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Ferrocene-Appended Aryl Triazole for Electrochemical Recognition of Phosphate Ions

Qian-Yong Cao,[†,‡] Tuhin Pradhan,[†] Sungtae Kim,[†] and Jong Seung Kim*,[†]

Department of Chemistry, Korea University, Seoul 136-701, Korea, and Department of Chemistry, Nanchang University, Nanchang 330031, P. R. China

jongskim@korea.ac.kr

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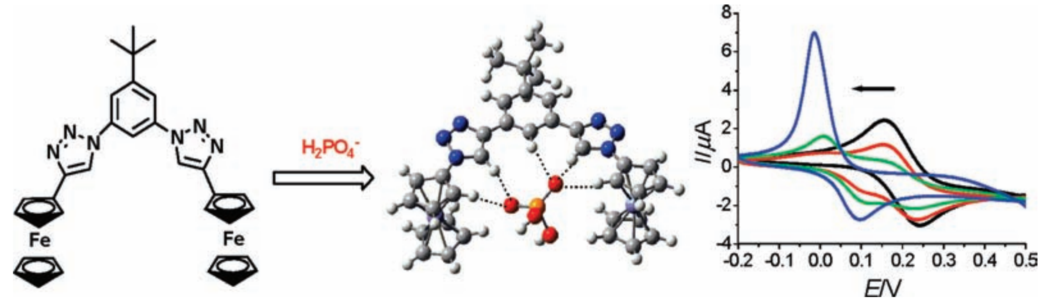
ABSTRACT



A neutral ferrocene-appended aryl triazole receptor 1 for phosphate anions has been synthesized and characterized by X-ray crystal analysis. Among various anions, 1 shows a distinct electrochemical recognition of phosphate anions by its multiple H-bonding ($C{-}H\cdots O$) with a tetrahedral anion, which is supported by density functional theory based theoretical calculation and ^{1}H NMR titration results.

Anions play an important role in a wide range of chemical and biological processes, and the development of anion selective receptors has been actively investigated.[1] In particular, the binding of phosphate ions and their derivatives (such as pyrophosphate) represents an important aspect in this field, as required by their essential roles not only in signal transduction and energy storage in biological systems[2] but also in the eutrophication of waterways through the usage of fertilizers.[3] To date, many synthetic receptors incorporating neutral or cationic NH hydrogen bonding donor groups (*e.g.,* pyrrole, indole, ammonium, guanidinium, urea, thiourea, and amide) or cationic CH hydrogen bonding donor motifs (*e.g.,* imidazolium and triazolium) have been reported.[4] However, to the best of our knowledge, receptors with pure neutral CH H-bonding donors have not yet been exploited for the purpose of phosphate anion recognition.

Recently, the role of disubstituted aryl-1,2,3-triazoles in anion coordination has attracted much attention,[5] because the 1,2,3-triazole ring shows great polarity (dipole moment $\sim$5D) and that of the C5−H bond creates an

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[†] Korea University.

[‡] Nanchang University.

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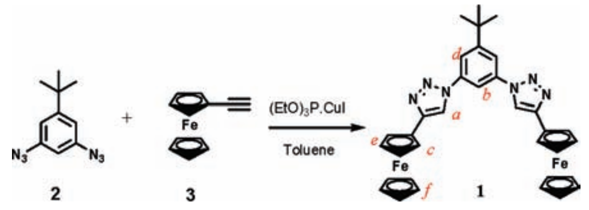
electropositive site that can function as an effective C−H···X$^-$ hydrogen bonding. In this regard, some of aryl triazole based receptors including macrocycles,[6] foldamers,[7] and short flexible oligomers[8] have been prepared and were found to show a high affinity and selectivity for chloride ions over other anions. In addition, 1,2,3-triazole-linked dendrimers[9] and some other triazole-containing molecules[10] showing a binding ability toward phosphate anions were also reported.

