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Multifunctional and Chiral Porphyrins: Model Receptors for Chiral Recognition

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Introduction

Metal complexes of porphyrins and related aromatic macrocycles are important prosthetic groups and coenzymes, working as redox and rearrangement catalysts (cytochrome and vitamin B_{12}), photoreaction centers (chlorophyll), and oxygen carriers (hemoglobin). These functions are produced by both the unique features of porphyrins and controlled interactions between porphyrins and the surrounding proteins. Several pioneering works demonstrated that these functions can be artificially reconstituted in simple systems even in the absence of proteins by introducing appropriate substituents into porphyrins. For example, reversible dioxygen binding and electron transfer to quinones were successfully modeled by simple systems consisting of a functionalized porphyrin without proteins.[1]

In addition to the biologically important functions of porphyrins as prosthetic groups, porphyrins provide a potentially useful framework for artificial receptors and catalysts with several unique features:

1. An approximately planar structure owing to the π-electron conjugation. This gives a facile design of receptors having a geometrically well-defined binding pocket consisting of a porphyrin framework and recognition groups.

2. A number of metals incorporated with varying recognitions and catalytic activities.

3. Several distinct functionalization sites. A porphyrin has the meso position and β-position, central metal, and inner nitrogens for functionalization sites (Figure 1).

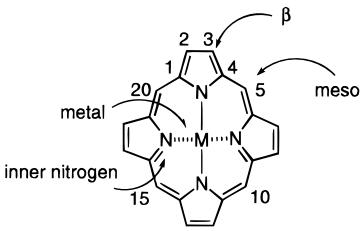

FIGURE 1. Porphyrin and its functionalization sites.

4. Chromophores for detecting subtle changes in interactions between porphyrin and surrounding molecules. UV−vis, circular dichroism, fluorescence, and resonance Raman spectroscopy have been successfully used to probe the intermolecular interactions. ^{1}H NMR spectroscopy is also useful owing to the profound ring current effects on the chemical shifts of the protons close to the porphyrin plane.

5. Characteristic redox chemistry at both metal and ligand.

6. Important photochemical behavior as an electron donor and an acceptor.

Porphyrinoid macrocycles are a related subject of interest. A number of novel ligands have been synthesized, which have been reviewed by several groups recently.[2] In this Account, we describe recent developments of the design, preparation, and molecular recognition of chiral and multifunctional porphyrins from the Kyoto group.

Porphyrin Receptors Bearing Convergent Recognition Groups

To construct a convergent array of recognition and catalytic groups on the porphyrin framework, it is advantageous to place them on the aromatic groups at meso positions, owing to the facile synthetic route and rigid fixation of the functional groups. Aromatic aldehydes having various substituents can be easily obtained, which can be condensed with appropriate pyrroles to yield 5,10,15,20-tetraarylporphyrins.[3] 5,15-Disubstituted porphyrins[4] (**1** and **2**) having convergent recognition groups (Zn and OH) were prepared by the reaction of dipyrromethanes with appropriate aromatic aldehydes (Scheme 1). A 5,10-disubstituted porphyrin[5] (**3**) was similarly prepared by condensation of tripyrrole, pyrrole, and aldehyde. For this family of compounds, atropisomers exist as typically shown for the trans (**1**) and cis (**2**) isomers. Control of the atropisomerization is an important subject of study and is described later.

Poor solubility is always a problem when we attach various polar substituents to the porphyrin framework. Generally, the solubility of the porphyrins in organic solvents rapidly decreases upon introducing polar substituents. This prevents the proper manipulation of the sample, and spectroscopic studies are very limited. We

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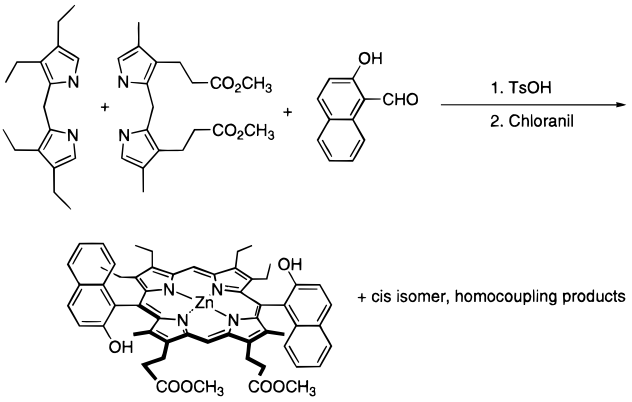
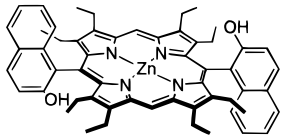
Scheme 1



found that introduction of long alkyl groups dramatically improves the solubility of porphyrins bearing polar sub-



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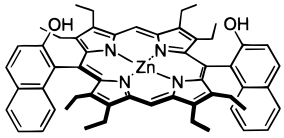

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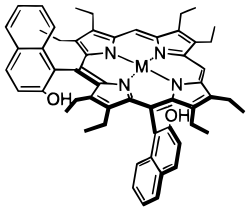

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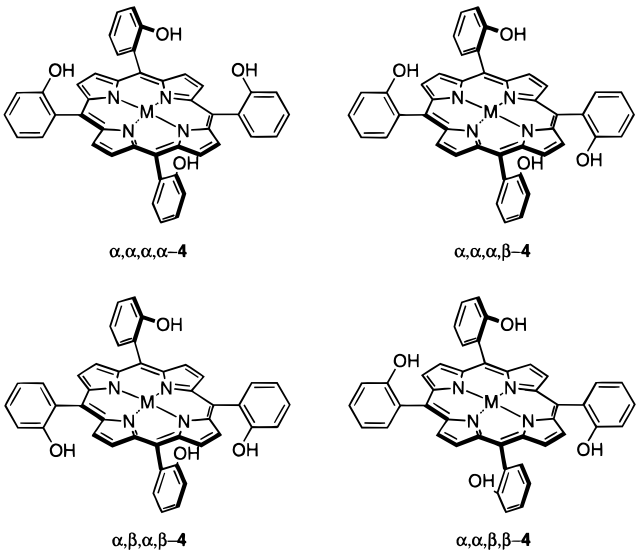
stituents in organic solvents. For instance, 5,10,15,20-tetrakis(2-hydroxyphenyl)porphyrin **4** has poor solubility in common organic solvents such as chloroform and toluene. Introduction of nonyl groups to the phenyl rings much improved the solubility so that the alkylated porphyrin was soluble (>1 mg/mL) in most organic solvents, even in hexane.[6] Similarly, 5,10,15,20-tetrakis(2-carboxyphenyl)porphyrin, which was hardly soluble in most solvents, was solubilized in organic solvent by introducing alkyl groups on the phenyl rings (see **16**).

