# Recognition of α-Amino Acid Esters by Zinc Porphyrin Derivatives via Coordination and Hydrogen Bonding Interactions. Evidence for Two-Point Fixation from Thermodynamic and Induced Circular Dichroism Spectroscopic Studies

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Association constants between [*trans*-5,15-bis(2-hydroxy-1-naphthyl)-2,3,7,8,12,13,17,18-octaethylporphyrinato]-zinc(II) (**1**) and a series of α-amino acid esters ($RCHNH_2CO_2CH_3$) were determined in chloroform by use of a UV-vis titration method. Association constants increased in the order Ala-OMe < Gly-OMe < Val-OMe < Leu-OMe, showing a preference for bulky amino acid esters. Contributions from the metal coordination and hydrogen bonding interactions to the total free energy change were estimated by use of reference compounds having no hydrogen bonding site. The free energy change for the binding of Leu-OMe to **1** in chloroform at 15 °C was −5.3 kcal/mol, which was separated into two contributions, (1) the metal coordination interaction $\Delta G_{MC} = -3.8$ kcal/mol and (2) the hydrogen bonding interaction $\Delta G_{HB} = -1.5$ kcal/mol. Circular dichroism (CD) induced in the porphyrin Soret band of **1** by complexation with optically active amino acid esters was of the split type for all the amino acid esters examined, whereas induced CD of a reference host, [*trans*-5,15-bis(2-methoxy-1-naphthyl)-2,3,7,8,12,13,-17,18-octaethylporphyrinato]zinc(II) (**2**), was reduced in intensity and not of the split type. We found that the fixation of the carbonyl group of the guest by two-point recognition caused marked enhancements in induced CD. We suggest that the induced CD of **1** was caused by the coupling between the magnetic transition dipole moment of the carbonyl group of guest and the electric transition dipole moment of the Soret band of host.

Differentiation of amino acids or their derivatives is a key step in protein synthesis, and how aminoacyl-transfer RNA synthases can recognize a specific amino acid is an interesting problem from a chemical point of view. Consequently, recognition of amino acids or their derivatives has been a challenging subject in biomimetic chemistry.[1] Multiple interactions should be employed to recognize amino acids such as hydrogen bonding, coordination interaction, Coulomb interaction, hydrophobic interaction, charge-transfer interaction, etc. As a simple model for multiple recognition of amino acid derivatives, we constructed a host molecule bearing both coordination and hydrogen bonding recognition sites, *trans*-[5,15-bis(2-hydroxy-1-naphthyl)-2,3,7,8,-12,13,17,18-octaethylporphyrinato]zinc(II) (**1**).[2] Host-guest interactions were characterized by thermodynamic (UV-vis titration), circular dichroism (CD), and $^1$H NMR spectroscopic studies.

Circular dichroism spectroscopy has been widely used in order to elucidate the conformation of the host-guest complex including hemoproteins.[3] It has also been used to investigate intermolecular interactions between porphyrins and other chromophores.[4] However, for naturally occurring porphyrin-protein complexes, it is usually difficult to determine which interaction plays a critical role in inducing CD among many intra- and intermolecular interactions, which in turn leads to the difficulty of interpretation of the CD spectra. Because of the structural simplicity, the present host-guest system is also a good model to investigate the mechanism of CD induced in the achiral porphyrin chromophore by a chiral environment.

## Experimental Section

$^1$H NMR spectra were recorded on either a JEOL GX-400 or a JEOL JNM FX 90Q FT NMR spectrometer, and chemical shifts are reported relative to internal $Me_4Si$. UV-vis spectra were recorded on either a Hitachi U-3410 spectrometer or a Hewlett-Packard 8452 diode array spectrophotometer with a thermostated cell compartment. Circular dichroism spectra were recorded on a JASCO J-600 spectropolarimeter with a thermostated cell compartment, which is calibrated with an aqueous solution containing 0.06 wt % ammonium *d*-camphor-10-sulfonate. Mass spectra were obtained with a JEOL JMS DX-300 mass spectrometer. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 $F_{254}$.

**Materials.** *trans*-5,15-Bis(2-hydroxy-1-naphthyl)-2,3,7,8,12,13,17,-18-octaethylporphyrin was prepared according to the reported method.[5]

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Zinc was incorporated by the method reported in the literature,[6] and the zinc complex **1** obtained was recrystallized from dichloromethane–hexane; mp >250 °C dec; TLC $R_f$ 0.39 ($CHCl_3$); UV–vis ($CHCl_3$) $\lambda_{max}$ [nm (log ε)] 419 (5.45), 544 (4.26), 580 (4.09); FAB MS (3-nitrobenzyl alcohol matrix, chloroform solvent) shows a cluster of peaks at 881–888 amu (calcd for $C_{56}H_{56}N_4O_2Zn{\cdot}H^+$ 881 and 883). Anal. Calcd for $C_{56}H_{56}N_4O_2Zn$: C, 76.22; H, 6.40; N, 6.35. Found: C, 75.45; H, 6.32; N, 6.15.