For practical application, a good receptor should display easily detectable optical and/or electrochemical signals and undergo readily discernible changes in these signals after binding with a given guest species. These design criteria make electrochemical sensing systems based on a ferrocene molecule very attractive. Ferrocene is a good electrochemical response element due to its strong π-donating ability and good reversibility when it displays a one-electron oxidation at a low potential (0.5 V vs a saturated calomel electrode). Some ferrocene-based receptors for anions have been reported to reveal a negative shift in the redox potential of the ferrocene/ferrocenium redox couple upon the addition of target ions.[11] The magnitude of the electrochemical shift ($\Delta E_{1/2}$) upon complexation represents a quantitative measurement of the perturbation of the redox center.

Taking advantage of the strong C−H···X$^-$ interaction between the aryl triazole and the anions and the advantageous electrochemical properties of ferrocene, we thus envisioned that plugging of the ferrocenyl unit onto the aryl triazole could provide novel electrochemical chemosensors with which the binding affinity for anions can be detected by changes of electrochemical signaling of the receptors. With this purpose in mind, a novel ferrocene-containing triazole **1** (Scheme 1) has been designed and synthesized. Its anion binding ability was investigated by monitoring substrate-induced changes in their electrochemical signaling (cyclic voltammetry (CV) and differential pulse voltammetry (DPV)) and ^{1}H NMR spectra. The detailed binding mechanisms of **1** toward anions have been explored by calculations based on density functional theory (DFT) as well.

Scheme 1. Preparation Route of **1**



Using ‘click’ chemistry conditions,[12] receptor **1** was easily prepared in moderate yield (72%) by a coupling reaction of 3,5-diazido-1-*tert*-butylbenzene (**2**)[6a] with ethynylferrocene (**3**)[13] in toluene under reflux with $(EtO)_3P\cdot CuI$ as the catalyst (Scheme 1). Formation of the 1,2,3-triazole ring was confirmed by ^{1}H NMR: appearance of the triazol-*H* signal as a singlet at 8.01 ppm (in $CDCl_3$; see Supporting Information). In addition, the ^{1}H NMR peaks of the ferrocene are characteristic with the free Cp found at 4.15 ppm, whereas protons of the substituted cyclopentadienyl moiety appeared at 4.83 and 4.38 ppm for the α and β proton, respectively.

The single crystal of **1** was also obtained *via* slow diffusion of hexane to its CH_2Cl_2 solution (Figure 1). In the solid state, **1** shows a *syn*−*syn* conformation which is different from the *anti*−*anti* conformation of the related hydroxyl group substituted aryl triazole.[8a] In addition, the two triazole rings are a bit twisted to its appended phenyl ring with a dihedral angle of 34.9(2)° and 24.0(2)°, respectively.

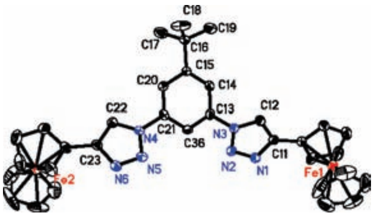


Figure 1. X-ray structure of **1**. The hydrogen atoms were omitted for clarity.

The optimized conformation of **1** in the gas phase, calculated at the B3LYP/6-31G* level of theory (Figure S1), is similar to that investigated in the solid state. We found that this *syn*−*syn* conformation, however, can easily change to its *anti*−*anti* conformation (Figure S1) by the

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rotation of ~120° around both of the C(aryl)−N(triazole) bonds with a low energy gap (0.48 kcal/mol, in the gas phase).

