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Molecular recognition: New chiral metalloporphyrins as receptor models

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New chiral metalloporphyrins capable of multi-point recognition are prepared and their recognition behavior, especially chiral recognition, is studied. The first part of the paper is concerned with general formalism for multi-point recognition, where uniqueness of multi-point recognition, isolation of interaction in terms of free energy, enthalpy and entropy, and the meaning of these thermodynamic parameters are discussed. Enantioselective binding of amino acid esters to two new chiral porphyrins is investigated by UV-vis, NMR and IR spectroscopic methods. Chiral recognition is achieved by combination of three recognition interactions between host and guest.

INTRODUCTION

Molecular recognition has been studied on the basis of the guiding principle that complimentary host-guest pair should recognize each other.[1,2] Thus we can design a host for a specific guest by introducing recognition groups to the host molecule in a complimentary fashion. Hydrogen bonding, Coulombic interaction, hydrophobic interaction and coordination interaction have been successfully used as the recognition forces between host and guest. In this approach, the overall host-guest interaction can be separated into pair-wise interaction between the recognition groups. Therefore the molecular recognition driven by pair-wise interactions is called multi-point recognition. Chiral recognition can also be achieved by extending this complimentary principle.[3] In the present paper, we describe the thermodynamic and statistical mechanical analysis of the multi-point recognition, the application of the analysis to the chiral recognition, and experimental studies of chiral metalloporphyrin as a receptor model.

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THERMODYNAMICS OF CHIRAL RECOGNITION

Chiral recognition

A chiral molecule has at least four atoms geometrically arranged so that it has no symmetry axis of reflection.[4] To achieve chiral recognition, at least four pairs of interaction should take place between host and guest. The minimum number of pairing for chiral recognition can be fewer if the specific shape of host or guest restricts the orientation of a guest molecule in the host-guest complex. Thus if the planar host prevents the access of guest from the other side, three pairs of interaction can result in chiral recognition. If the cylindrical host can bind the guest within the cavity, two pairs of interaction can result in chiral recognition (Figure 1).

Multi-point recognition

If the intermolecular interaction can be approximately taken as the sum of the interactions between recognition

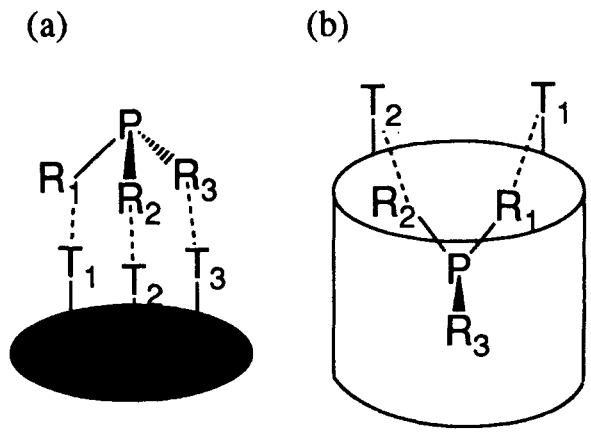


Figure 1 The minimum number of recognition pairs for chiral recognition. (a) For a planar host, the host plane and group P of guest undergo steric repulsion. Thus three recognition pairs are the minimum. (b) For a cylindrical host, two pairs of recognition can result in chiral recognition.

groups of host and guest, we call it multi-point recognition. Suppose that the host has m recognition groups and the guest has n recognition groups. In biological host-guest system, m is larger than n. We number these recognition groups from 1 to m and 1 to n. There are $m!$ and $n!$ ways of numbering for this. We can define the equilibrium constant for each recognition pairing as follows. The equilibrium constant K_{11} is defined for the equilibrium between non-interacting host-guest pair and the host-guest pair having interaction between group 1 of host and group 1 of guest. The equilibrium constant K_{12} is defined for the equilibrium between non-interacting host-guest pair and the host-guest pair having interaction between group 1 of host and group 2 of guest. The other equilibrium constant K_{1j} is similarly defined. The equilibrium constant K_{22} is defined in a somewhat different way. It represents the equilibrium between the state with group 1 of host and group 1 of guest interacting and the state with additional interaction between group 2 of host and group 2 of guest (Figure 2a). The equilibrium constant K_{23} is defined for the equilibrium between the state with group 1 of host and group 1 of guest interacting and the host-guest pair having interaction between group 2 of host and group 3 of guest. In general, the equilibrium constant, K_{ij} is the equilibrium between the state with group $k(k < i$ and $k < j)$ of host and group $k(k < i$ and $k < j)$ of guest interacting and the state with additional interaction between group i of host and group j of guest (Figure 2b). We can construct a matrix from these equilibrium constants (Figure 3).