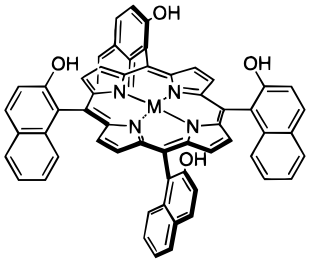
Controlling Atropisomerization

Introduction of functional groups on the meso aromatic rings gives a variety of porphyrins having a binding pocket consisting of functional groups and central metal (or inner nitrogens). Substituents introduced into the aromatic groups at the meso positions would be expected to fluctuate owing to the rotation about the phenyl-meso carbon bonds. Gottwald and Ullman were the first to report the atropisomerization rate of **4** (Scheme 2),[7] which

Scheme 2



was 1.5×10^{-5} s^{-1} in methanol at 23 °C. The atropisomerization rates for a variety of metalloporphyrins have been reported.[8] Controlling this bond rotation is the prerequisite for the proper function of the recognition groups. We found two solutions for controlling the rotation of the meso aromatic groups. Firstly, it was prevented by introducing alkyl groups on the β-positions adjacent to the meso naphthyl groups (for example, see **1**). Secondly, a porphyrin bearing four meso naphthyl groups and no β-alkyl groups does not isomerize. For instance, atropisomerization of 5,10,15,20-tetrakis(2-hydroxy-1-naphthyl)porphyrin **5** did not occur after refluxing



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in toluene for 2 h. This porphyrin showed high affinity for quinone derivatives, particularly for 2,3,5,6-tetramethoxy-1,4-benzoquinone, with a binding constant of 610 000 M^{-1} at 298 K in toluene via four hydrogen bonds as confirmed by X-ray crystallographic studies.[9]

Central Metal as Lewis Acidic Site

When metalloporphyrins are used as a receptor, a metal ion in the center of porphyrin framework can serve as a Lewis acidic site, binding Lewis bases such as amines. We compared the properties of two metal ions, Rh and Zn, as an interaction site in detail. Rhodium porphyrins show strong affinity for amines and amino acid derivatives even in polar solvents, while zinc porphyrin can bind amines only in nonpolar solvents such as toluene and chloroform. As multifunctional receptors, zinc is advantageous over

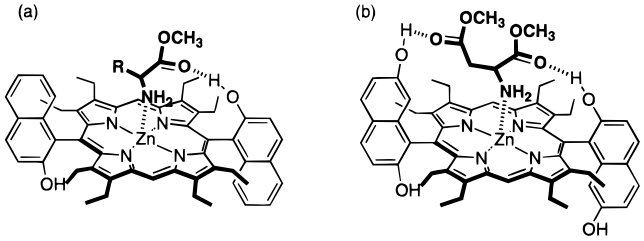


FIGURE 2. Schematic representation of binding of amino acid esters to multifunctional zinc porphyrin receptors: (a) Ditopic binding of Leu-OMe by **1**, and (b) tritopic binding of Asp(OMe)-OMe by **7**.

Table 1. Binding Constants of Amino Acid Esters by Zinc Porphyrin Receptors in $CHCl_3$ at 30 °C

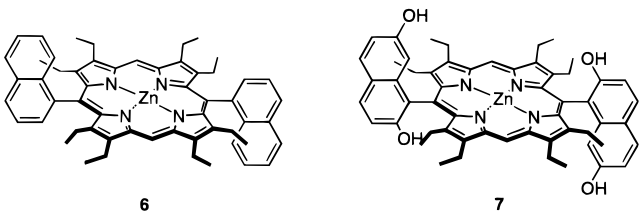
	K(**1**)	K(**7**)	K(**6**)
Leu-OMe	7300	13600	500
Asp(OMe)-OMe	2250	45800	290

rhodium owing to its weak coordinating interaction. Since the Rh···L interaction (L = ligand) is too strong, it is difficult to estimate the contribution of the second weak interaction precisely.

Multiple Recognition and Binding Kinetics

Combination of weak interactions is ubiquitous in specific binding of substrate by enzymes and of ligand by receptors. Multiple weak interactions are favored over one strong interaction because they result in (1) high selectivity for a variety of molecules and (2) fast association and dissociation kinetics.

We carried out a systematic study of molecular recognition via multiple interactions, focusing on the selectivity and binding kinetics. [*trans*-5,15-bis(2-hydroxy-1-naphthyl)porphyrinato]zinc **1** was prepared as a receptor for amino acid esters. UV−vis, ^{1}H NMR, and CD spectroscopy showed that ditopic receptor **1** binds amino acid methyl ester in chloroform through the Zn···NH_2 coordinating interaction and OH···O=C hydrogen bonding (Figure 2a).[10] The phenolic proton of **1** moved upfield upon addition of Leu-OMe, indicating that this hydroxyl group is hydrogen bonded to the ligand. The binding constants by receptor **1** are approximately 1 order of magnitude larger that those of receptor **6**, which does not have the phenolic hydroxyl group (Table 1).[11] These spectroscopic and thermodynamic data indicate that amino acid esters are bound to **1** as shown in Figure 2a.



6 **7**

For a comparative study, the trifunctionalized zinc porphyrin receptor **7** was prepared.[12] This porphyrin receptor showed marked affinity for amino acid esters with a polar side chain, particularly for dimethyl aspartate, as shown in Tables 1 and 2. Comparison of the binding

Table 2. Binding Constants of Amino Acid Esters by Zinc Porphyrin Receptors in $CHCl_3$ at 25 °C[a]

	K(**1**)	K(**7**)	K(**7**)/K(**1**)
Leu-OMe	6010	7620	1.27
Val-OMe	4490	7800	1.74
Ala-OMe	1490	4010	2.69
Trp-OMe	5720	18200	3.18
Asp(OMe)-OMe	1560	20900	13.4
Glu(OMe)-OMe	890	7820	8.77

[a] $CHCl_3$ containing 1% ethanol was used.

constants and analysis of the complexation-induced shifts of the phenolic OH protons in the ^{1}H NMR spectra revealed that the three interactions are simultaneously operating in the dimethyl aspartate−**7** complex as schematically shown in Figure 2b. Interestingly, this porphyrin receptor can discriminate the two similar amino acid esters, dimethyl aspartate and dimethyl glutamate.

