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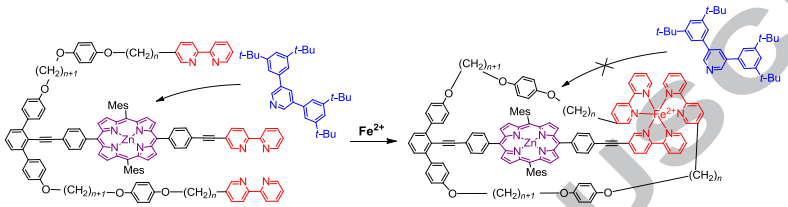

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Allosteric Regulation of the Ligand-binding Ability of Zn-porphyrin by Metal Complexation

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ABSTRACT

Zn-porphyrin with bipyridyl units at the ends of a conjugated chain, in addition to two alkyl side chains, was prepared as an artificial allosteric system. The axial ligand-binding ability of the compound was considerably reduced by the formation of a Fe(bpy)$_3$-type complex. The degree of the allosteric suppression strongly depended on both alkyl chain length and the steric demand of the pyridyl ligand.

The design and construction of artificial allosteric systems have recently been attracting considerable interest as intelligent catalysts, drug delivery reagents, and molecular machines.[1] As metalloporphyrins are extremely valuable functional units for the construction of artificial enzymes,[2] a designed allosteric system with a metalloporphyrin unit as an active site would find a wide range of applications in catalysis and receptors with switchable activity.[3] One of the most effective methods for controlling substrate-accessibility to an active site is steric shielding, which has already been applied to the allosteric regulation of catalytic activity of salen complexes.[4] However, this shielding method has not been investigated in detail for use in the allosteric regulation of ligand-binding, or for controlling the catalytic ability of metalloporphyrins. We recently reported a unique method for inducing a large conformational change in alkyl chains by metal complexation.[5] We also applied this conformational change to alter the binding constant between the Zn-porphyrin unit and axial ligands. Unfortunately, the conformational change had only a limited effect on the binding constant (1.2 times enhancement by Fe(II)), which was probably due to the large separation between the Zn-porphyrin unit and the alkyl chains. Here, we reconsider the configuration of the functional units of the newly designed allosteric system **1**, in which Zn-porphyrin was embedded in the middle of the conjugated backbone (Fig. 1). The conjugated chain had a bipyridyl unit at one end and a 1,1':3',1"-terphenyl-4,2',4"-triyl unit at the other, to which two additional bipyridyl units were attached as terminal groups through flexible alkyl chain bridges. Thus, compound **1** had a rigid bipyridyl group on one side and two flexible bipyridyl groups on the opposite side. When MX_2 (M = metal cation, X = counter anion) was added to a solution of **1**, the two flexible bipyridyl groups would come across above and below the Zn-porphyrin surface, producing an [M(bpy)$_3$]-type complex, where the alkyl chain bridges are expected to shield the Zn-porphyrin and restrain its axial ligand-binding ability. In this report, we present the preparation of **1** and the allosteric regulation of the axial ligand-binding activity.

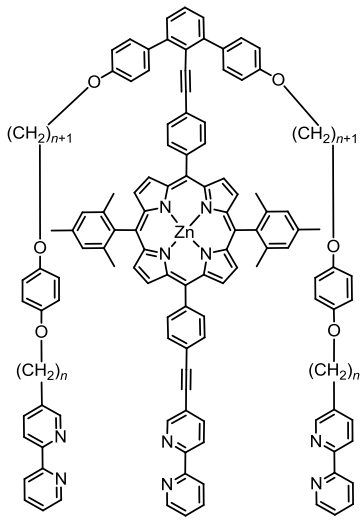

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Figure 1. Chemical Structure of allosteric system **1**.

