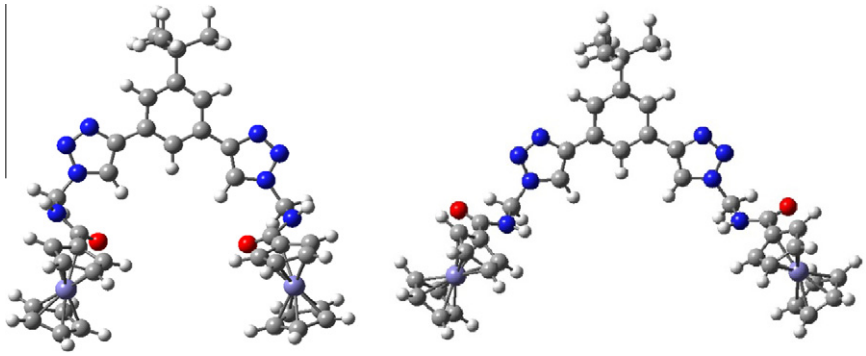

Figure 1. Optimized structures of '*anti*' (left) and '*syn*' (right) conformations of **1**.

amide and triazole donor groups, **1** (Scheme 1). The 'cleft-form' frameworks possessing well-defined binding cavity of multiple donor moieties to increase anion binding are well established.[13] We find that this simple modification really improves its anion-binding affinity via both sites, with amide N–H···anion interactions being more strongly than triazole (C–H)···anion interactions. However, for the control compound **2**, only the amide donor takes part strongly in N–H···anion interaction especially for chloride and fluoride anions.

With (chlorocarbonyl)ferrocene as starting material,[14] we first synthesized the key intermediate ferrocenecarboxylic propargylamide by literature method.[15] Then by 'click' reaction,[16] receptor **1** was easily prepared in moderate yield (72%) by coupling 3,5-diazido-1-tert-butylbenzene[7a] with ferrocenecarboxylic propargylamide in toluene under reflux with $(EtO)_3P{\cdot}CuI$ as catalyst. The reference compound **2** was prepared by the similar method. Their structures were confirmed by spectroscopic data (^1H NMR, ^{13}C NMR, and MS), as well as by X-ray structure analysis in the case of **2**.[17] The X-ray structure of **2** shows that the two binding units are in the *anti*-conformation, and a one-dimensional supramolecular assembly is found in its packing structure by the intermolecular hydrogen bond via amide group (N–H···O 2.85 Å, symmetry code: x, $0.5-y$, $0.5+z$, Fig. S1).

Though we could not get the single crystal structure of **1**, its optimized conformation in the gas phase, calculated by density functional theory (DFT) at B3LYP/6-31G* level of theory, shows a 'cleft-form' conformation (Fig. 1). The two triazole protons are pointed inward the cavity, while the two amide protons are pointed outward the cavity. The ferrocene moieties are almost parallel with a separation of 9.95 Å (calcd) in '*anti*' conformation. Though the amide and triazole binding sites show an '*anti*' conformation in the optimized conformation, we found that it can easily change to its '*syn*' conformation by the rotation of ~129.12° (around $C(H_2)$–N(H) bond) with a low energy gap (~10.12 kcal/mol, calcd), which is more favorable for binding anions via the chelate effect. The required energy (~10.12 kcal/mol) for the conversion of '*anti*' to '*syn*' conformation can easily be compensated by the binding energy of anion with **1**

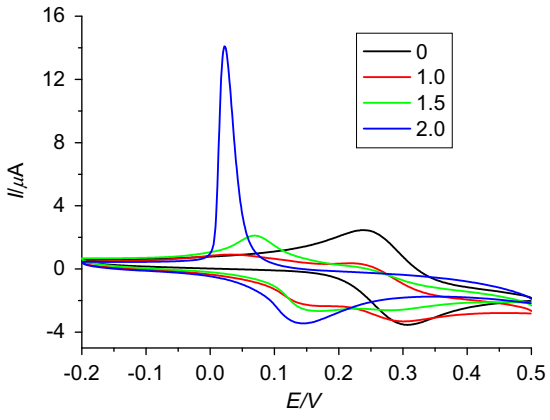

Figure 2. CV titration profile of **1** (0.2 mM) upon addition of various amount of $H_2PO_4^-$ in CH_2Cl_2 solution. Reference electrode = $Ag/AgNO_3$; supporting electrolyte = $[n\text{-}Bu_4N]PF_6$ (0.1 M); scan rate = 100 mV S^{-1}.