The equilibrium constant for the overall complexation is given by

$$K = \prod_{i=1}^{n} K_{ii}$$

The matrix shown in Figure 3 has non-zero diagonal elements and almost zero off-diagonal elements if the following two conditions are satisfied.

(1) The host and the guest are the correct pair.
(2) The numbering of the recognition groups is correct.

We can construct $n!$ $m!$ matrices and the corresponding $n!$ $m!$ equilibrium constants K. We arrange the equilibrium constants in the decreasing order, K_1, K_2, ···. If $K_1 >> K_2$, then the recognition is unique, namely only one isomer exists in the host-guest complex. If the number of recognition groups of host is equal to that of guest, namely $n = m$, the probability of finding the correct numbering is $1/n!$ on the assumption that the ground state of the host-guest complex is unique (not degenerate). This procedure also provides the algorithm to find a complimentary pair of a multi-point recognition system.

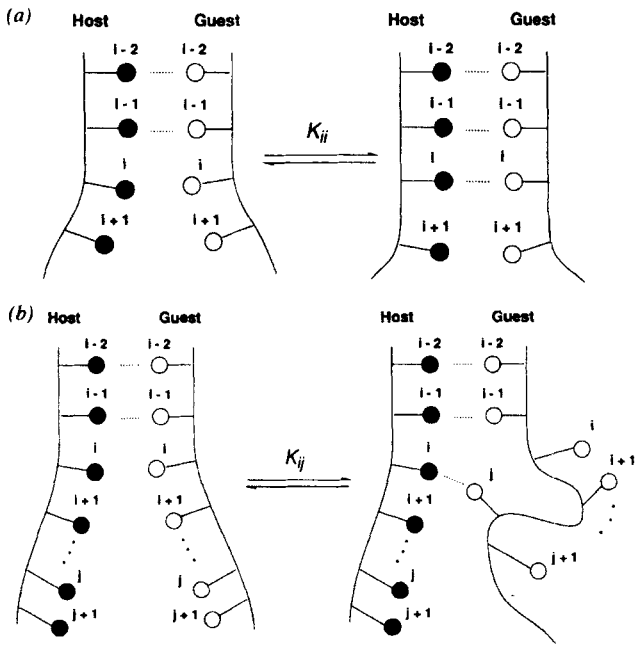


Figure 2 (a) The definition of the equilibrium constant K_{ii}. (b) The definition of the equilibrium constant K_{ij}.

Isolation of pair interactions in a multi-point molecular recognition

We assume that we have a correct host-guest pair and find a correct numbering of recognition groups. One can express the total free energy change as a sum of the terms associated with each recognition pair. We will define the free energy between the recognition groups as follows. To be concrete we will consider the three-point recognition system. The initial thermodynamic state (A) is a solution containing the standard concentration (1 M) of host and guest and these two species will *not* interact with each other. The final thermodynamic state (D) is a solution of the standard concentration of host-guest complex, where three pairs of interactions, R_1–T_1, R_2–T_2 and R_3–T_3, are operating. The free energy difference between state A and state D, $\Delta G°$, can be obtained from

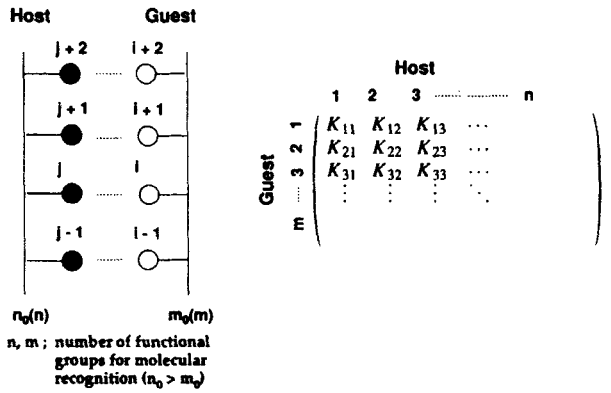


Figure 3 The matrix constructed from the equilibrium constants of the elementary interaction of multi-point recognition.