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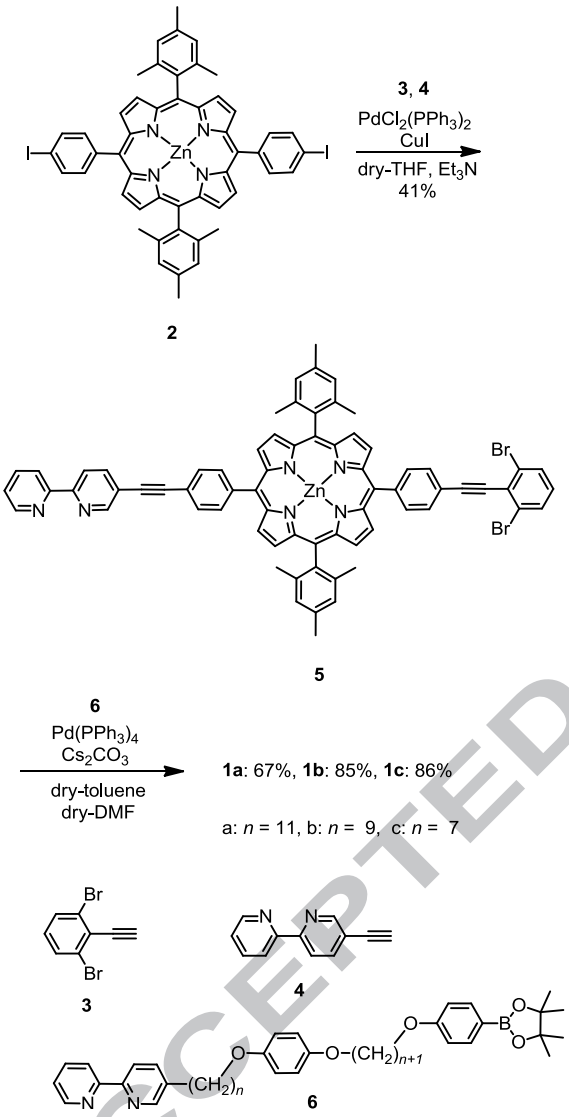
The length of the alkyl chain is significant in this system, as it affects both the stability of the [M(bpy)$_3$]-type complexes and the degree of shielding at the axial ligand-binding site in the Zn-porphyrin unit (see below). Molecular mechanics (MMFF) calculations were performed for **1** with alkyl chains of different lengths, and the results suggested that alkyl chains of n = 7–11 were suitable for the formation of the stable metal complex as well as effective shielding of the porphyrin unit.[6]



Scheme 1. Synthesis of **1**.

Allosteric system **1** was synthesized according to Scheme 1. The three-component Sonogashira coupling reaction[7] of Zn-porphyrin **2**[8] with terminal alkynes **3**[9] and **4**[5] afford Zn-porphyrin **5** in acceptable yield (41%). Side chain unit **6** was prepared from hydroquinone by stepwise condensation with bipyridyl- and pinacole borate-terminated alkyl bromides (Scheme S1). The Suzuki-Miyaura coupling reaction between **5** and **6** afforded **1** as a purple solid in moderate yields (67-86%).[10] The structures of **1** were unambiguously characterized by NMR and FAB MS measurements.

An aliquot of $Fe(BF_4)_2$ (3×10^{-4} M) in toluene/acetonitrile (1/1 (v/v)) was added to a solution of **1a** (2×10^{-5} M) in the same solvent. The complexation of **1a** (n = 11) and Fe(II) in the resulting solution was monitored by means of UV-vis spectral measurement (Fig. 2). Before the addition of Fe(II), the solution of **1a** showed the characteristic Soret band absorption (440 nm) and Q-band absorption (550−630 nm) of the Zn-porphyrin skeleton. Addition of the Fe(II) solution resulted in the appearance of the characteristic metal-ligand charge transfer (MLCT) absorption for Fe(II)(bpy)$_3$-type complexes at around 500 nm.[11] The intensity of this absorption increased linearly till it reached a plateau, which was brought about by increasing the concentration of Fe(II) to 1 equiv in the solution (Fig. 2 inset). These results indicate quantitative formation ($K_{\mathbf{1a•Fe}} > 10^6$ M^{-1}) of Fe(II)(bpy)$_3$-type complex **1a•Fe**. The production of the 1:1 complex **1a•Fe** is further supported by an MS ion peak observed at m/z = 2537 ([**1a•Fe**]$_2^+$•BF_4^-, calcd for $C_{160}H_{170}BF_4FeN_{10}O_6Zn$: 2534).

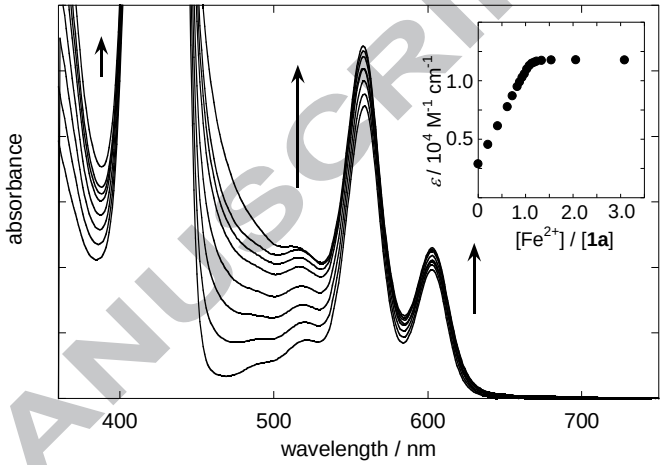
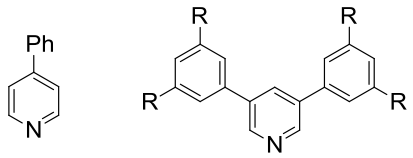