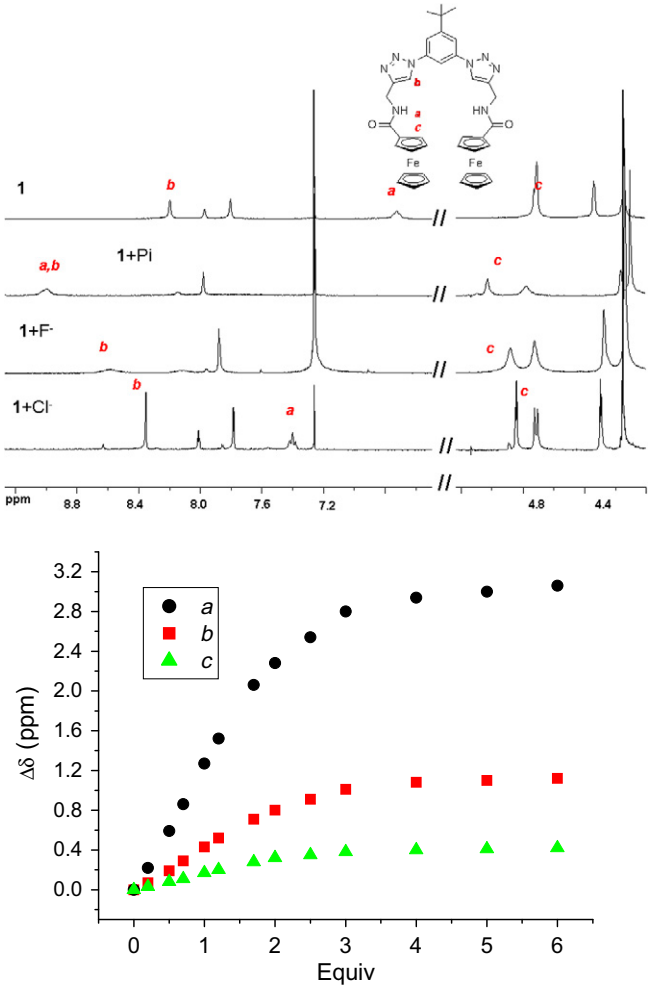

Figure 3. (Top) Partial ^1H NMR spectrum of **1** ($CDCl_3$, 16 mM) and after addition 2.0 equiv of Cl^-, $H_2PO_4^-$ and F^-. (Bottom) Chemical shift changes for several protons of **1** upon addition of $H_2PO_4^-$.

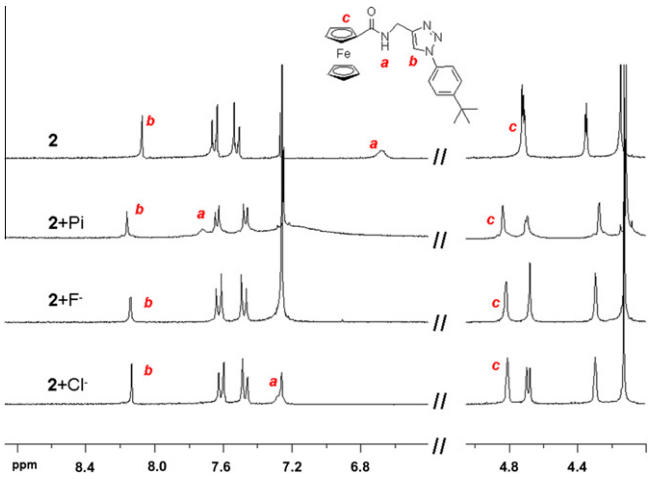

Figure 4. Partial ^{1}H NMR spectrum of **2** ($CDCl_3$, 27 mM) and after addition 2.0 equiv of Cl^-, $H_2PO_4^-$ and F^-.

(e.g. ~−37.25 kcal/mol with chloride anion for example, calcd in gas phase, BSSE corrected) in the 'cleft-form' of '*syn*' conformation.

