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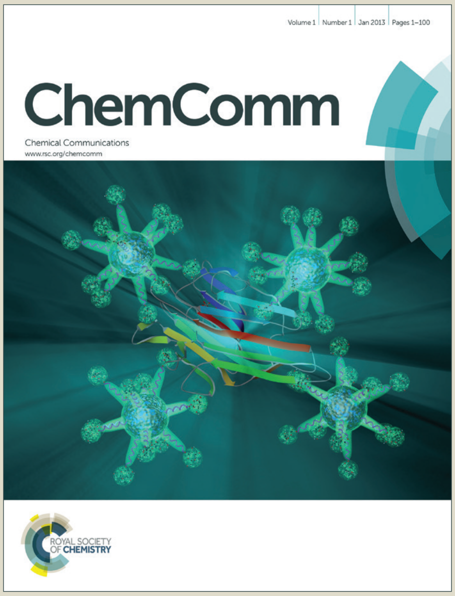

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A Triazole-bearing picket fence type nickel porphyrin as a cyanide selective allosteric host

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Kyeong-Im Hong, Hongsik Yoon, and Woo-Dong Jang*

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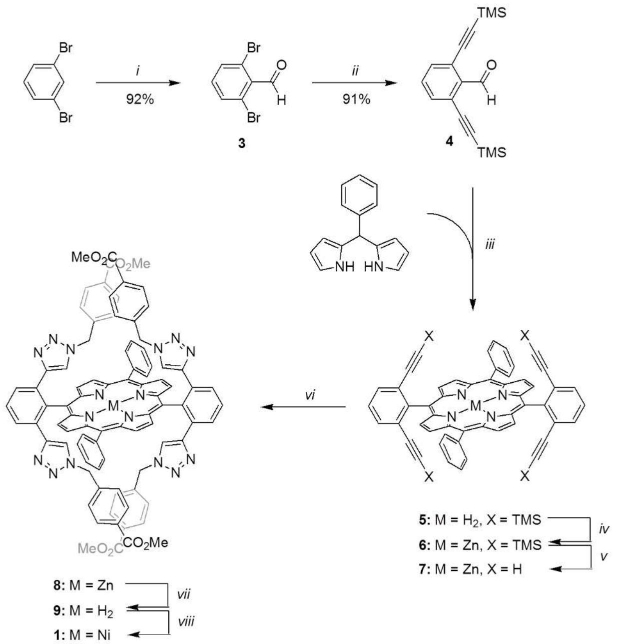
A triazole-bearing picket fence type nickel porphyrin (1) has been synthesized as a host compound for anion binding. Among various anionic species examined, cyanide was the only one that affected a spectral change of 1. Moreover, 1 exhibited strong homotropic positive allosterism against cyanide binding due to electronic effect as well as multiple hydrogen bonds formed between cyanide and the triazole groups.

Allosteric control is the most important and essential regulatory mechanism for maintaining homeostasis in biological systems.[1] Proteins with multiple guest-binding sites often display allosteric binding phenomena.[2] In this process, the first guest binding induces a conformational change in the host protein, which influences the binding affinity of additional guests. The binding of molecular oxygen to hemoglobin is a representative example. Hemoglobin is an assembly of four globular protein subunits. When the first oxygen binds to a certain subunit, conformational rearrangement of the whole protein is initiated, and the binding affinities of other subunits to molecular oxygen are enhanced. Therefore, the oxygen binding isotherm to hemoglobin becomes a sigmoidal curve.[3] Such cooperative binding is of great interest in the design of functional materials.[4] Chemists have tried to synthesize multiple guest binding host systems to establish synthetic receptors displaying positive allosterism because such positive allosteric systems could be utilized for signal amplification.[5] Recently, we have reported several porphyrin-based allosteric host systems. Among these hosts, a porphyrin-based molecular tweezer exhibited strong heterotopic positive allosterism, while a porphyrin-based macrocycle exhibited homotopic positive allosterism, which could be modulated by the addition of additional guests.[6] Although several porphyrin-based allosteric host systems have been successfully designed, application of the allosteric effect to signal amplification has scarcely been established. In this communication, we report the design of a triazole-bearing picket fence type nickel porphyrin (**1**; scheme 1) as an allosteric host, which was utilized for the selective detection of cyanide ion.