[*trans*-5,15-Bis(2-methoxy-1-naphthyl)-2,3,7,8,12,13,17,18-octaethylporphyrinato]zinc(II) (**2**) was prepared by methylation of the two hydroxyl groups of **1** with methyl iodide using potassium carbonate as a base in acetone and purified by column chromatography on silica gel, followed by recrystallization from dichloromethane–hexane: mp >300 °C; TLC $R_f$ 0.67 ($CHCl_3$); $^1H$ NMR ($CDCl_3$, ppm) δ 0.85 (t, 12 H, $CH_3$), 1.85 (t, 12 H, $CH_3$), 2.4 (m, 4 H, $CH_2$), 2.7 (m, 4 H, $CH_2$), 3.8 (s, 6 H, $OCH_3$), 4.0 (m, 8 H, $CH_2$), 6.5–8.5 (m, 12 H, naphthalene ring protons), 10.25 (s, 2 H, meso); IR (KBr) no OH; UV–vis ($CHCl_3$) $\lambda_{max}$ [nm (log ε)] 418 (5.53), 544 (4.27), 580 (4.00); FAB MS (3-nitrobenzyl alcohol matrix, chloroform solvent) shows a cluster of peaks at 909–940 amu (calcd for $C_{58}H_{60}N_4O_2Zn{\cdot}H^+$ 909 and 911). Anal. Calcd for $C_{58}H_{60}N_4O_2Zn{\cdot}2CH_2Cl_2$: C, 66.70; H, 5.97; N, 5.19. Found: C, 66.73; H, 5.98; N, 5.17.

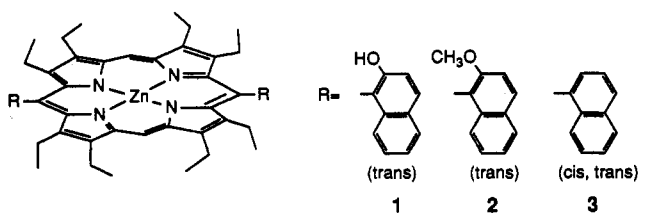
*trans*-5,15-Bis(1-naphthyl)-2,3,7,8,12,13,17,18-octaethylporphyrin was prepared according to the literature,[5] and the zinc complex **3** was obtained in the usual manner.[6] Complex **3** was used as a trans and cis isomer mixture: mp >300 °C; TLC $R_f$ 0.52 ($CHCl_3$:hexane = 1:1); UV–vis ($CHCl_3$) $\lambda_{max}$ [nm (log ε)] 416 (5.55), 542 (4.25), 578 (4.00); FAB MS (3-nitrobenzyl alcohol matrix, chloroform solvent) shows a cluster of peaks at 849–854 amu (calcd for $C_{56}H_{56}N_4Zn{\cdot}H^+$ 849 and 851). Anal. Calcd for $C_{56}H_{56}N_4Zn{\cdot}CH_2Cl_2{\cdot}0.5C_6H_{14}$: C, 73.65; H, 6.70; N, 5.73. Found: C, 74.42; H, 6.45; N, 6.00.

Amino acid methyl ester hydrochlorides used were commercially available or were prepared from the corresponding amino acids by the thionyl chloride method.[7] After neutralization and extraction with dichloromethane, all amino acid esters except tryptophan methyl ester were freshly distilled just before use for UV–vis titration, CD measurements, or $^1H$ NMR titration experiments. 4-Heptylamine and *n*-butylamine were also commercially available and distilled.

**UV–Vis Spectrophotometric Titration.** To a solution of $3.4 \times 10^{-6}$–$5.3 \times 10^{-6}$ M of **1** (or **2** or **3**) in chloroform was added a stock solution of α-amino acid ester in chloroform at 15 °C, and changes in absorbance at 414–416 nm and at 428–430 nm of the Soret band were monitored at eight different concentrations of the guest molecules. The association constants were calculated assuming 1:1 complexation[8] by use of a computer-assisted nonlinear least squares method within 4% error. The concentration range of α-amino acid esters was $3 \times 10^{-5}$–$1 \times 10^{-2}$ M for host **1** and $3 \times 10^{-4}$–$7 \times 10^{-2}$ M for hosts **2** and **3**.

## Results and Discussion

Three host porphyrins **1–3** were prepared in order to investigate the relationship between the structure of the hosts and their recognition abilities for amino acid esters. Host **1** has two




recognition sites, a metal coordination site and a hydrogen bond donor site, while host **2** lacks the hydrogen bond donor site and host **3** lacks the hydrogen bonding site. We used hosts **2** and **3** as reference hosts in order to evaluate additional stabilizing energies associated with the hydrogen bonding interaction.

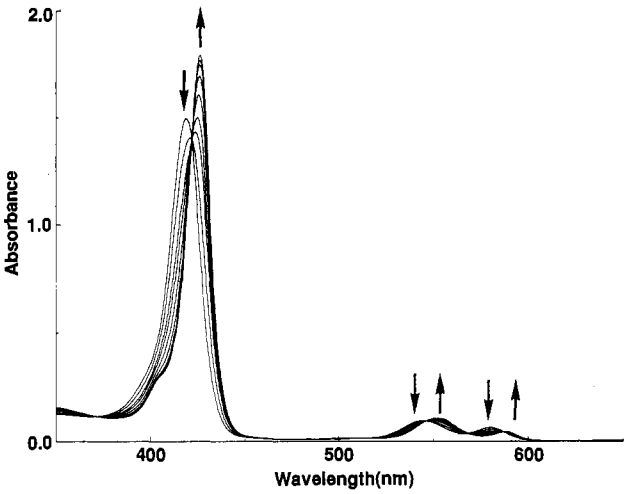



**Figure 1.** Electronic absorption spectra of a solution of host **1** ($5.3 \times 10^{-6}$ M) in the presence of varying concentrations of L-leucine methyl ester (0, $3.03 \times 10^{-5}$, $9.01 \times 10^{-5}$, $1.49 \times 10^{-4}$, $2.90 \times 10^{-4}$, $6.02 \times 10^{-4}$, $1.22 \times 10^{-3}$, $1.82 \times 10^{-3}$, $3.28 \times 10^{-3}$ M) in chloroform at 15 °C. Arrows indicate absorbance changes with increasing guest concentrations.