the experimentally determined equilibrium constant K and the relationship of $\Delta G° = -RT \ln K$.

$$\text{Host} + \text{Guest} = \text{Complex};\ \Delta G° \text{ (kcal/mol)}$$

We will assume two more thermodynamic states (B and C) between the initial and the final state (Figure 4). In state B, only the recognition group R_1 of host and T_1 of guest interact with each other and other recognition groups, R_2, T_2, R_3 and T_3 have no specific interaction. In state C, two pairs of interactions, R_1–T_1 and R_2–T_2, are operating and there is no specific interaction between R_3 and T_3. We will define the free energy between R_1 and T_1 (ΔG_{11}) as the free energy difference between state A and state B. Similarly the free energy between R_2 and T_2 (ΔG_{22}) can be defined as the free energy difference between state B and state C, and so on. Usually we cannot isolate the intermediate states, B and C, experimentally since these states are not stable. We use reference host or reference guest to estimate the free energy of these states. As shown in Figure 5, the recognition groups of host (R_2 and R_3) are replaced with a group (R_0) which exhibits no specific interaction with T_2 nor T_3. The equilibrium constant determined for this host can be used to approximate the free energy difference between state A and state B, namely we set $\Delta G_{11} \sim \Delta G_{11}'$. Similarly reference host with R_3 replaced with R_0 can be used to estimate the free energy difference between state B and state C. To use this procedure, the free energy change in the first step, $-\Delta G_{11}'$, should be large enough so that the binding is actually observed. If the interaction between R_1 and T_1 is too weak, we cannot determine the equilibrium constant for reference host. The host-guest system should be designed so that the interaction between group A and group B is thus large enough.

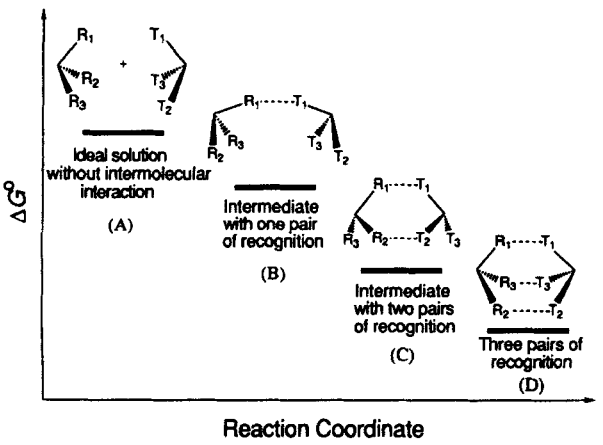


Figure 4 The hypothetical intermediate states in multi-point recognition. These free energy changes can be determined by use of reference host.

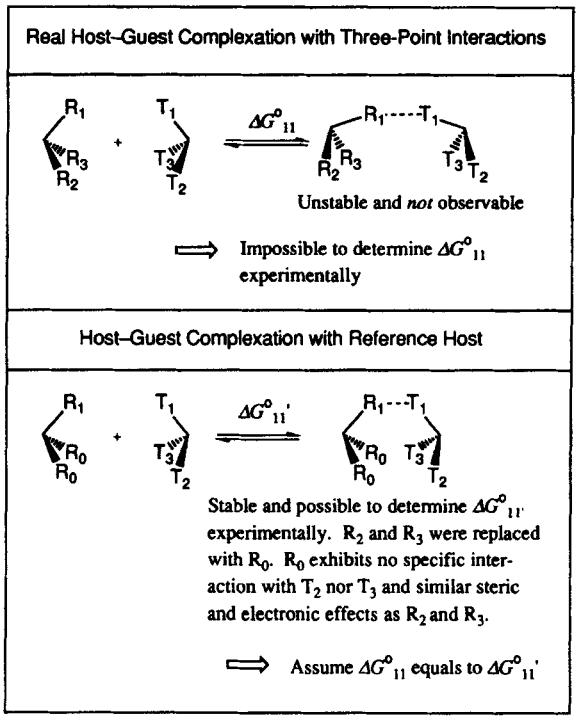


Figure 5 Reference host to determine the intermediate state in the multi-point recognition.