The recognition ability of **1** toward various anions (F^-, Cl^-, Br^-, I^-, PF_6^-, ClO_4^-, HSO_4^-, CH_3COO^-, $H_2PO_4^-$ and $HP_2O_7^{3-}$) in the form of their corresponding tetrabutylammonium salts (TBA^+) was first investigated by cyclic voltammetry (CV) and differential pulse voltammetry (DPV)[14] 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 a half wave potential ($E_{1/2}$) value of 200 mV (vs $Ag/AgNO_3$). Upon addition of 2.0 equiv of various anions, **1** shows electrochemical signal sensing only to $H_2PO_4^-$ and $HP_2O_7^{3-}$, with a cathodic shift ($\Delta E_{1/2}$) of ~ −200 mV and ~ −180 mV, respectively, due to the complexation between anions and **1**. It can be explained that the electron density in anions is transferred to the ferrocenyl center, and consequently the ferrocene moiety in **1** is oxidized more easily to a ferrocenium ion.

The CVs and DPVs of **1** upon addition of various amounts of $H_2PO_4^-$ are shown in Figures 2 and S2. Upon the addition of $H_2PO_4^-$, the redox potential of **1** shows a 'two wave behavior' with decreasing original redox potential at 200 mV and a concomitantly increasing new redox potential band at 40 mV, which is attributed to the formation of the $\mathbf{1}\cdot H_2PO_4^-$ complex in the solution. This displacement of the redox peaks was saturated with about 2.0 equiv of $H_2PO_4^-$. The same 'two wave behavior' of **1** was also observed upon addition $HP_2O_7^{3-}$ with similar sensitivity (Figures S3−S4).

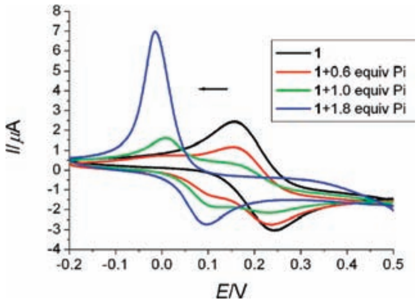

Figure 2. CV titration profile of **1** (0.2 mM) upon addition of various amount of $H_2PO_4^-$ in CH_2Cl_2 solution. Reference electrode = $Ag/AgNO_3$; supporting electrolyte = $[n\text{-}Bu_4N]PF_6$ (0.1 M); scan rate = 100 mV s^{1-}.

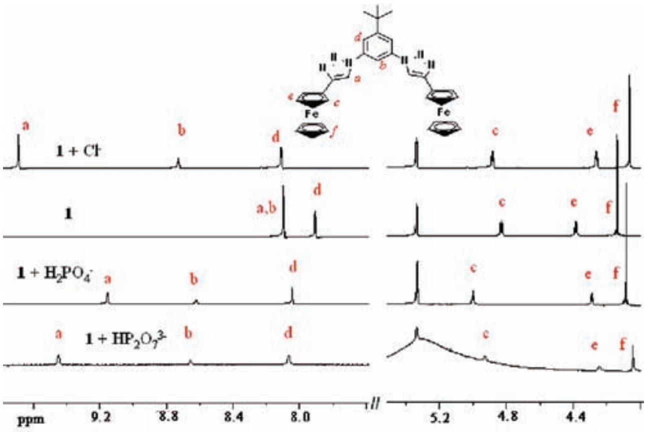

Figure 3. Partial ^1H NMR spectrum of **1** (CD_2Cl_2, 8 mM) and after addition 70 equiv of Cl^-, $H_2PO_4^-$, and $HP_2O_7^{3-}$. The broad peak in 5.3 ppm after addition of $HP_2O_7^{3-}$ can be attributed to OH protons of anion.