**Table I.** Association Constants Observed for the Binding of Amino Acid Esters and Related Compounds to Hosts **1** and **2** in Chloroform at 15 °C

| guest | $K_a(\mathbf{1})/M^{-1}$ | $K_a(\mathbf{2})/M^{-1}$ | $K_a(\mathbf{1})/K_a(\mathbf{2})$ |
|---|---|---|---|
| Gly-OMe | $(3.46 \pm 0.04) \times 10^3$ | $(9.15 \pm 0.19) \times 10^2$ | 3.8 |
| L-Ala-OMe | $(2.23 \pm 0.03) \times 10^3$ | $(3.29 \pm 0.06) \times 10^2$ | 6.8 |
| L-Val-OMe | $(8.07 \pm 0.11) \times 10^3$ | $(3.51 \pm 0.07) \times 10^2$ | 23.0 |
| L-Leu-OMe | $(1.09 \pm 0.015) \times 10^4$ | $(2.72 \pm 0.06) \times 10^2$ | 40.0 |
| L-Phe-OMe | $(3.66 \pm 0.05) \times 10^3$ | $(9.89 \pm 0.17) \times 10^2$ | 3.8 |
| L-Trp-OMe | $(1.02 \pm 0.008) \times 10^4$ | $(1.63 \pm 0.01) \times 10^3$ | 6.3 |
| L-Asp-Ome | $(2.28 \pm 0.05) \times 10^3$ | $(3.03 \pm 0.06) \times 10^2$ | 7.5 |
| L-Glu-OMe | $(1.71 \pm 0.02) \times 10^3$ | $(2.16 \pm 0.02) \times 10^2$ | 7.9 |
| L-Leu-OBu$^t$ | $(1.78 \pm 0.03) \times 10^3$ | –[b] | –[c] |
| (*S*)-leucinol[a] | $(9.87 \pm 0.12) \times 10^3$ | $(5.29 \pm 0.09) \times 10^3$ | –[d] |
| 4-heptylamine | $(4.25 \pm 0.05) \times 10^3$ | $(1.50 \pm 0.04) \times 10^3$ | 2.8 |
| *n*-butylamine | $(4.45 \pm 0.04) \times 10^3$ | $(1.57 \pm 0.04) \times 10^3$ | 2.8 |

[a] Association constant between (*S*)-leucinol and **3** was $(2.48 \pm 0.05) \times 10^3$ $M^{-1}$. [b] $K_a(\mathbf{3}) = (3.90 \pm 0.10) \times 10^2$ $M^{-1}$. [c] $K_a(\mathbf{1})/K_a(\mathbf{3}) = 4.5$. [d] $K_a(\mathbf{1})/K_a(\mathbf{3}) = 4.0$.

Complexation experiments were performed in chloroform solution. Visible spectroscopy, CD spectroscopy, and $^1H$ NMR spectroscopy were employed to observe the specific interactions between the hosts and the guests.

**UV–Vis Spectrophotometric Titration.** A representative example of visible spectral change of host **1** induced by the addition of amino acid esters is shown in Figure 1. Several isosbestic points are observed in the spectra, indicating 1:1 complexation between **1** and the guest molecule. Least-squares curve fitting of the absorbance change to the theoretical relation based on the assumption of 1:1 complexation afforded the association constants $K_a$. The association constants are summarized in Table I.

Association constants between **1** and amino acid esters were in the range $2.0 \times 10^3$–$1.1 \times 10^4$ $M^{-1}$, while those between **2** and

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(9) The association enhancements due to hydrogen bonding were also estimated by use of a reference host **3**, which lacks the hydrogen bonding site. In this case the difference in the steric repulsion energies between the hydrogen bonding complex and the reference non-hydrogen bonding complex was assumed to be negligible. The $\Delta G_{HB}$ was thus estimated to be –0.8 to –0.9 kcal/mol for Leu-OBu$^t$ and leucinol, respectively (Table II). We also estimated the hydrogen bonding energy in a similar system, where the binding of Leu-OMe, Val-OMe, Pro-OMe, Phe-OMe, and Ala-OMe to [*trans*-5,15-bis(2-hydroxyphenyl)-2,3,17,18-tetraethyl-10-phenylporphyrinato]zinc(II) was investigated by use of a reference host. In these systems, the values of $\Delta G_{HB}$ ranged from –0.9 to –1.4 kcal/mol (to be submitted). These results indicate that the order of magnitude of $\Delta G_{HB}$ should not change to a large extent by changing the reference system. However care must be taken when comparing the values of $\Delta G_{HB}$ obtained on the basis of the different reference system.