In Table 3 are summarized the thermodynamic parameters for binding. The values of $-\Delta H°$ and $-\Delta S°$ increase with an increasing number of interactions operating in the ligand−receptor complex, from one (**6**−Leu-OMe, one coordination), two (**5**−Leu-OMe, coordination and one hydrogen bond), and three (**7**−Asp-OMe, coordination and two hydrogen bonds). These results show that the ligand−receptor complex becomes more ordered as the number of ligand−receptor interactions increases. From these data, we can estimate the entropy change from dissociated ligand and receptor to the complex with one coordinating interaction to be −15.4 cal·K^{-1}·mol^{-1}, from one coordinating interaction to two interactions (one coordinating and one hydrogen bond) −7.3 cal·K^{-1}·mol^{-1}, and from two interactions to three interactions (one coordinating and two hydrogen bonds) −4.1 cal·K^{-1}·mol^{-1}. The enthalpy changes of the corresponding processes were −8.3, −4.1, and −2.2 kcal·mol^{-1}, respectively. Clearly, compensation between enthalpy and entropy is operating. As the number of recognition interactions increases, smaller values of $-\Delta H°$ can lead to larger values of $-\Delta S°$. This implies that the interaction energy can be used more effectively to produce an ordered state in the multiple interaction system. The effective formation of an ordered complex is particularly important for chiral recognition (*vide infra*).

The value of $\Delta S°$ for the complex formation between porphyrin **6** and leucine methyl ester *in vacuo* by statistical thermodynamics can be calculated according to eq 1,

$$S_{\mathrm{trans}} = R\{1.5 \ln M_{\mathrm{w}} + 1.5 \ln T - \ln C + 1.3554\} \quad (1)$$

where R is the gas constant, T is the temperature in Kelvin, C in the concentration in mol·L^{-1}, and M_{w} is the molecular weight in atomic units. Formation enthalpy, translational entropy, and rotational entropy for zinc porphyrin, leucine methyl ester, and their complex were calculated by a semiempirical molecular orbital method[13] and are listed in Table 4. The observed value of $-\Delta S°$ (−22.7 cal·K^{-1}·mol^{-1}) for one coordinating interaction complex was much smaller, less than one-half the calculated translational entropy change (−39.8 cal·K^{-1}·mol^{-1}). This difference can be ascribed to (1) the entropy gain owing to the

Table 3. Free Energy Changes ($\Delta G°$/kcal·mol^{-1}, 15 °C), Enthalpy Changes ($\Delta H°$/kcal·mol^{-1}), and Entropy Changes ($\Delta S°$/cal·K^{-1}·mol^{-1}) in the Binding of Amino Acid Esters by Functionalized Zinc Porphyrins in $CHCl_3$

	7			**1**			**6**		
	$\Delta G°$	$\Delta H°$	$\Delta S°$	$\Delta G°$	$\Delta H°$	$\Delta S°$	$\Delta G°$	$\Delta H°$	$\Delta S°$
Leu-OMe	−5.96	−12.5	−22.7	−5.86	−12.4	−22.7	−3.86	−8.3	−15.4
Asp(OMe)-OMe	−6.88	−14.6	−26.8	−4.95	−11.2	−21.7	*a*	*a*	*a*
Glu(OMe)-OMe	−6.16	−13.3	−24.8	−4.75	−11.0	−21.7	*a*	*a*	*a*

[a] Not determined.

Table 4. Formation Enthalpy (ΔH_f/kcal·mol^{-1}), Translational Entropy (S_{trans}/cal·K^{-1}·mol^{-1}), and Rotational Entropy (S_{rot}/cal·K^{-1}·mol^{-1}) of Zinc Porphyrin, Leucine Methyl Ester, and Their Complex at 25 °C[a]

	Zn porphine	Leu-OMe	complex	changes upon complexation
ΔH_f	202.5	−105.7	93.0	−3.8
S_{trans}	43.6	40.8	44.6	−39.8
S_{rot}	34.8	30.0	36.8	−28.1

[a] Based on the PM3 calculation by MOPAC version 5.

replaced ligand and (2) the solvation effects. The order of entropy changes $-\Delta S$(translational) > $-\Delta S$(rotational) > $-\Delta S$(internal rotational) > $-\Delta S$(vibrational)[14] parallels that of the entropy loss as the number of recognition interactions increases from monodentate, bidentate, to multidentate binding. This can explain the observation that the ligand is more effectively fixed as the number of interactions increases.

Kinetic aspects of recognition processes are important for designing functionalized receptors and catalysts. Noncovalent forces, particularly combinations of multiple interactions, are advantageous over covalent forces for fast association and fast dissociation. This is particularly important for fast kinetic processes such as enzymatic catalysis, electron flow in metabolism, and photosynthesis. If the dissociation is slow, the whole kinetic process will be affected. The dynamics of the binding are very sensitive to subtle changes in ligand and receptor structures, as seen for the binding dynamics of aromatic guests to cyclodextrin, in which the association rate was decreased by a factor of 50 by replacing a methyl group in guest by an ethyl group.[15] For metalloporphyrin receptors, the association and dissociation rates are very dependent on the nature of the metals. The use of a zinc ion as a central metal leads to a fast rate for complex formation and dissociation. Little is known, however, of the effects of multiple interactions on the binding kinetics.

We compared the association and dissociation rates for a series of complexes between multifunctional porphyrins (**1**, **6**, and **7**) and amino acid esters. In Table 5 are listed the rate constants determined by the ^{1}H NMR relaxation time measurements. When the association rate and the dissociation rate were compared between the **1**−Asp-(OMe)-OMe complex (ditopic binding) and the **7**−Asp-(OMe)-OMe complex (tritopic binding), there is a large acceleration of association and a small deceleration of dissociation. Therefore the additional hydrogen bonding shifts the equilibrium toward complex formation without much expense of slow dissociation. These results suggest that a combination of weak interactions leads to tight

Table 5. Rate Constants for Association (k_1) and Dissociation (k_{-1}) of Complexes between Zinc Porphyrin Receptors and Amino Acid Methyl Esters[a]

	Leu-OMe		Asp(OMe)-OMe	
	$k_1/10^9$ s^{-1}·M^{-1}	$k_{-1}/10^5$ s^{-1}	$k_1/10^9$ s^{-1}·M^{-1}	$k_{-1}/10^5$ s^{-1}
6	0.75	15.0	0.72	25.0
1	2.5	3.3	1.2	5.3
7	1.6	1.2	16.0	3.6

[a] Estimated by ^{1}H NMR relaxation time measurements at 30 °C in $CDCl_3$.