The recognition ability of **1** toward various monoanions (F^-, Cl^-, Br^-, I^-, AcO^-, NO_3^-, HSO_4^- and $H_2PO_4^-$) in the form of their corresponding tetrabutylammonium salts (TBA^+) was first investigated by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) in CH_2Cl_2 solution containing 0.1 M $TBAPF_6$ as a supporting electrolyte. The free receptor **1** shows a reversible one-electron redox wave with the half wave potential ($E_{1/2}$) value of 270 mV (versus $Ag/AgNO_3$). Upon addition of 2.0 equiv of various anions (Fig 2, Figs. S2–S4), **1** shows only marked electrochemical signal changes to F^- and $H_2PO_4^-$, with a negative shift of 140 mV and 130 mV respectively. The evolution of CVs and DPVs of **1** upon addition of both anions gives a 'two wave behavior', with decreasing original redox potential at 270 mV and concomitantly increasing new redox potential band at a more negative position, which is obviously attributed to the formation of **1**·$H_2PO_4^-$ or **1**·F^- complex in the solution. The control compound **2** also shows electrochemical sensing to F^- and $H_2PO_4^-$ (Figs. S5–S8), but with relative less potential shift ($E_{1/2}$ ~−50 mV). In addition, upon titration of F^- or $H_2PO_4^-$ to **2**, its redox potential shows a 'shifting behavior', in which a second redox wave is positively shifted compared to the free receptor. The larger potential shift and the 'two wave behavior' of **1** compared with the 'shifting behavior' of **2** imply that **1** shows a higher binding ability to anions than **2**.

Both compounds show high energy (HE) absorption bands at λ <330 nm assigned to the π–π* transitions of cyclopentadiene or benzene rings, and a weaker low energy (LE) absorption in the region 400–500 nm assigned to a ferrocenyl-based metal-to-ligand (MLCT) band (Fig. S9). Upon addition of anions into the solution of **1** or **2**, both receptors show observable UV–vis spectral changes to F^- and $H_2PO_4^-$. Since the spectral changes are small, their binding properties were investigated by ^{1}H NMR spectroscopy.

The binding ability of **1** and **2** for the selected anions (F^-, Cl^-, and $H_2PO_4^-$ was investigated by ^{1}H NMR spectra in $CDCl_3$ solution (Fig 3). The titration of $H_2PO_4^-$ to **1** produced a considerable shift in signals of the amide protons (H*a*), the triazole protons (H*b*), and the α protons in the cyclopentadieneyl ring (H*c*), demonstrating that these protons participate in hydrogen bonding to the $H_2PO_4^-$ ion. For example, 2 equiv of $H_2PO_4^-$ induces these protons to be downshifted up to 2.3, 0.8, and 0.3 ppm, respectively. Judging by the changes in the NMR spectra, the amide donors bind the anion more strongly than triazole groups, followed by ferrocene C–H, which is in accordance with the sequence of their expected H acidity.[18] The titration curve of **1** and $H_2PO_4^-$ is fitted to a 1:1 binding model as confirmed by Job plot analysis (Fig. 3 and S11), and generates the binding constant of 2.15 (5) × 10^2 M^{-1} by using the EQNMR program,[19] which is much larger than that of the ferrocene-appended aryl-triazole receptor[11c] as a result of the incorporation of amide donors into this system.

The titration of Cl^- or F^- into **1** shows similar downfield shift in signals of H*a*, H*b*, and H*c*, demonstrating that these protons are also involved in the ligand-anion binding. The changes of these protons upon titration of Cl^- are smaller than that upon titration of $H_2PO_4^-$, which may be ascribed to its weaker basicity and spherical geometry. While the titration of strong basic F^- leads amide protons first downfield shift and then disappearing quickly for deprotonation, which is often observed in some amide-base anion receptors.[20]

The anions (F^-, Cl^- and $H_2PO_4^-$) binding behavior of **2** is different from that of **1** (Fig. 4). Upon titration to **2,** these anions produced only a considerable shift in signals of the amide proton (H*a*), and little changes in H*b* and H*c* protons, indicating the presence of

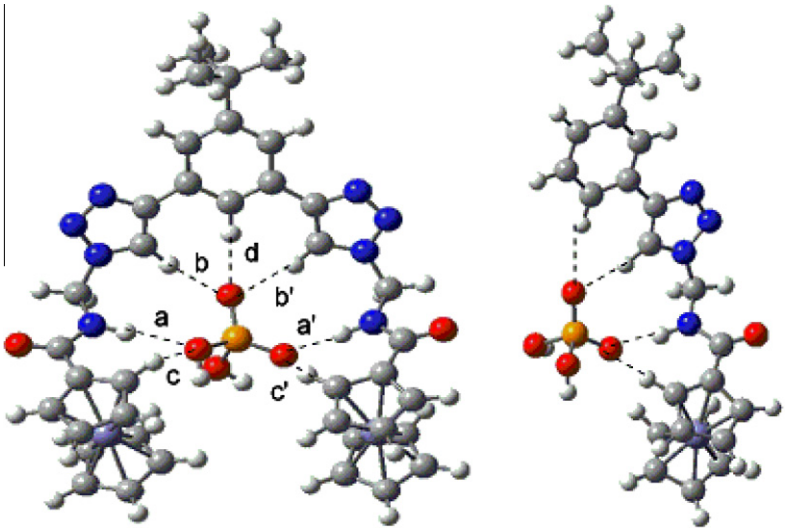

Figure 5. Calculated structure (B3LYP/6-31G*) of **1**·$H_2PO_4^-$ (left) and **2**·$H_2PO_4^-$ (right) complexes. Nitrogen, oxygen, phosphorous, carbon and hydrogen atoms are represented as blue, red, orange, gray and white balls respectively. Dotted line indicates H-bonding. The calculated H-bond distances indicated by the symbols are respectively 2.17 Å (a), 1.92 Å (a′), 2.09 Å (b), 2.21 Å (b′), 2.41 Å (c), 2.33 Å (c′) and 2.35 Å (d).