Scheme 1. Synthesis of **1**. Reagents and conditions: i) n-BuLi, diisopropyl amine, DMF, THF, -78 °C, 40 min; ii)TMS-acetylene, CuI, Pd$(PPh_3)_2Cl_2$, Et_3N, THF, in N_2, reflux; iii) propionic acid, reflux, 2 h; iv) $Zn(OAc)_2$, CH_2Cl_2/MeOH, 25 °C, 6h; v) tetrabutylammonium fluoride, THF, 25 °C, 2 h; vi) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, THF/H_2O, reflux, vii) TFA, CH_2Cl_2, 25 °C, 3 h; viii) Ni(II) acetylacetonate, Toluene, reflux, 24 h.

The synthesis of **1** is outlined in scheme 1. Briefly, a formyl group was introduced to 1,3-dibromobenzene to obtain **3**. A Sonogashira coupling reaction between **3** and trimethylsilyl (TMS)-acetylene was conducted to obtain **4**. Subsequently, the acid catalyzed condensation reaction of **4** with phenyldipyrrolemethane and subsequent oxidation resulted in the TMS-acetylene-bearing porphyrin (**5**). After introduction of zinc ion (**6**) and deprotection of the TMS groups (**7**), methyl-4-(azidomethyl)benzoate was introduced using a CuI-catalyzed alkyne-azide click reaction to obtain **8**. Finally, the central zinc ion of **8** was removed by acid treatment, and then nickel ion was introduced to obtain **1**.

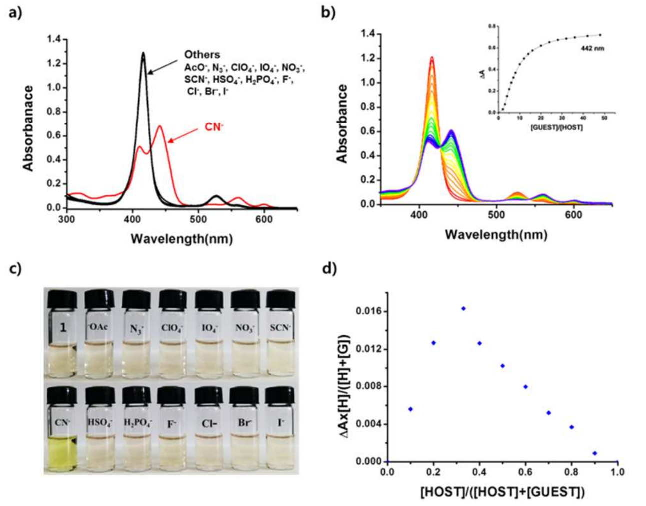


Figure 1. Absorption and visual change of **1** by addition of anions in 0.5% H_2O/MeCN. a) absorption spectra of **1** (6 μM) in the presence of various anions (50 eq.), b) UV/Vis titration of CN$^-$ (0-50 eq.) to **1** (inset: binding isotherm monitored at 442 nm), c) visual change by addition of various anions (50 eq.) to **1**, d) Job's plot of **1** with CN$^-$.