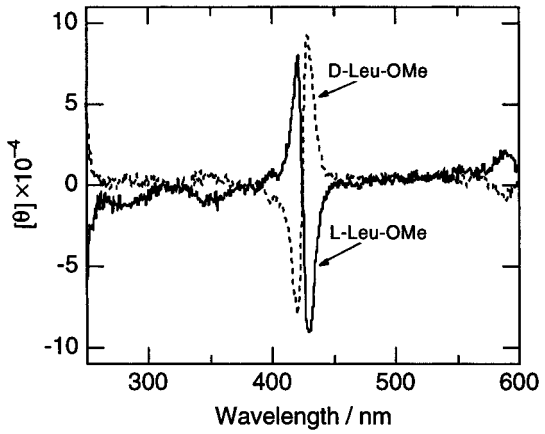


FIGURE 3. Circular dichroism spectra of a complex between L- and D-leucine methyl ester and bifunctional zinc porphyrin receptor **1** in chloroform at 15 °C.

complexation without retarding the kinetic processes, ideal behavior like that of the binding sites of enzymes, where high specificity can be achieved without suffering from a slow dissociation rate.

Induced Circular Dichroism as a Probe for Binding Mode

The chiral amino acid ester−porphyrin receptor (**1**) complexes exhibit characteristic bisignate CD only if ditopic binding of amino acid esters occurs. For instance, if the phenolic OH groups of **1** are protected with methyl groups and the OH···O═C hydrogen bond is broken, the induced CD disappears. L-Amino acid esters consistently induced bisignate induced CD in the Soret band with a negative Cotton effect at longer wavelengths and a positive Cotton effect at shorter wavelengths (Figure 3). We proposed a mechanism for the bisignate CD spectrum, where coupling between the electric and magnetic transition moments of the carbonyl groups of the amino acid esters and the electric transition moments of the porphyrin chromophores lead to the observed Cotton effects.[16] An advantage of the porphyrin is that the electronic structure of porphyrin associated with the Soret transition

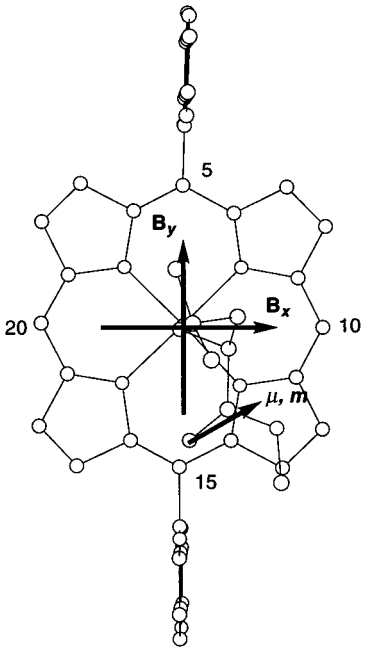
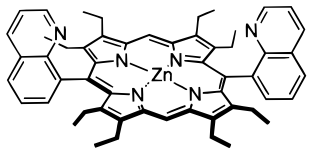


FIGURE 4. Electric and magnetic transition moments of carbonyl chromophore and porphyrin chromophore.

is conveniently approximated by the four-orbital model,[17] which greatly simplifies the theoretical treatment of the transitions. The Soret band consists of two nearly degenerate transitions, B_x and B_y, which are perpendicular to each other. In Figure 4 is shown the orientation of the transition moments of the ligand and receptor in the complex as deduced from the X-ray crystallographic study of a related complex. With this orientation, molecular orbital calculations showed that the rotational strength induced in the B_x transition has a sign opposite to that induced in the B_y transition. This prediction agreed with the observed induced CD patterns.

The induced CD of carbohydrate−**8** complexes was also explained similarly by the coupling between the transition moments of the OH groups and the CO groups and those of the porphyrin.[18]



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In natural product chemistry, CD originating from exciton coupling between the identical chromophores is a powerful technique for determining the absolute stereochemistry of a molecule.[19] In the porphyrin−amino acid ester system, there are strong differences in energy and the nature of the transition between the two chromophores. Our studies revealed that, even in this system, distinct CD was observed and the chirality of the supramolecules can be sensitively detected by it. Therefore, CD spectroscopy is powerful for elucidating the binding mode in a supramolecular system.

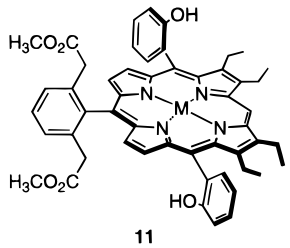
The induced CD spectra observed for the artificial receptor−ligand complexes give important information on the mechanism of the optical activity of hemoproteins.[20] Porphyrin itself is achiral, but hemoproteins exhibit characteristic induced CD in the Soret band, reflecting the interaction between achiral porphyrin and chiral proteins. Induced CD in porphyrins has been used to probe the conformational changes in proteins. The above studies showed that the carbonyl group and the OH group can induce CD in a heme if they are fixed near the porphyrin plane, implying that changes in the relative orientation of the protein peptide chain to the porphyrin can be sensitively detected by induced CD.

Intrinsically Chiral Porphyrins

There are several strategies for designing chiral porphyrins. By introducing substituents into the rigid porphyrin framework, a chiral porphyrin can be prepared without any chiral auxiliary substituents. The first chiral porphyrin of the strapped type was prepared according to this idea, although enantiomer separation was unsuccessful.[21] Later, Inoue *et al.* separated enantiomers of the strapped porphyrin and used the porphyrin as a P-450-type oxygenation catalyst.[22,23]

Meso-substituted C_2 symmetric porphyrins attract interest due to their simplicity and versatile synthetic procedures. *trans*-5,15-Disubstituted porphyrin **9** and *trans*-5,10-disubstituted porphyrin **10** were prepared by us (Figure 6).[24] The chirality of **9** and **10** can be understood if one sees that they belong to the same point group as *trans*-1,2-disubstituted cyclohexane/cyclobutane and *trans*-1,3-disubstituted cyclohexane/2-cyclobutanone, respectively (Figure 5).