**Table II.** Hydrogen Bonding, Metal Coordination, and Total Free Energy Changes (kcal/mol) Evaluated by Use of Reference Hosts and Guests at 15 °C

| host | guest | $\Delta G_{HB}$ | $\Delta G_{MC}$ | $\Delta G_{Total}$ | reference compd |
|---|---|---|---|---|---|
| 1 | Gly-OMe | −0.2 | −4.5 | −4.7 | *n*-butylamine |
| 1 | L-Leu-OMe | −1.5 | −3.8 | −5.3 | 4-heptylamine |
| 1 | L-Leu-OBu$^t$ | −0.9 | −3.4 | −4.3 | 3[a] |
| 1 | (*S*)-leucinol | −0.8 | −4.5 | −5.3 | 3[a] |
| 2 | (*S*)-leucinol | −0.4 | −4.5 | −4.9 | 3[a] |

[a] $\Delta G_{HB} = -RT \ln [K_a(1 \text{ or } 2) - \text{guest})/K_a(3 - \text{guest})]$.

amino acid esters were in the range $2.0 \times 10^2$–$1.6 \times 10^3$ $M^{-1}$. The higher recognition capacity of host **1** than host **2** can be ascribed to the hydrogen bonding interaction between the carbonyl oxygen of amino acid esters and the hydroxyl group on the naphthyl moiety of **1**. For aliphatic amino acid esters, **1** showed a preference for bulky amino acid esters. The association constants increased in the order Ala-OMe < Gly-OMe < Val-OMe < Leu-OMe. This trend may reflect the geometrical complementarity between the guest and the recognition cavity of host **1** and can be ascribed to the stronger London's dispersion forces between host and guest for bulkier amino acid esters.[10] Host **2** showed the opposite preference for the aliphatic amino acid ester series, the least bulky guest (Gly-OMe) being bound most strongly. These observations suggest that the recognition site in **2** is more sterically crowded due to the methoxy groups.

Aromatic amino acid esters exhibited somewhat different association behavior. Because of the low solubility of aromatic amino acid esters in chloroform, UV–vis spectrophotometric titration studies were carried out for only Phe-OMe and Trp-OMe. These amino acid esters were bound to host **2** more strongly than aliphatic amino acid esters. Since host **2** has no hydrogen bond donor site, the association enhancements of aromatic amino acid esters should be ascribed to other interactions. A space-filling model suggested that aryl–aryl stacking interactions stabilize the association complex.

The magnitude of association constants of Asp-OMe and Glu-OMe to host **1** was similar to that of Ala-OMe to host **1**. This indicates that the presence of a carboxy group in the amino acid residue does not lead to an increase in the magnitude of association constants.

The ratio of $K_a(1)$ to $K_a(2)$ is a qualitative measure of the association enhancement due to hydrogen bonding interaction. In the aliphatic series of amino acid esters, the ratio increases as the residue becomes bulkier, with Leu-OMe being the largest. This trend may be ascribed to the conformational change of amino acid esters upon complexation to the porphyrin host. The coordination interaction between the amino group in the guest and the zinc in the host makes the residue tilt away from the porphyrin plane, due to steric repulsions between the bulky residue (R) of the guest and the porphyrin plane. These steric repulsions would direct the ester group to the hydroxyl group of the naphthyl moiety, leading to a favorable conformation for hydrogen bonding to take place.

The ratio of $K_a(1)$ to $K_a(2)$ involves contributions from steric repulsions between the methyl group of **2** with the amino acid esters and any electrostatic (dipolar or quadrupolar) interaction between the amino moiety of the guest and electric field produced by the host in addition to the hydrogen bonding interaction. Free energy changes due to hydrogen bonding can be estimated by correcting the ratio of $K_a(1)$ to $K_a(2)$ for the above interactions using reference guest molecules,[1m] which are primary amines with similar bulkiness and have no hydrogen bonding sites. We used 4-heptylamine as a reference guest for Leu-OMe and *n*-butylamine for Gly-OMe, respectively. Association enhancements due to hydrogen bonding ($K_{HB}$) were thus estimated from the equation:

$$K_{HB} = \frac{K_a(1 - \text{Guest})/K_a(2 - \text{Guest})}{K_a(1 - \text{Reference Guest})/K_a(2 - \text{Reference Guest})}$$

The values of hydrogen bonding free energy are summarized in Table II, together with the values of $\Delta G_{MC}$ and $\Delta G_{Total}$, which are calculated by the equations:

$$\Delta G_{HB} = -RT \ln K_{HB}$$

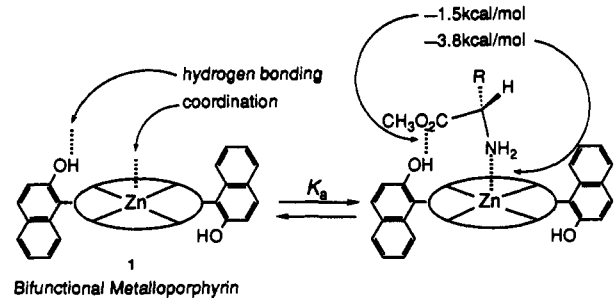
$$\Delta G_{Total} = -RT \ln K_a(1)$$

$$\Delta G_{MC} = \Delta G_{Total} - \Delta G_{HB}$$

The $\Delta G_{MC}$ term involves contributions from entropy changes upon complexation and steric repulsion energies such as those between the naphthyl groups of host and the amino acid residue of guest in addition to the metal coordination energy. The contribution from hydrogen bonding to free energy change of association ($\Delta G_{HB}$) was evaluated as −1.5 kcal/mol for Leu-OMe (Scheme I) and −0.2 kcal/mol for Gly-OMe, respectively.[9] The larger magnitude of $\Delta G_{MC}$ for a less bulky aliphatic amino acid ester (Gly-OMe) than a bulkier one (Leu-OMe) suggests that the former guest may not lose rotational entropy upon coordination, allowing nearly free rotation along the N–$C_\alpha$ bond in the complex. On the other hand, aliphatic amino acid esters with bulkier residues (Leu-OMe and Val-OMe) may lose a considerable amount of the rotational entropy upon coordination. The difference in $\Delta G_{MC}$ can thus be explained by the differences in the rotational entropy. In addition, the rotational restriction in the case of Leu-OMe will allow the carbonyl group to be in close proximity to the hydroxyl group of the naphthyl group. A space-filling model suggested that the hydrogen bonding interaction between the carbonyl oxygen atom and the naphthyl hydroxyl group is entropically favorable in the Leu-OMe–**1** complex. We suppose that this mechanism will account for the differences in $\Delta G_{HB}$ and $\Delta G_{MC}$ observed for the binding to the host **1**.