The UV/Vis absorption of **1** in 0.5% H_2O/MeCN was measured. **1** exhibited strong Soret absorption at 416 nm and weak Q band absorptions around 527 and 560 nm. As reported in our previous paper, the triazole-bearing picket fence zinc porphyrin exhibited very strong binding affinities to anionic guest species through the cooperative effects of C-H hydrogen bonds and an axial ligation interaction with the central zinc ion.[7] Because a nickel ion in the porphyrin center has relatively weaker Lewis acidic character than zinc ion, we expected that the binding affinity of anionic species would be relatively weaker with **1** than our previously reported triazole-bearing picket fence type zinc porphyrin. To confirm the binding affinities of anions to **1**, various anions were added to **1** in 0.5% H_2O/MeCN. As expected, most of the anionic species did not show a UV/Vis absorption change upon addition of a large excess of the anion (Figure 1a). Very interestingly, only the addition of cyanide ion caused a strong spectral shift of **1**, and in a UV/Vis titration study, the Soret and Q band absorptions gradually red-shifted with clear isosbestic points at 389, 428, 508, and 543 nm (Figure 1b). The binding of cyanide to **1** could also be observed with the naked eye due to a pronounced color change of the solution. As shown in Figure 1c, the cyanide containing solution exhibited a definite color change while the other solutions did not show any color change. Unlike the zinc porphyrin, the nickel porphyrin can accommodate two axial ligands to form a hexa-coordinate state. Therefore, we would expect 1:2 host-guest complex formation between **1** and cyanide ions, and the continuous variation method (Job's plot) indicated 1:2 binding of cyanide ions to **1** (Figure 1d).

The strong binding affinity of cyanide to **1** can be explained by the formation of multiple C-H hydrogen bondings between triazole groups and cyanide. To confirm the effect of triazole groups, cyanide was titrated to the tetraphenyl nickel porphyrin (NiTPP; Figure 2), structural analog of **1** without triazole groups. As result, NiTPP exhibited almost negligible absorption changes even 1000 eq. of cyanide addition in CH_2Cl_2, indicating the cooperative effect of hydrogen bondings to the coordination of cyanide (Figure S1).

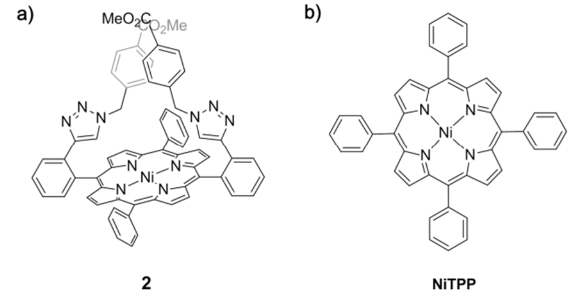


Figure 2. Structure of **2** and **NiTPP**

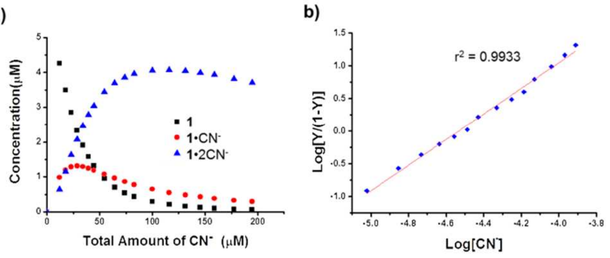


Figure 3. a) Concentration changes of **1**, **1**•CN$^-$, and **1**•2CN$^-$ upon successive addition of cyanide, b) Hill plot of **1** with cyanide.

Upon cyanide binding to **1**, the binding isotherm exhibited a sigmoidal curve (inset of Figure 1b), indicating positive allosteric behavior in the binding of cyanide to **1**. Figure 3a shows concentration changes of **1**, **1**•CN$^-$, and **1**•2CN$^-$ upon successive additions of cyanide, where the concentrations were estimated by spectral analysis using commercially available Hypspec software. This graph also clearly indicates **1** has a strong positive allosterism for cyanide binding. The cyanide binding profile was analysed using the nonlinear curve fitting method and the Hill equation: $\log(y/(1-y)) = n \log[\mathrm{CN}^-] + \log K$, where y, K, and n are the fractional saturation of host, the association constant, and the Hill coefficient, respectively.[8] The Hill plot (Figure 3b) showed a linear correlation between $\log(y/(1-y))$ and $\log[\mathrm{CN}^-]$ with a Hill coefficient of 1.96; indicating a strong positive allosteric effect exists in cyanide binding. The strong positive allosteric effect can be explained by electronic effect as well as structural changes of **1**. By the axial coordination of CN$^-$, **1** becomes paramagnetic hexacoordination state via less stable square pyramidal pentacoordiation state. On the other hand, because the triazole groups are attached to the meso phenyl rings of porphyrin, the initial cyanide binding may change the dihedral angles between the meso phenyl rings and the porphyrin plane to form stable hydrogen bonds between cyanide and the triazole groups.