Chiral porphyrin **11**, having three recognition groups with different natures, a Lewis acid (Zn), a hydrogen-bonding donor (OH), and a steric interaction/hydrogen-bonding acceptor (CH_2COOCH_3), was prepared as an enantioselective receptor for amino acid derivatives.[25]



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Comparison of binding affinities among a series of ligands and a ^{1}H NMR study suggest that the Zn···NH_2 coordination and OH···O=C hydrogen bonding fix the ligand orientation and interactions between the CH_2COOCH_3 group of **11** and the side chain of amino acid esters become different between L- and D-amino acid esters. This receptor showed binding for amino acid esters with moderate enantiomeric excesses in the range 33−47% at 15 °C in $CHCl_3$. The enantiomeric excess increased with increasing the hydrogen-bonding energy between the OH group of **11** and the C=O group of the guest, demonstrating that chiral discrimination originates from restriction of the rotational freedom of the guest via ditopic binding.

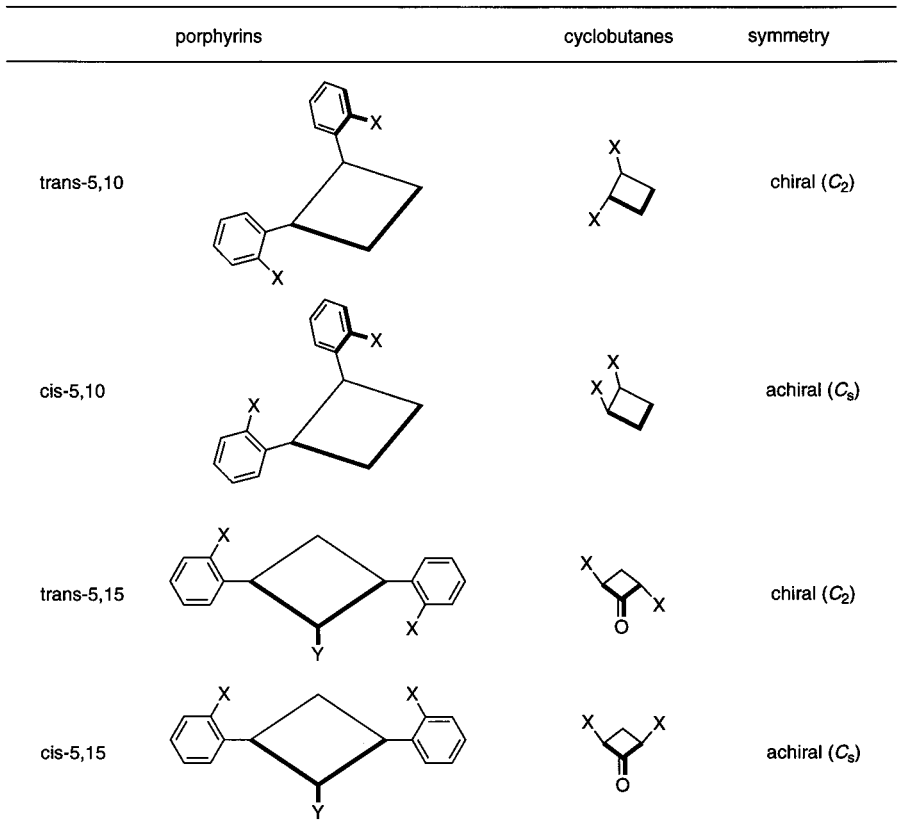


FIGURE 5. Symmetry of *trans*-5,10- and 5,15-disubstituted porphyrins and simpler cyclobutane derivatives.

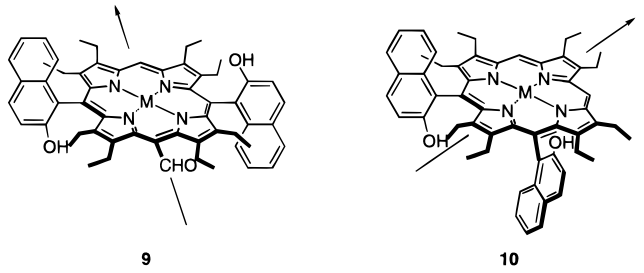


FIGURE 6. C_2 symmetric chiral porphyrins. C_2 axes are shown by arrows.

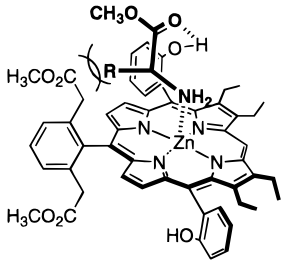


FIGURE 7. Schematic representation of binding of chiral amino acid esters to multifunctional chiral zinc porphyrin receptors.

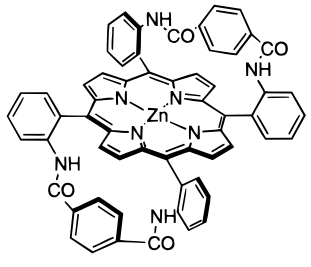
Interestingly, the D/L-enantioselectivity was predictable from the nature of the ligand−receptor interactions. One enantiomer of **11** systematically preferred the L-enantiomer of most of the amino acid esters except for Ser. This enantioselectivity can be readily explained if we assume that steric repulsion exists between the CH_2COOCH_3 group in that enantiomer of **11** and the side chain groups of most of the amino acid esters, while attractive hydrogen bonding exists between the CH_2COOCH_3 group and the serine OH group (Figure 7).