To explain the differences in $\Delta G_{Total}$ observed for the binding to host **1**, another factor, the rigidity of the guest molecules, should be important. Because of the differences in the bulkiness of the residues of the guests, the energy barrier for rotation around the $\alpha$-carbon–carbonyl carbon would change, resulting in the difference in distribution of the distances between amino nitrogen and carbonyl oxygen atoms. In order to be bound through two-point fixation, the distance should be fixed. In the case of Leu-OMe, the bulky *sec*-butyl group may fix the N···O(=C) distance to some extent even in the uncomplexed state, and consequently, entropy loss upon two-point fixation will be smaller. On the other hand, in the case of Gly-OMe, the distance fluctuates in the uncomplexed state, resulting in a large entropy loss upon two-point fixation.

**Scheme I**




**$^1$H NMR Studies.** The hydrogen bonding interaction was also studied by $^1$H NMR spectroscopy. The spectral change of host **1** in $CDCl_3$ at 22 °C induced by the addition of L-Leu-OMe is shown in Figure 2. The signal of the naphthyl hydroxyl protons shifted to lower magnetic field as the concentration of L-Leu-

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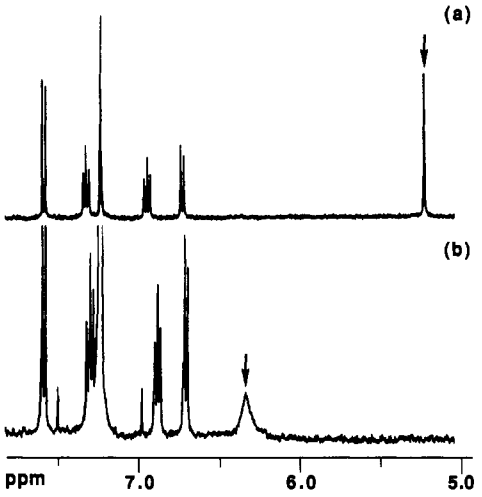


**Figure 2.** $^1$H NMR of host **1** (2.3 mM) (a) in the absence of and (b) in the presence of L-leucine methyl ester (32 mM) in $CDCl_3$ at 22 °C. The signals of hydroxyl protons of **1** are indicated by arrows.

**Table III.** Induced CD of the Complexes of Hosts **1** or **2** with Amino Acid Esters in Chloroform Solution at 15 °C[a]

| | [θ] (×10$^{-4}$)[b] | |
|---|---|---|
| | **1** | **2** |
| | 3.0 (421 nm) | |
| L-Ala-OMe | 0.0 (426 nm) | –[c] |
| | –2.6 (431 nm) | |
| | 8.5 (422 nm) | |
| L-Val-OMe | 0.0 (426 nm) | –[c] |
| | –7.8 (431 nm) | |
| | 8.3 (422 nm) | |
| L-Leu-OMe | 0.0 (425 nm) | –[c] |
| | –9.9 (430 nm) | |
| | 4.5 (422 nm) | |
| L-Phe-OMe | 0.0 (425 nm) | –4.5 (426 nm) |
| | –9.3 (430 nm) | |
| | 9.7 (422 nm) | |
| L-Trp-OMe | 0.0 (426 nm) | –6.9 (427 nm) |
| | –15.1 (431 nm) | |
| | 3.8 (422 nm) | |
| L-Asp-OMe | 0.0 (425 nm) | –[c] |
| | –4.2 (430 nm) | |
| | 3.9 (422 nm) | |
| L-Glu-OMe | 0.0 (425 nm) | –[c] |
| | –3.1 (430 nm) | |
| | 5.6 (421 nm) | |
| L-Leu-OBu$^t$ | 0.0 (426 nm) | –[d] |
| | –8.7 (432 nm) | |
| (*S*)-leucinol | –2.7 (430 nm) | –3.2 (430 nm)[e] |

[a] All the CD spectra were recorded under the conditions that more than 90% of the porphyrin was complexed with a guest. Induced CD spectra were also measured for D-amino acid esters. It was confirmed that the spectra were mirror image of the L-isomer. [b] Errors were within ±10%. [c] Negligibly small. [d] Not measured for host **2** but negligibly small for host **3**. [e] Negligibly small for host **3**.