Such structural alteration would provide suitable space for access of a second cyanide guest on the opposite face of the porphyrin. Therefore, the binding affinity of the second cyanide may be greatly enhanced. In fact, the first and second binding constants for cyanide binding to **1** were estimated to be 2.4 x 10^4 and 6.8 x 10^4 M^{-1}, respectively, using Hypspec. To confirm the effect of hydrogen bonding on the second guest binding, we newly synthesized **2** (Figure 2), which has only two triazole groups in same face of nickel porphyrin. Therefore, the first guest binding takes place with the aid of C-H hydrogen bonding. However, the second guest binding should be taken place without aid of hydrogen bonding. The first and second binding constants and Hill coefficient for cyanide binding to **2** were estimated to 1.9 x 10^3, 1.2 x 10^3 and 1.22, respectively (Figure S2 and Table S1). This result indicates that the electronic effect also exist in the positive allosterism of CN^- binding to **1** and **2**. Because **1** exhibited significantly increased Hill coefficient than **2**, the result obviously evidences the contribution of C-H hydrogen bonding.

One merit of porphyrins is a typically strong extinction coefficient, which enables colorimetric detection of cyanide ions at a low detection limit. In figure 1b, the UV/Vis absorption spectrum of **1** continuously changed with respect to the concentration of cyanide from 2 to 10 μM. From this data, a calibration curve for quantification of cyanide concentration could be constructed. More importantly, the change of Q band (from 510 to 580 nm) absorption showed clear symmetry, which could be utilized for ratiometric determination of the concentration. Analysis using a single wavelength often gives errors in the concentration of an analyte because the background absorption can increase the intensity of absorption at a typical point. Ratiometric analysis may provide a clear solution to this problem.

Until now, various mechanisms have been utilized for the detection of cyanide.[9] Among them, the coordination of cyanide to metal ions has often been utilized for demetallation from chromophoric host compounds.[10] The spectral change of **1** could also be induced by demetallation of nickel ion from the porphyrin core. If this were the case, the free base form of porphyrin would exhibit strong fluorescence emission. Upon fluorescence emission measurement, we could not confirm any fluorescence emission increment in **1** even after the addition of a large excess of cyanide. Moreover, the ^{1}H NMR spectrum of **1** also showed strong peak broadening with the addition of cyanide due to formation of the paramagnetic hexacoordinate state (Figure 4). Therefore, we can conclude that the binding of nickel ion to the porphyrin core is very tight and avoids undesirable absorption changes of **1** due to demetallation.

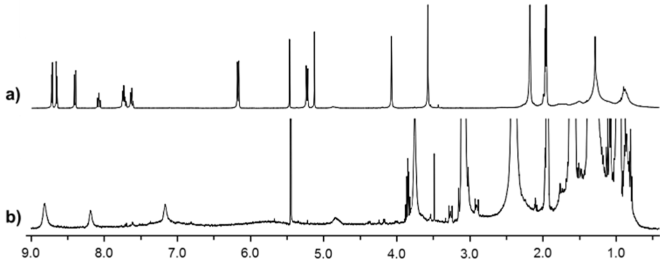


Figure 4. NMR spectra of a) **1** and b) **1** with cyanide (10 eq.) in CD_3CN, 400 MHz.

In summary, a triazole-bearing picket fence type nickel porphyrin has been designed as a host compound for anion binding. The porphyrin exhibited strong homotropic positive allosterism with cyanide binding due to multiple hydrogen bonds formed between cyanide and triazole groups. Such hosts exhibiting strong binding affinity and an allosteric mechanism could be utilized for further applications in signal amplification.

Notes and references

Department of Chemistry, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-749, Korea, E-mail: wdjang@yonsei.ac.kr.

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