Synthesis of C_2 symmetric strapped porphyrin (**12**·H_2) is straightforward as shown in Scheme 3.[26] The reaction of α,α,β,β-tetrakis(2-aminophenyl)porphyrin having an achiral framework with dissymmetric bridging reagents yields meso and racemic porphyrins. In Table 6 are listed the binding constants of amino acid esters by two enantiomers of **12**·Zn. The enantioselectivity toward amino acid esters was quite high, which originates from the different acidities of the two NH groups owing to the electron-withdrawing effects of the nitro group. The

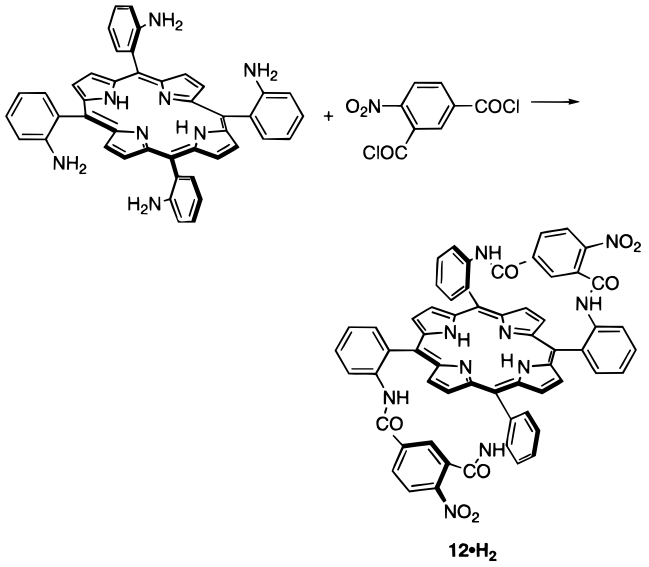
Table 6. Binding Constants (M^{-1}) between 12·Zn and *ent*-12·Zn and Amino Acid Esters in CH_2Cl_2 at 20 °C and Free Energy Differences (kcal·mol^{-1})

	Phe-OMe	Val-OMe	Ala-OMe
(+)-**12**·Zn	7.1×10^4	1.1×10^5	4.4×10^4
(−)-**12**·Zn	5.0×10^5	8.2×10^5	1.8×10^5
$\Delta\Delta G°$	1.14	1.17	0.82

enantiomeric excesses for phenylalanine methyl ester, alanine methyl ester, valine methyl ester, and leucine ethyl



Scheme 3



12•H$_2$

ester at 20 °C in CH_2Cl_2 were 75−80%. In the ligand−receptor complex, three interactions, the Zn···NH_2 coordination, NH···O═C hydrogen bonding, and the phenyl group···side chain steric interaction, are simultaneously operating, leading to the high enantioselectivity.

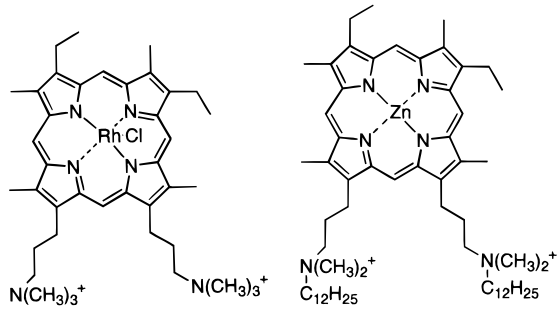
Other examples for intrinsically chiral porphyrins are etioporphyrins (C_{4h}) having a bulky meso substituent[27] or an alkyl group at an inner nitrogen.[28] Aida *et al.* reported a more dynamic system consisting of a fully substituted porphyrin with D_2 symmetry. The chirality was induced by addition of a chiral guest, and the porphyrin remained chiral after replacing the chiral guest with an achiral guest.[29]

Extrinsic Chiral Porphyrins

Another strategy for preparing chiral porphyrins is to attach a chiral group to an achiral porphyrin (extrinsic chiral porphyrin). Groves *et al.* reported a chiral porphyrin having a chiral amino acid moiety attached to an achiral porphyrin framework. This porphyrin was able to catalyze the P-450-type oxygenation reaction enantioselectively.[30] Following this work, several extrinsic chiral porphyrins were reported.[31] Chiral dimeric porphyrins were also prepared using a variety of chiral bridges such as Tröger's base,[32] cyclohexanediamine,[33] cholesterol,[34] and binaphthyl.[35]

Molecular Recognition in Water and Protein Recognition by Porphyrins with Divergent Functional Groups

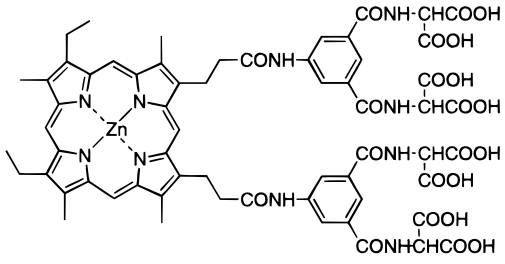
Introduction of divergent functional groups into the porphyrin was used to modify the solubility as exemplified for the alkylated porphyrins with improved solubility in organic solvents. A rhodium porphyrin (**13**)[36] and a zinc porphyrin (**14**)[37] having two divergent ammonium groups were soluble in water and served as a receptor and a carrier for nucleotides, respectively. The ammonium groups make the porphyrin water-soluble, and they can also interact with the anionic phosphate groups of nucleotide. The rhodium porphyrin has strong affinity with a slow association/dissociation rate, while the zinc porphyrin has moderate affinity with a fast association/dissociation rate. Accordingly, the rhodium porphyrin worked as a receptor for nucleic acids in water, and the zinc porphyrin as a carrier of nucleotides across a liquid membrane. The binding constants between the rhodium porphyrin and dAMP (deoxyadenosine monophosphate) showed sigmoidal dependence on pH with a binding constant 500 M^{-1} at pH < 6.5 and 1000 M^{-1} at pH > 8. These results revealed that the Coulombic interaction between the phosphate group of ligand and the ammonium group of the receptor contributes to the tight binding. We estimated that the contribution of the coordination interaction between rhodium and the amino group to $\Delta G°$ of overall binding was −3.2 kcal/mol while that of the Coulombic interaction between ammonium and phosphate was −0.4 kcal/mol.



13 **14**

The zinc porphyrin **14** having ammonium groups with long alkyl chains acts as a carrier for nucleotides. The rate of transport of AMP was much faster than those of other nucleotides.