strong amide-anion interaction and very weak C–H···anion interactions between **2** and the anions in solutions.

To further understand the different binding behavior of **1** and **2**, DFT calculations of the anions ($H_2PO_4^-$, F^-, and Cl^-) with host molecule have been performed. The optimized structures of the systems, **1**·$H_2PO_4^-$ and **2**·$H_2PO_4^-$ are given in Figure 5. In the presence of $H_2PO_4^-$, the host **1** prefers '*syn*' conformation rather than '*anti*' conformation for creating an electropositive cavity for the anions by rotation of the amide group. According to the suggested geometry cutoffs for D–H···A hydrogen bond definition[21] (where D and A represent H-bond donor and acceptor), the amide protons (H*a*), the triazole protons (H*b*), and the cyclopentadienyl α-protons (H*c*) in **1**·$H_2PO_4^-$ complex make H-bonding with $H_2PO_4^-$. The average distances (calcd), N–H*a*···O (2.04 Å) <C–H*b*···O (2.15 Å) <N–H*c*···O (2.38 Å), indicate that amide···anion interaction is stronger than CH···anion interaction, which is in accordance with the ^{1}H NMR titration results. However, in **2**·$H_2PO_4^-$ complex, the triazole CH proton and amide proton may adopt either '*anti*' or '*syn*' conformation (complex with '*syn*' conformation is energetically more stable than that with '*anti*'), but in contrast to **1**, only one arm in **2** can participate in H-bonding with $H_2PO_4^-$ lacking a 'cleft-form' geometry. More interestingly, for F^- and Cl^- ions, despite the fact that the triazole, cyclopentadienyl (α-protons), and amide protons of **1** participate in binding with ions, only amide protons in **2** participate in binding (cf. Fig. S15). This may be due to the following reasons: being a polyatomic ion, $H_2PO_4^-$ has the bigger size with tetrahedral geometry, which facilitates to bind not only with amide protons but also with other neighboring protons in **2**. On the other hand, F^- and Cl^-, in comparison to $H_2PO_4^-$, have much smaller volume with spherical geometry, which preferably bind with the amide proton of **2** due to its highest acidic nature among all the types (amide, triazole, benzene and cyclopentadienyl protons). Besides, **2** with one arm is unable to make 'cleft-form' geometry while **1** with 'cleft-form' geometry provides the various protons additional chances to come close to the ions simultaneously and to bind with the ions.

In conclusion, a neutral 'cleft-form' anion receptor (**1**) bearing amide and triazole donors has been designed and synthesized. We found that receptor **1** can bind anions via amide N–H···anion interaction, triazole and ferrocene C–H···anion interaction, with the binding ability order: amide NH > triazole CH > ferrocene CH, which is confirmed by theoretical calculation and NMR titration results. By contrast, in its non-'cleft-form' system **2**, only the amide group takes part strongly in N–H···anion interaction. In addition, **1** showed marked electrochemical signal changes to $H_2PO_4^-$ and F^- over other anions.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.118.

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17. *X-ray data for 2*: $C_{24}H_{26}FeN_4O$, $M_w = 442.34$, yellow, size: $0.35 \times 0.21 \times 0.16$ mm^3, monoclinic, space group $P2_1/c$, $a = 17.267(3)$ Å, $b = 12.767(3)$ Å, $c = 10.038(2)$ Å, $\beta = 99.688(12)$ °, $V = 2181.3(7)$ Å^3, $T = 293(2)$ K, $Z = 4$, $D = 1.347$ Mg/m^3, $\rho = 0.714$ mm^{-1}, $F(000) = 928$; 17187 reflections measured, of which 5326 were unique ($R_{int} = 0.0401$). 272 refined parameters, final $R_1 = 0.0629$ for reflections with $I > 2\sigma(I)$, $wR_2 = 0.1112$ (all data), GOF = 0.983. Final largest diffraction peak and hole: 0.248 and −0.280 e. Å^{-3}.
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