This approach is easily extended to a more general system, a multi-point recognition system. Then the total free energy change can be given by

$$\Delta G_{total} = \Delta G_1 + \Delta G_2 + \cdots + \Delta G_n.$$

where $\Delta G°_i$ is the free energy difference between the (i–1) th intermediate state and the i th intermediate state. The 0 th state is the initial state and the n th state is the final state. The i th state is the hypothetical state in which i pairs of interaction are operating and ($n - i$) pairs of interactions are absent.

Isolation of interaction enthalpy and interaction entropy

The enthalpy and entropy changes associated with a recognition pair can be similarly isolated. We assume (n–1) intermediate states. The enthalpy change (ΔH_i) and the entropy change (ΔS_i) are defined as the difference between the (i–1)th state and the ith state.

$$\Delta H_{total} = \Delta H_1 + \Delta H_2 + \cdots + \Delta H_n.$$

$$\Delta S_{total} = \Delta S_1 + \Delta S_2 + \cdots + \Delta S_n.$$

The meaning of these terms is as follows. The enthalpy change ($\Delta H°_i$) is the potential energy change of the following process. The initial state is the host-guest complex where the group 1 of host and group 1 of guest, group 2 of host and group 2 of guest, ···, group (i–1) of

host and group (i–1) of guest interact each other. We allow group i of host to approach to group i of guest until the equilibrium position is attained. The potential energy change is equal to ΔH°_{i}. The entropy term can be similarly defined.

The overall entropy change (ΔS°_{total}) can be separated into contribution from translation (S_{trans}), rotation (S_{rot}), internal rotation ($S_{int.rot}$), vibration (S_{vib}), electronic motion (S_{elec}), and solvation (S_{solv}).

$$\begin{aligned}\Delta S_{total} = &\sum_{\text{complex}} (S_{\text{trans}} + S_{\text{rot}} + S_{\text{int.rot}} + S_{\text{vib}} + S_{\text{electronic}} \\ &+ S_{\text{solvation}}) \\ &- \sum_{\text{host}} (S_{\text{trans}} + S_{\text{rot}} + S_{\text{int.rot}} + S_{\text{vib}} + S_{\text{electronic}} \\ &+ S_{\text{solvation}}) \\ &- \sum_{\text{guest}} (S_{\text{trans}} + S_{\text{rot}} + S_{\text{int.rot}} + S_{\text{vib}} + S_{\text{electronic}} \\ &+ S_{\text{solvation}}) \\ &= \Delta S_{\text{trans}} + \Delta S_{\text{rot}} + \Delta S_{\text{int.rot}} + \Delta S_{\text{vib}} \\ &+ \Delta S_{\text{electronic}} + \Delta S_{\text{solvation}}\end{aligned}$$

For simplicity, we neglect the contribution from solvation interaction in the following discussion. In a nonpolar solvent such as hexane or tetrachloromethane, the solvation energy is relatively small and meaningful conclusion can be obtained from the consideration neglecting a solvation term.

The entropy terms (ΔS_1, ΔS_2 ···) can be assigned to the entropy term (ΔS_{trans}, ΔS_{rot} ···) as follows. The term ΔS°_{i} involves the motional state changes when (i–1) pairs of interaction are operating and additionally, the i th group of host and the i th group of guest are allowed to interact (Figure 2a). For example, the term ΔS°_{1} involves the restriction of translational entropy and rotational entropy caused by the host-guest complexation. Similarly the term ΔS°_{2} involves the loss of rotational entropy and internal rotational entropy due to the second interaction. To have an idea about the magnitude of these entropy terms, translational entropy and rotational entropy are calculated by the use of the following equations.[5]