Electron transfer occurring in metabolic processes is regulated by controlling the protein−protein distance and orientation through an appropriate interfacial zone on the protein surface. Amino acid side chains on the protein surface are responsible for this recognition. We designed a porphyrin derivative having an assembly of recognition groups for a protein or a redox counterpart. By introducing interaction groups at the β-positions, we prepared a meso porphyrin having eight carboxylate groups in the side chain. The meso porphyrin moiety is to be recognized by protein (apomyoglobin), and eight carboxylates serve as interaction groups toward a cationic redox counterpart. When this porphyrin (**15**) was reconstituted



15

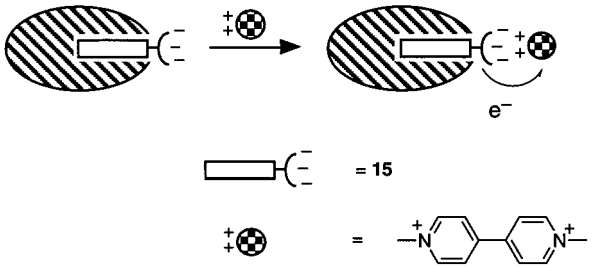
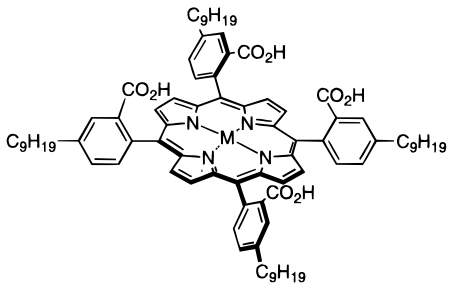


FIGURE 8. Reconstituted myoglobin with porphyrin octacarboxylate.

into myoglobin,[38] the reconstituted protein worked as an artificial electron transfer protein, which photochemically reduces viologen efficiently through an electrostatic attractive interaction between the anionic charge on the carboxylates and the cationic charge on viologen (Figure 8). From the fluorescence lifetime determination, the rate of electron transfer from the singlet excited state of porphyrin to viologen was estimated to be on the order of 10^7 s^{-1}. This study demonstrated that synthetic modification of porphyrins can alter the functions of heme proteins.

Convergent and Divergent Recognition Groups: Self-Assembly

Porphyrin assembly has attracted interest due to the important role of porphyrins in the photoreaction center. A number of covalently linked porphyrin assemblies have been reported.[39] We can extend our strategy to design a functionalized porphyrin, which spontaneously forms an assembly. A porphyrin having four carboxylic acid groups **16** dimerized through multiple hydrogen bonding to



16

construct a binding pocket for a guest in nonpolar solvents such as toluene, benzene, chloroform, and dichloromethane. In polar solvents such as methanol, dimethyl sulfoxide, and THF, the hydrogen bonds break and only the monomeric form exists. The binding pocket formed in the dimer was particularly well organized for binding of diamines such as pyrazine.[40] Dimeric **16** bound pyrazine in its dimeric binding pocket with a binding constant larger than 10^7 M^{-1} in CH_2Cl_2 at 25 °C. Interestingly, a pyrazine derivative with a side chain can also be bound similarly as shown in Figure 9. If we attach other recognition groups to the side chain of pyrazine, this 2:1 complex becomes a supramolecular unit having additional recognition groups. This unique ternary complex can be used as a further building block for higher self-assembling

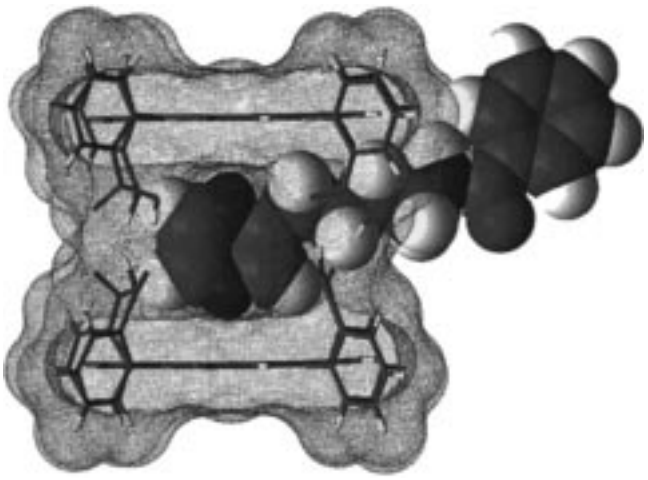


FIGURE 9. Dimeric porphyrin binding a pyrazine derivative having a side chain.

systems. This opens a new strategy for preparation of complex molecular architectures which are not accessible from synthetic organic chemistry.

Concluding Remarks

Design and synthesis of multifunctional porphyrins and its application to chiral recognition are described. As general requirements for the receptor design, control of solubility and kinetics features are discussed. Control of atropisomerization is particularly important for designing receptors using a porphyrin framework. Multiple recognition is characterized by enthalpy changes and entropy changes associated with each interaction between recognition groups. Efficient chiral recognition is related to an efficiently produced ordered state, which can be measured through entropic changes upon formation of a "bond" between recognition groups. Finally, applications of multifunctional porphyrins to protein recognition and self-assembly are described.

References

(1) For reviews of functionalized porphyrins, see: (a) Morgan, B.; Dolphin, D. *Synthesis and Structure of Biomimetic Porphyrins*; Morgan, B., Dolphin, D., Eds.; Springer-Verlag: Berlin, 1987; Vol. 64, p 115. (b) Kim, R. M.; Fate, G. D.; Gonzales, J. E.; Lahiri, J.; Ungashe, S. B.; Groves, J. T. *NATO ASI Ser., Ser. C* **1995**, *459 (Bioinorganic Chemistry)*, 49−56. (c) Ogoshi, H.; Mizutani, T. *Biomimetic Reactions Catalyzed by Metalloporphyrins*; Murakami, Y., Ed.; Elsevier: Oxford, U.K., 1996; Vol. 4, pp 337−385.

(2) (a) Sessler, J. L.; Kral, V.; Hoehner, M. C.; Chin, K. O. A.; Davila, R. M. *Pure Appl. Chem.* **1996**, *68*, 1291−1295. (b) Vogel, E. *Pure Appl. Chem.* **1996**, *68*, 1355−1360. (c) Floriani, C. *J. Chem. Soc., Chem. Commun.* **1996**, 1257−1263.

(3) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827−836.

(4) Ogoshi, H.; Sugimoto, H.; Nishiguchi, T.; Watanabe, T.; Matsuda, Y.; Yoshida, Z. *Chem. Lett.* **1978**, 29.

(5) Aoyama, Y.; Saita, K.; Toi, H.; Ogoshi, H.; Okamoto, Y. *Tetrahedron Lett.* **1987**, *28*, 4853.

(6) Hayashi, T.; Asai, T.; Hokazono, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 12210.