OMe increased. This clearly indicates that hydrogen bonding between the carbonyl oxygen of the guest and the naphthyl hydroxyl group occurs.[11]

**Circular Dichroism Studies of Complexation.** The circular dichroism (CD) spectra induced in the Soret region upon complexation with optically active α-amino acid esters were specific for the host–guest combination. The complex between **1** and L- (and D-) Leu-OMe, where hydrogen bonding is operating, showed split Cotton effects in the Soret region (Figure 3a). On the contrary, **2**-L- (and D-) Leu-OMe complex exhibited no appreciable Cotton effect.[12] These two types of induced CD were recognized for all aliphatic and aromatic amino acid esters; that is, the induced CD in **1** is of the split type and that in **2** is not (Table III).[13] It is noteworthy that all the hydrogen bonding host–guest complexes (**1**–amino acid esters) exhibit split Cotton effects. Thus, the hydrogen bonding interaction can be easily detected and studied by measuring induced CD for the present system.[14] Furthermore, in all complexes with L-amino acid esters, the longer-wavelength peak of the Soret band was negative and the shorter-wavelength peak was positive. These results suggest that the induced CD reflects the spatial orientation around the

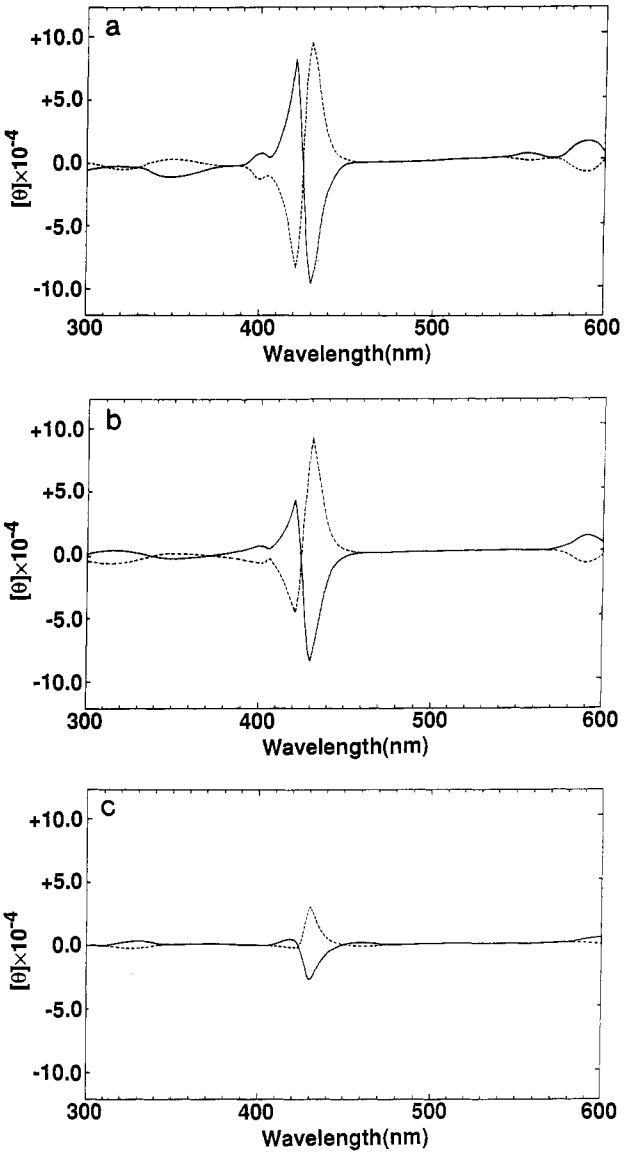


**Figure 3.** Circular dichroism spectra of a solution of host **1** ($4.8 \times 10^{-6}$ M) and (a) L- (—) and D- (- - -) leucine methyl ester ($3.3 \times 10^{-3}$ M), (b) L- (—) and D- (- - -) phenylalanine methyl ester ($3.3 \times 10^{-3}$ M), and (c) (*S*)- (—) and (*R*)- (- - -) leucinol ($5.7 \times 10^{-3}$ M) in chloroform at 15 °C.

(11) (a) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082. (b) Tadayoni, B. M.; Huff, J.; Rebek, J., Jr. *Ibid.* **1991**, *113*, 2247. (c) Vincent, C.; Hirst, S. C.; Garcia-Tellado, F.; Hamilton, A. D. *Ibid.* **1991**, *113*, 5466.

(12) Host **2** did not show any Cotton effects in the presence of much more concentrated chiral amino acid ester. For example, no Cotton effects were observed for a solution of **2** in L-Val-OMe–$CHCl_3$ = 1:1 (v/v).

(13) Most of natural hemoproteins exhibit single-peak CD in the Soret region, and some exhibit split Cotton effects; see: Myer, Y. P.; Pande, A. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 3, pp 271–322.

(14) The association constant was also determined by CD titration. By use of CD titration, the only hydrogen-bonded complex can be detected and we can evaluate the association constant for the hydrogen-bonded complex and non-hydrogen-bonded complex separately. The association constant for the **1**–L-Val-OMe complex determined by this method was $7.8 \times 10^3$ $M^{-1}$, in a good agreement with that determined by UV–vis titration.

chiral carbon directly. For aliphatic amino acid ester–**1** complexes, positive and negative peaks of the CD induced in the Soret region exhibited almost the same intensity, while for aromatic amino acid ester–**1** complexes, the induced CD was not symmetric and the longer-wavelength peak of the induced CD (the negative peak in the case of L-amino acid esters) was stronger than the shorter-wavelength peak (Figure 3b). The single-peak CD observed for the complexes between **2** and the aromatic amino acid esters can be explained by the coupling between the electric transition dipole moment of the aromatic moiety of the guest and that of the porphyrin chromophore. On the basis of the UV–vis titration experiments, it is evident that aryl–aryl interactions between hosts and guests are operating. Therefore, in the case of the complexes between host **1** and aromatic amino acid esters, two interactions (hydrogen bonding and aryl–aryl interaction) make the contribution to the observed Cotton effects additively.