$$S_{trans} = R\left\{\frac{3}{2}\ln\left(\frac{Mw}{\text{amu}}\right) + \frac{3}{2}\left(\frac{T}{\text{K}}\right) - \ln\left(\frac{C}{\text{M}}\right) + 1.3554\right\}$$

$$S_{rot} = R\left\{\frac{1}{2}\ln\left(\frac{I_1 I_2 I_3}{\text{amu}^3\text{Å}^6}\right) + \frac{3}{2}\left(\frac{T}{\text{K}}\right) - \ln\sigma - 2.7106\right\}$$

where T is the temperature in Kelvin, C is the concentration in M, Mw is the molecular weight in atomic unit (amu), and I_1, I_2, I_3 are the moment of inertia in amu^3·Å^6. From these equations it is clearly seen that translational entropy and rotational entropy are relatively insensitive to the variation in the molecular structure. They only depend on the logarithm of molecular weight and moment of inertia, respectively. The translational and rotational entropy are of the order of 30 to 40 cal·K^{-1}·mol^{-1} for a typical organic molecule with molecular weight of 100–1000. These values correspond to approximately 10 kcal·mol^{-1} at room temperature. The internal rotational entropy is smaller, in the order of 5 cal·K^{-1}·mol^{-1} but it is sensitive to the molecular structure. Detailed discussion is reported in the literature.[6]

To illustrate the magnitude of entropy in the molecular recognition process, the translational and rotational entropy and heat of formation are listed in Table 1, where complexation between zinc porphyrin and leucine methyl ester is used as a typical bimolecular complexation. These thermodynamic parameters were calculated by semi-empirical molecular orbital calculation package, MOPAC. As seen in Table 1, the translational entropy and the rotational entropy are of similar magnitude between zinc porphyrin and leucine methyl ester. The entropy changes upon complexation due to translational and rotational changes are −39.8 and −28.1 cal·K^{-1}·mol^{-1}, respectively.

The motional changes and entropy changes associated with one-point recognition are summarized in Table 2. As discussed above, the enthalpy and entropy can be assigned to each recognition pair, and we can give the definite meaning to the values of ΔH_i and ΔS_i on the basis of the intermediate states in the multi-point molecular recognition.

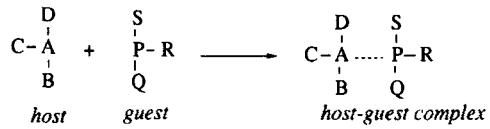
The sign and magnitude of the enthalpy and entropy terms are important. If we can neglect the solvation

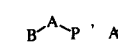
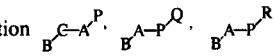
Table 1 Thermodynamic Parameters, Heat of Formation and Translational and Rotational Entropy for the Typical Bimolecular Complexation between Zinc Porphyrin and Leucine Methyl Ester[a]

	Zn Porphyrin	Leu-OMe	Complex between Zn Porphyrin and Leu-OMe	Changes in Complex Formation[b]
Heat of Formation (kcal·mol^{-1})	202.48	−105.69	93.04	−3.75
Translational Entropy (cal·K^{-1}·mol^{-1})	43.63	40.81	44.60	−39.84
Rotational Entropy (cal·K^{-1}·mol^{-1})	34.80	30.04	36.75	−28.09

[a]These parameters were obtained by the semi-empirical molecular orbital calculations, MOPAC, version 5, Stewart, J. J. P. *QCPE Bull.* **1989**, 9, 10. [b]Calculated from ΔH(Complex) − ΔH (Zn porphyrin) − ΔH (Leu-OMe), and ΔS(Complex) − ΔS (Zn porphyrin) − ΔS (Leu-OMe).