Figure 2. UV-vis spectra resulting from the titration of **1a** (2×10^{-5} M) with $Fe(BF_4)_2$•$6H_2O$ in a toluene/acetonitrile (1/1 (v/v)) solution (3×10^{-4} M). The inset shows the change in the absorbance of MLCT band at 500 nm as a function of Fe(II):**1a** concentration.

The degree of shielding at the axial ligand-binding Zn site in **1•Fe** was investigated by adding an axial ligand. 4-Phenylpyridine (**L1**) was first selected for this purpose (Fig. 3), and the ligand-binding constants for Zn coordination were compared before and after the Fe(bpy)$_3$ complexation (Table 1). The axial ligand-binding ability of **1a** was investigated by means of UV-vis titration. The selective formation of 1:1 complexes of Zn-porphyrins and pyridine derivatives is a well-established phenomenon.[12] The titration was carried out by the addition of a solution of ligand **L1** to a solution of **1a** (5×10^{-5} M) in toluene/acetonitrile (1/1 (v/v)) (Fig. 4). On adding the solution, the porphyrin Q-band of **1a** was red-shifted, which was attributed to the axial coordination of **L1** to the Zn center in **1**. The binding constant $K_{\mathbf{1a•L1}}$ was determined as $0.867 \pm 0.014 \times 10^4$ M^{-1} from the curve fitting, using the change in the absorbance at 608 nm (Fig. 4(b)).



L1 **L2**: R = H **L3**: R = *t*-Bu

Figure 3. Chemical structures of pyridyl ligands.

Similar UV-vis titration of **1a•Fe** (**1a**: 2×10^{-5} M in the presence of 1 equiv of $Fe(BF_4)_2$) in toluene/acetonitrile (1:1 v/v) with the addition of **L1** gave the binding constant $K_{\mathbf{(1a•Fe)•L1}}$ = $0.528 \pm 0.005 \times 10^4$ M^{-1} (Fig. S2). These results suggest that the formation of Fe(II)(bpy)$_3$-type complexes reduces the stability of the axial coordinated complex, (**1a•Fe**)•**L1**. The degree of the allosteric suppression for the binding of axial ligands **L*n*** with

1a•Fe compared to that with **1a** can be defined by $K_{\mathbf{1a•Ln}}/K_{\mathbf{(1a•Fe)•Ln}}$, with the higher values indicating more suppression (Table 1). Sterically more demanding ligands **L2** and **L3** were prepared to enhance the degree of the allosteric suppression (Fig. 3), with the value for $K_{\mathbf{1a•L3}}/K_{\mathbf{(1a•Fe)•L3}}$ calculated to be 1.93, which was higher than that for **L1** (Table 1, entries 1 and 3). This suggests that the steric demand of a ligand is an important factor in controlling the ligand-binding activity.