It is also noteworthy that in our study **1**, however, rarely showed electrochemical sensing of Cl^- although aryl triazole was reported as a marked Cl^- receptor over other anions.[6−8] To clearly understand this unexpected phenomenon, ^1H NMR titration of receptor **1** with various amounts of Cl^-, $H_2PO_4^-$, and $HP_2O_7^{3-}$ was implemented in a CD_2Cl_2 solution (Figures 3, 4, and S5−S7). In contrast to the electrochemical response, titration of Cl^- to **1** produced considerable changes in chemical shift of triazole protons (H_a) and inner cavity aryl protons (H_b) because of its strong H-bonding with Cl^-. When 70 equiv of chloride were added, the triazole proton H_a peak markedly shifted downfield from 8.09 to 9.69 ppm, and the H_b peak shifted downfield from 8.09 to 8.73 ppm, respectively. The titration curve from the chemical shift changes of H_a was programmed with EQNMR[15] to provide a 1:1 binding mode with a binding constant of 62.0 M^{-1} (Figure 4), which is similar to that of reported results.[8] In addition, the titration of $H_2PO_4^-$ or $HP_2O_7^{3-}$ to a solution of **1** also produced considerable changes in H_a and H_b peaks, demonstrating that these protons may also be involved in the ligand-anion binding system. The α protons in the cyclopentadieneyl ring (H_c) also show a downfield shift

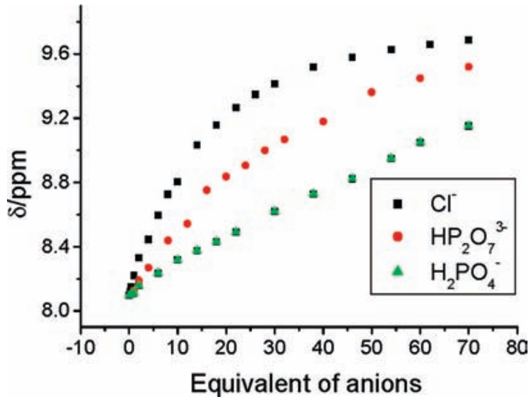

Figure 4. Changes in the triazole proton (H_a) chemical shift of **1** (CD_2Cl_2, 8 mM, 25 °C) upon the addition of different anions.

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[14] DPV removes the effect of electrode capacitive charging, resulting in measurements of only the Faradaic processes and hence in much higher signals than conventional voltammetries: Bard, A.; Faulkner, L. *Electrochemical Methods*, 2nd ed.; Wiley: New York, 2001.

with $\Delta\delta$ value of 0.17 and 0.1 ppm, respectively, upon addition of $H_2PO_4^-$ and $HP_2O_7^{3-}$. Since these protons barely change with Cl^- ($\Delta\delta$ 0.05 ppm with 70 equiv of Cl^-), we propose at this stage that the H_c is not involved in H-bonding with Cl^- unlike $H_2PO_4^-$ or $HP_2O_7^{3-}$ anions. As expected, the absence of direct contact between the ferrocene moiety and Cl^- leads to a very weak charge transfer from Cl^- to a ferrocene moiety of **1**, and therefore **1** rarely showed electrochemical sensing of Cl^-.

The binding affinity order of **1** can be expressed as $Cl^- > HP_2O_7^{3-} > H_2PO_4^-$ in regard to the chemical shift changes of H_a (Figure 4). Despite this selectivity, no electrochemical response of **1** for Cl^- was indicated because the ferrocene moiety of **1** did not take part in the H-bonding to Cl^- whereas it did in the case of $H_2PO_4^-$ and $HP_2O_7^{3-}$, which are highly consistent with NMR experiments and DFT calculations (see below).