Because the Soret band consists of two nearly degenerate transitions ($B_x$ and $B_y$) in a porphyrin plane,[15] the two being perpendicular to each other, it is reasonable to assume that the positive and negative peaks are assignable to the two nearly degenerate transitions. We considered three possible mechanisms for the split-type Cotton effects:[16] (1) the hydrogen bonding would fix the orientation of the carbonyl group of guest, and consequently, the coupling between the magnetic transition dipole moment of the carbonyl group and the electric transition dipole moment of the Soret transitions of porphyrins will cause the Cotton effects in the Soret band; (2) the hydrogen bonding would make the naphthyl group tilt in a chiral fashion, and the coupling of the electric transition dipole moment of the naphthyl group and the electric transition dipole moment of the Soret band will cause the Cotton effects; or (3) ruffling of the porphyrin plane to a chiral form in the hydrogen-bonded complex would result in the Cotton effects.

Mechanism 2 was first ruled out, since the coupling between the naphthyl electric transition dipole moment and the two Soret electric transition dipole moments should induce Cotton effects with the same sign in both $B_x$ and $B_y$ bands as shown below. On the basis of Tinoco's theory,[17] the coupling between two electric transition dipole moments will give the rotational strength $R_A$:

$$R_A = -\frac{2\pi}{c}\frac{\nu_a\nu_b V_{ij}(\mathbf{R}_i - \mathbf{R}_j)\cdot(\boldsymbol{\mu}_j \times \boldsymbol{\mu}_i)}{h(\nu_b^2 - \nu_a^2)}$$

where $\nu_a$ and $\nu_b$ are the transition frequencies for the porphyrin Soret band and the $\pi$–$\pi^*$ transition of the naphthyl group, respectively, $\boldsymbol{\mu}_i$ and $\boldsymbol{\mu}_j$ are the electric transition dipole moments of the porphyrin Soret band and the $\pi$–$\pi^*$ transition of the naphthyl group, respectively, $c$ is the velocity of light in vacuum, and $h$ is Planck's constant. The perturbation term $V_{ij}$, the potential energy, can be calculated by use of the dipole–dipole approximation:

$$V_{ij} = \frac{|\boldsymbol{\mu}_i||\boldsymbol{\mu}_j|}{r_{ij}^3}\{\mathbf{e}_i\cdot\mathbf{e}_j - 3(\mathbf{e}_i\cdot\mathbf{e}_{ij})\cdot(\mathbf{e}_j\cdot\mathbf{e}_{ij})\}$$

where $\mathbf{e}_i$ and $\mathbf{e}_j$ are unit vectors parallel to the electric transition dipole moment $\boldsymbol{\mu}_i$ and $\boldsymbol{\mu}_j$, respectively, and $\mathbf{e}_{ij}$ is a unit vector parallel to a line connecting centers of the chromophores of porphyrin and the naphthyl group. When we substitute $\mathbf{e}_i = (\cos\varphi, \sin\varphi, 0)$, $\mathbf{e}_j = (0, \sin\theta, \cos\theta)$, and $\mathbf{e}_{ij} = (1, 0, 0)$ in the above equations, where $\theta$ is the tilt angle of the naphthyl group and $\varphi$ is the angle of electric transition dipole moments in the porphyrin plane (Figure 4), then we obtain

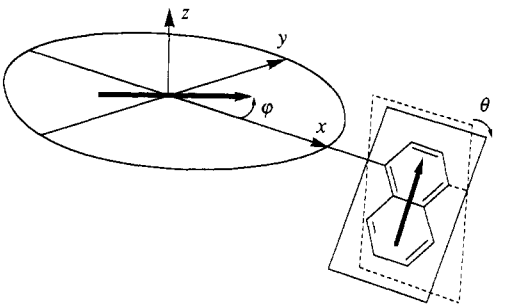


**Figure 4.** Orientation of electric transition dipole moments of porphyrin and naphthyl chromophores.

$$R_A \propto \sin^2\varphi \sin\theta\cos\theta$$

Therefore, the sign of the rotational strength does not vary even if the angle $\varphi$ varies. This relation suggests that the induced CD caused by mechanism 2 cannot be of the split type.

Mechanism 1 can explain the split Cotton effects if the angle between the magnetic transition dipole moment of the carbonyl group and the electric transition dipole moments of the Soret band is appropriate. According to Tinoco's formalism based on perturbation theory,[17] the rotational strength expected on the basis of this mechanism can be calculated from the equations:

$$R_x = \frac{2\nu_a \text{ Im } V_1\boldsymbol{\mu}_x\cdot\mathbf{m}}{h(\nu_b^2 - \nu_a^2)}$$

$$R_y = \frac{2\nu_a \text{ Im } V_2\boldsymbol{\mu}_y\cdot\mathbf{m}}{h(\nu_b^2 - \nu_a^2)}$$