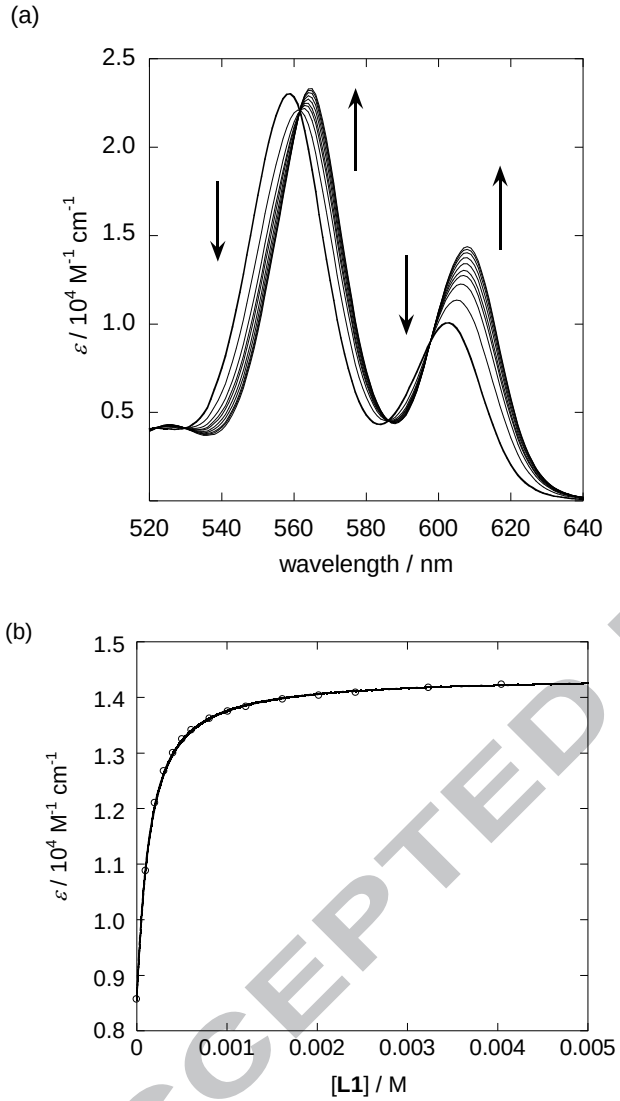


Figure 4. (a) UV-vis spectra resulting from the titration of **1a** (5×10^{-5} M) with **L1** in a toluene/acetonitrile (1/1 (v/v)) solution. (b) The change in the molar extinction coefficient of Q-band at 608 nm as a function of concentration of **L1**. The solid line is a theoretical binding curve obtained by a curve fitting.

Interestingly, the absolute values of binding constants of **L3** were found to be approximately four times higher than those of **L1** and **L2** due to stronger Lewis basicity of the nitrogen atom in **L3**.[13] A slightly smaller value of $K_{\mathbf{1a•L2}}/K_{\mathbf{(1a•Fe)•L2}}$ suggest that the suppression effect is orientation-dependent on the phenyl substituents on the axial pyridine ring.[14]

The degree of suppression of the accessibility of the ligand could be further increased by utilizing Zn-porphyrin **1** with a shorter alkyl chain. UV-vis titration using **1b** (n = 9) or **1c** (n = 7) were performed, and the binding constants with the bulkiest ligand (**L3**) in the presence and absence of Fe(II) were determined. The axial ligand-binding constant of **1** was relatively insensitive to the alkyl chain length; however, the degree of the allosteric suppression was dramatically enhanced ($K_{\mathbf{1•L3}}/K_{\mathbf{(1•Fe)•L3}}$ = 4.12 for **1b** (n = 9) and 4.53 for **1c** (n = 7)).

Table 1. The binding constants and the degrees of the allosteric suppression[a]

entry	1	Ln	$K_{\mathbf{1•Ln}}$ ($\times 10^{-4}$ M^{-1})	$K_{\mathbf{(1•Fe)•Ln}}$ ($\times 10^{-4}$ M^{-1})	$K_{\mathbf{1•Ln}}/K_{\mathbf{(1•Fe)•Ln}}$
1	**1a**	**L1**	0.867 ± 0.014	0.528 ± 0.005	1.62 ± 0.03
2	**1a**	**L2**	0.707 ± 0.005	0.465 ± 0.006	1.52 ± 0.02
3	**1a**	**L3**	3.34 ± 0.08	1.73 ± 0.02	1.93 ± 0.05
4	**1b**	**L3**	3.68 ± 0.07	0.882 ± 0.008	4.12 ± 0.09
5	**1c**	**L3**	2.94 ± 0.05	0.649 ± 0.012	4.53 ± 0.11

[a] Procedures and conditions are described in Supplementary Material.

In conclusion, we developed a novel methodology for the allosteric regulation of the axial ligand-binding ability of a Zn-porphyrin unit. Ligand accessibility to the Zn atom was considerably restrained when a metal ion (Fe(II)) was added as an external stimulus. This induced the formation of $Fe(bpy)_3$-type complex, **1•Fe**, in which two alkyl chain bridges came across above and below the Zn center in the porphyrin unit. The degree of the allosteric suppression was strongly enhanced by utilizing the sterically demanding pyridyl ligand and the allosteric system with shorter alkyl chains. The method presented in this paper is applicable for the preparation of metalloporphyrin catalysts and receptors with allosterically switchable activity.

Acknowledgments

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13. UV-vis titration of **5** (2×10^{-5} M) in toluene/acetonitrile (1:1 v/v) with the addition of **L3** gave the binding constant $K_{\mathbf{5}\cdot\mathbf{L3}} = 3.43 \pm 0.06 \times 10^4$ M^{-1} (Fig. S11). This value is essentially identical to those obtained for **1** in Table 1. These results suggest that the superior metal-binding ability of **L3**. Attractive interaction between the alkyl chain and **L3** is ruled out.
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Supplementary Material

Synthetic procedures, characterization data, UV-vis titration data, and MMFF optimized structures. This material is available free of charge via the Internet.