DFT calculations have been performed to understand the binding mode of anions ($H_2PO_4^-$ and Cl^-) with a host molecule. The optimized structures of the systems, $\mathbf{1}\cdot Cl^-$ and $\mathbf{1}\cdot H_2PO_4^-$, are given in Figure 5. In the presence of anions, the host **1** prefers an *anti–anti* conformation rather than a *syn–syn* conformation for creating an electropositive cavity for the anions by rotation of C(aryl)–N-(triazole) bonds, because 1,2,3-triazole C–H protons as well as inner cavity aryl protons simultaneously can participate in bonding to capture the anions. Further, the *anti–anti* conformation is thermodynamically more stable than the *syn–syn* conformation by 0.48 kcal/mol of energy (in gas phase). According to the suggested geometry cutoffs for D–H$\cdots$A hydrogen bond definition,[16] H$\cdots$A distances should be <3.0 Å and D–H$\cdots$A angles should be $>110°$, where D and A represent, respectively, the H-bond donor and acceptor. Details of the bond lengths and bond angles are tabulated in Table S1. All the labeled protons (H_a, H_b, and H_c) in the $\mathbf{1}\cdot H_2PO_4^-$ complex H-bond with $H_2PO_4^-$. Except for H_c, other labeled protons (H_a and H_b) in the $\mathbf{1}\cdot Cl^-$ complex H-bond with the chloride anion. The distance between the H_c proton and the Cl^- ion in the $\mathbf{1}\cdot Cl^-$ complex is ~3.56 Å, which is rather larger compared to that (~ 2.49 Å) between H_c and oxygens (O1 and O3) of $H_2PO_4^-$ in the $\mathbf{1}\cdot H_2PO_4^-$ complex. This calculation, which is in accord with the ^1H NMR titration results, predicts that $H_2PO_4^-$ binds more strongly than Cl^- with cyclopentadienyl α-protons (H_c) of the ferrocene moiety. As a result, electron donation from $H_2PO_4^-$ to the ferrocene moiety of host **1** takes place efficiently and its signature is reflected by a cathodic shift in both cyclic and differential pulse voltammetry. On the other hand, needless to say, Cl^- could not be detected electrochemically by the host **1**.

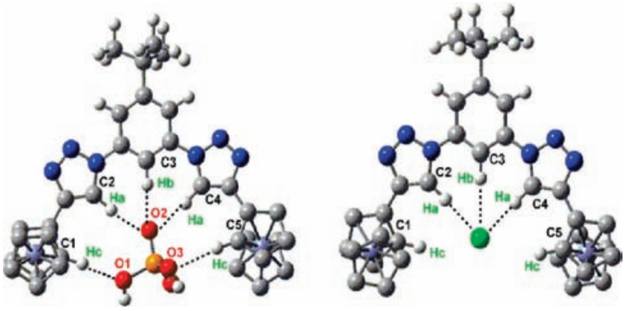

Figure 5. Calculated structure (B3LYP/6-31G*) of $\mathbf{1}\cdot H_2PO_4^-$ (left) and $\mathbf{1}\cdot Cl^-$ (right) complexes. Hydrogen atoms (except H_c) of ferrocene rings are omitted for clarity. Chloride atom is represented as green ball, and oxygen atoms are represented as red balls. Two triazole moieties are nearly in plane arrangement with appended phenyl ring in both $\mathbf{1}\cdot H_2PO_4^-$ and $\mathbf{1}\cdot Cl^-$ complexes (twisted angle is ~5°–10° in $\mathbf{1}\cdot H_2PO_4^-$ and ~10° in $\mathbf{1}\cdot Cl^-$).

In conclusion, a neutral ferrocene-appended aryl triazole receptor **1** for anions has been designed and synthesized. We found that **1** selectively recognizes a phosphate anion in such a manner that all of the triazole C–H, benzene C–H, and ferrocene C–H bonds in **1** take part in the C–H$\cdots$O hydrogen bonding, which induces a large cathodic shift in both cyclic and differential pulse voltammetry and ^1H NMR chemical shifts. By contrast, for the Cl^- binding, ferrocene CH of **1** is excluded for the H-bonding, inducing no changes in CV. DFT calculations and ^1H NMR experiments clearly elucidate different H-bonding patterns of **1** for phosphate and chloride anions, respectively. The present results still serve to underscore the utility of new recognition motifs in the design of novel anion electrochemical chemosensors, and the design based on the present article can be further modified to construct more developed systems.

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Supporting Information Available. Experimental procedures, characterization data of compound, computational details, additional electrochemical data, and crystallographic data (CIF) have been described in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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