where $R_x$ and $R_y$ are the rotational strengths induced in the Soret region, $\nu_a$ and $\nu_b$ are the transition frequencies for the porphyrin Soret band and the n–$\pi^*$ transition of a carbonyl group, respectively, $\boldsymbol{\mu}_x$ and $\boldsymbol{\mu}_y$ are the two electric transition dipole moments of the nearly degenerate porphyrin Soret bands $B_x$ and $B_y$, respectively, and $\mathbf{m}$ is the magnetic transition dipole moment of the carbonyl group. For example, if we can assume that $V_1 = V_2$ and both of the angles between $\mathbf{m}$ and $\boldsymbol{\mu}_x$ and between $\mathbf{m}$ and $\boldsymbol{\mu}_y$ are 45°, $R_x$ will be equal to $-R_y$, resulting in the split Cotton effects.[18] The hydrogen bonding between the carbonyl oxygen of amino acid esters and the hydroxyl group of the naphthyl group of host **1** will fix the orientation of the carbonyl group in the complex. X-ray diffraction analysis[19] of the crystal of a complex of chlororhodium(III) *trans*-5,15-bis(2-hydroxy-1-naphthyl)-2,3,17,18-tetraethyl-7,13-dimethyl-8,12-bis(methoxycarbonylethyl)porphyrin and L-Leu-OMe indicated that the angle between the carbonyl C=O axis and a line connecting two naphthyl groups is about 45°. The molecular orbital calculations are now under way to confirm this mechanism theoretically.

In order to verify mechanism 1 experimentally, the CD spectrum of **1**–(*S*)-leucinol was measured. The Cotton effects induced in the Soret band were very weak and were not of the split type (Figure 3c and Table III). On the basis of the UV–vis spectral titration studies it was confirmed that (*S*)-leucinol was hydrogen bonded to host **1** (Table II). The only structural difference between (*S*)-leucinol and L-Leu-OMe is the presence or absence of a carbonyl group. Therefore, these observations indicate that the presence and fixation of the carbonyl group is important for the split Cotton effects. It should also be noted that there is a correlation between the magnitude of hydrogen bonding energies and the induced CD intensities. For example, Ala-OMe is bound to host **1** weakly, and the induced CD is also weak in intensity,

(15) (a) Gouterman, M. *J. Mol. Spectrosc.* **1961**, *6*, 138. (b) Weiss, C., Jr. *J. Mol. Spectrosc.* **1972**, *44*, 37.

(16) The possibility that the split Cotton effects were caused by porphyrin–porphyrin aggregation is excluded because the concentration of the porphyrin is as low as $5 \times 10^{-6}$ M and the naphthyl groups should prevent $\pi$–$\pi$ stacking of the porphyrin planes. $^1$H NMR spectroscopy also indicated that no self-aggregation occurs at a higher concentration of the host.

(17) Tinoco, I. *Adv. Chem. Phys.* **1962**, *4*, 113.

(18) Mizutani, T.; Nakashima, R. *Chem. Lett.* **1991**, 1491.

(19) Ogoshi, H.; Masuda, H.; Uzawa, T.; Aoyama, Y. Unpublished results.

whereas Leu-OMe is bound to host **1** strongly and the induced CD is also intense. These observations may reflect the tightness of the host–guest complex, where a less fluctuating carbonyl group will cause stronger induced CD. According to mechanism 1, the orientation of the carbonyl group can be sensitively detected by the ratio $|[\theta]_{421}|/|[\theta]_{430}|$ as long as contributions from other coupling to the induced CD is negligible. For aliphatic amino acid esters, the ratios are nearly 1 (0.8–1.2), whereas for both aromatic amino acid esters and L-Leu-OBu$^t$, the ratios are smaller than 1 (0.4–0.7). In the case of aromatic amino acid esters, the unsymmetrically induced CD may be caused by the coupling between the electric transition dipole moment of the aromatic group of the guest and those of the Soret band of the host. Alternatively, aryl–aryl stacking interactions between the aromatic moiety of the guest and the host may perturb the orientation of the carbonyl group to some extent. In the case of L-Leu-OBu$^t$, the carbonyl group may be tilted in the hydrogen-bonded complex due to the steric repulsions between the *tert*-butyl group and the porphyrin plane, leading to unsymmetrically induced CD.

Mechanism 3 is briefly considered. Ruffling of the porphyrin plane is recognized for many naturally occurring[20] and synthetic porphyrins.[21] However, it is unlikely that the deformation of the porphyrin plane occurs in such a way that the induced CD for the two degenerate Soret band is of the split type. As shown in Table III, all complexes between **1** and amino acid esters with varying bulkiness exhibited split Cotton effects. This observation suggests that the deformation is not the mechanism for the present case. However, we have no unambiguous evidence for ruling out this mechanism.

## Conclusions

The binding of α-amino acid esters to the porphyrin host bearing double recognition sites was investigated. Bulky amino acid esters were bound to host **1** more strongly than less bulky ones. The hydrogen bonding energies were estimated by use of a reference guest and host molecules. The contribution from hydrogen bonding to the free energy change of association were –0.2 to –1.5 kcal/mol. The difference in the hydrogen bonding free energy can be ascribed to the difference in conformational flexibility of amino acid esters, which varies with bulkiness of the amino acid residues. The induced CD spectra of the complexes exhibited characteristic split Cotton effects for the hydrogen bonding complexes between amino acid esters and host **1**. Therefore, the CD induced in the Soret band can be used as a probe for the hydrogen bonding interaction for the present host–guest systems. We propose that the induced CD was caused by the coupling between the magnetic transition dipole moment of the carbonyl group and the electric transition dipole moment of the Soret band of the porphyrin.

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(20) Scheer, H. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 2, pp 1–44.
(21) Barkigia, K. M.; Berber, M. D.; Fajer, J.; Medforth, C. J.; Renner, M. W.; Smith, K. M. *J. Am. Chem. Soc.* **1990**, *112*, 8851.