(7) Gottwald, L. K.; Ullman, E. F. *Tetrahedron Lett.* **1969**, *36*, 3071.
(8) (a) Walker, F. A.; Avery, G. L. *Tetrahedron Lett.* **1971**, *52*, 4949−4952. (b) Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 3660. (c) Hatano, K.; Anzai, K.; Kubo, T.; Tamai, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3518−3521. (d) Freitag, R. A.; Whitten, D. G. *J. Phys. Chem.* **1983**, *87*, 3918.
(9) Hayashi, T.; Miyahara, T.; Hashizume, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 2049−2051.
(10) Mizutani, T.; Ema, T.; Yoshida, T.; Kuroda, Y.; Ogoshi, H. *Inorg. Chem.* **1993**, *32*, 2072.
(11) Mizutani, T.; Murakami, T.; Ogoshi, H. *Tetrahedron Lett.* **1996**, *37*, 5369.
(12) Mizutani, T.; Murakami, T.; Kurahashi, T.; Ogoshi, H. *J. Org. Chem.* **1996**, *61*, 539.
(13) Stewart, J. J. P. *QCPE Bull.* **1989**, *9*, 10.
(14) For internal rotational entropy, see: Mizutani, T.; Ema, T.; Ogoshi, H. *Tetrahedron* **1995**, *51*, 473−484. Vibrational entropy is small and will not change much upon complexation except for that associated with recognition groups.
(15) Cramer, F.; Saenger, W.; Spatz, H.-C. *J. Am. Chem. Soc.* **1967**, *89*, 14−20.
(16) Mizutani, T.; Ema, T.; Yoshida, T.; Renne, T.; Ogoshi, H. *Inorg. Chem.* **1994**, *33*, 3558.
(17) (a) Gouterman, M. *J. Mol. Spectrosc.* **1961**, *6*, 138. (b) Gouterman, M.; Wagniere, G. H. *J. Mol. Spectrosc.* **1963**, *11*, 108.
(18) (a) Mizutani, T.; Murakami, T.; Matsumi, N.; Kurahashi, T.; Ogoshi, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1257. (b) Mizutani, T.; Kurahashi, T.; Murakami, T.; Matsumi, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *119*, 8991−9001.
(19) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.
(20) Hsu, M. C.; Woody, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 3515.
(21) Ogoshi, H.; Sugimoto, H.; Yoshida, Z. *Tetrahedron Lett.* **1976**, 4477−4480.
(22) Konishi, K.; Oda, K.-i.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 1313−1317.
(23) Chiang, L. C.; Konishi, K.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1992**, 254−256.
(24) Ogoshi, H.; Saita, K.; Sakurai, K.; Watanabe, T.; Toi, H.; Aoyama, Y. *Tetrahedron Lett.* **1986**, *27*, 6365.
(25) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240.
(26) Kuroda, Y.; Kato, Y.; Higashioji, T.; Hasegawa, J.; Kawanami, S.; Takahashi, M.; Shiraishi, N.; Tanabe, K.; Ogoshi, H. *J. Am. Chem. Soc.* **1995**, *117*, 10950−10958.
(27) Konishi, K.; Miyazaki, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1990**, *112*, 5639.
(28) Konishi, K.; Takahata, Y.; Aida, T.; Inoue, S.; Kuroda, R. *J. Am. Chem. Soc.* **1993**, *115*, 1169−1170.
(29) Furusho, Y.; Kimura, T.; Mizuno, Y.; Aida, T. *J. Am. Chem. Soc.* **1997**, *119*, 5267−5268.
(30) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.
(31) (a) Boitrel, B.; Lecas, A.; Rose, E. *Tetrahedron Lett.* **1988**, *29*, 5653−5656. (b) Naruta, Y.; Tani, F.; Maruyama, K. *Chem. Lett.* **1989**, 1269−1272. (c) O'Malley, S.; Kodadek, T. *J. Am. Chem. Soc.* **1989**, *111*, 9116−9117. (d) Ohkubo, K.; Sagawa, T.; Kuwata, M.; Hata, T.; Ishida, H. *J. Chem. Soc., Chem. Commun.* **1989**, 352−354. (e) O'Malley, S.; Kodadek, T. *Tetrahedron Lett.* **1991**, *22*, 2445. (f) Marx, T.; Breitmaier, E. *Liebigs Ann. Chem.* **1992**, 183−185. (g) Barry, J.; Kodadek, T. *Tetrahedron Lett.* **1994**, *36*, 2465. (h) Vilain, S.; Maillard, P.; Momenteau, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1697−1698. (i) Collman, J. P.; Lee, V. J.; Kellen-Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, *117*, 692−703.
(32) Crossley, M. J.; Hambley, T. W.; Mackay, L. G.; Try, A. C.; Walton, R. *J. Chem. Soc., Chem. Commun.* **1995**, 1077. Crossley, M. J.; Mackay, L. G.; Try, A. C. *J. Chem. Soc., Chem. Commun.* **1995**, 1925.
(33) (a) Ema, T.; Nemugaki, S.; Tsuboi, S.; Utaka, M. *Tetrahedron Lett.* **1995**, *36*, 5905. (b) Ema, T.; Misawa, S.; Nemugaki, S.; Sakai, T.; Utaka, M. *Chem. Lett.* **1997**, 487.
(34) Matile, S.; Berova, I.; Nakanishi, K.; Novkova, S.; Philipova, I.; Blagoev, B. *J. Am. Chem. Soc.* **1995**, *117*, 7021.
(35) Hayashi, T.; Nonoguchi, M.; Aya, T.; Ogoshi, H. *Tetrahedron Lett.* **1997**, *38*, 1603.
(36) Kuroda, Y.; Hatakeyama, H.; Inakoshi, N.; Ogoshi, H. *Tetrahedron Lett.* **1993**, *34*, 8285.
(37) Kuroda, Y.; Hatakeyama, H.; Seshimo, H.; Ogoshi, H. *Supramol. Chem.* **1994**, *3*, 267.
(38) Hayashi, T.; Takimura, T.; Ogoshi, H. *J. Am. Chem. Soc.* **1995**, *117*, 11606.
(39) Balzani, V.; Scandola, F. *Supramolecular Photochemistry*; Ellis Horwood Limited: Chichester, U.K., 1991.
(40) Kuroda, Y.; Kawashima, A.; Urai, T.; Ogoshi, H. *Tetrahedron Lett.* **1995**, *36*, 8449−8452. Kuroda, Y.; Kawashima, A.; Hayashi, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *119*, 4929−4933.

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