Table 2 Motional Changes and Entropy Changes in Multiple Molecular Recognition[a]



Motional Change		Change in Motional Freedom ΔS	
translation	PQRS (x, y, z)	−3	−30 to −40 eu
rotation	PQRS (x, y, z)	−3	−30 to −40 eu
vibration	A···P (stretching)	+1	0–1 eu
vibration	 (bending)	+2	0–1 eu
internal rotation		+3	5~10 × 3 eu

[a]We assume that only the motion of guest changes whilst that of host does not change.

interaction, all the entropy terms are negative. Among various terms, translational entropy and rotational entropy the largest. Internal rotation and vibration entropy are smaller and electronic entropy is the smallest. However the translational entropy and rotational entropy are relatively insensitive to the molecular structural variation. These entropy terms depend on molecular weight and moment of inertia, respectively. Although the internal rotational entropy per one degree of freedom is small, the number of degrees of freedom increases as the molecule becomes large. Therefore the internal rotational term may well be quite important for biopolymer such as proteins or DNA. Schematic diagram for the entropy changes during the multi-point recognition process is shown in Figure 6.

The entropy change from the initial state to the first intermediate state ($\Delta S°_1$) is large since the process involves the loss of translational entropy and rotational entropy and the slight gain of internal rotational entropy and vibrational entropy. The following entropy changes are usually smaller because the motional changes consist of internal rotations. This internal rotational entropy is sensitive to molecular structure. Its relationship to rigidity of a molecule is discussed elsewhere.[6] For example, an aromatic moiety is frequently used as a key fragment of the host structure. The internal rotation along the C=C bond of benzene is prohibited and the contribution of this internal rotational entropy to the binding process is almost zero. Therefore the entropy compensation is small, and the attractive interaction will be effectively used for recognition without loss of entropy if the benzene ring is used as a framework of the host molecule.

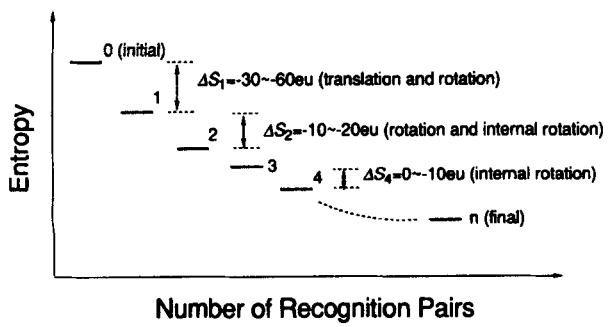


Figure 6 Changes in entropy in the elementary process of multipoint recognition.

Since the entropy term is always negative, the enthalpy term should be also negative to have the negative free energy changes. If the group i of host and group i of guest have an attractive interaction, the enthalpy term ($\Delta H°_i$) is negative. On the other hand, the interaction between the groups is repulsive, the enthalpy term is positive. If the attractive force is stronger, the enthalpy term becomes more negative. However it should be noted that the difference between $\Delta H°_i$ and $T\Delta S°_i$ is the entropy production, a measure of the irreversibility of the process. Therefore the smaller the difference, the more effective the process is. We should design the system so that the entropy production is minimum.

Chiral recognition by functionalized chiral porphyrin—I—

Porphyrin has several advantages as a framework for synthetic host. Some of the advantages are as follows: (1) Peripheral positions are available for functional groups, providing us wide choice for synthetic strategy of host molecule. (2) Various metal ions can be incorporated to the center. Thus the host-guest chemistry of metalloporphyrins holds a number of characteristic features of coordination chemistry. (3) We can use versatile molecular spectroscopic monitoring techniques. These spectroscopic techniques have been successfully utilized to elucidate host-guest intermolecular interaction and the conformational changes in host and guest.

The first chiral porphyrin was reported by Groves et al.[7] It was used for asymmetric epoxidation of olefins as a series of P-450 model studies. Groves' chiral porphyrin was prepared by attaching a chiral auxiliary group to achiral porphyrin framework. It is thus called an extrinsic chiral porphyrin. We have developed another strategy to synthesize a chiral porphyrin, in which an achiral porphyrin is modified to have C_2 symmetry (an intrinsic chiral porphyrin) by introducing achiral substituents.[8] In Figure 7 are shown the C_2 symmetric intrinsic chiral porphyrins. In the remaining part of this paper we give detailed account for **4, 5** and their related porphyrins.

We prepared a series of chiral porphyrins in which the interaction free energy can be separated into contribution from recognition pairing.[9] These hosts **6–9** were designed as receptor for amino acid esters. Host **6** has three

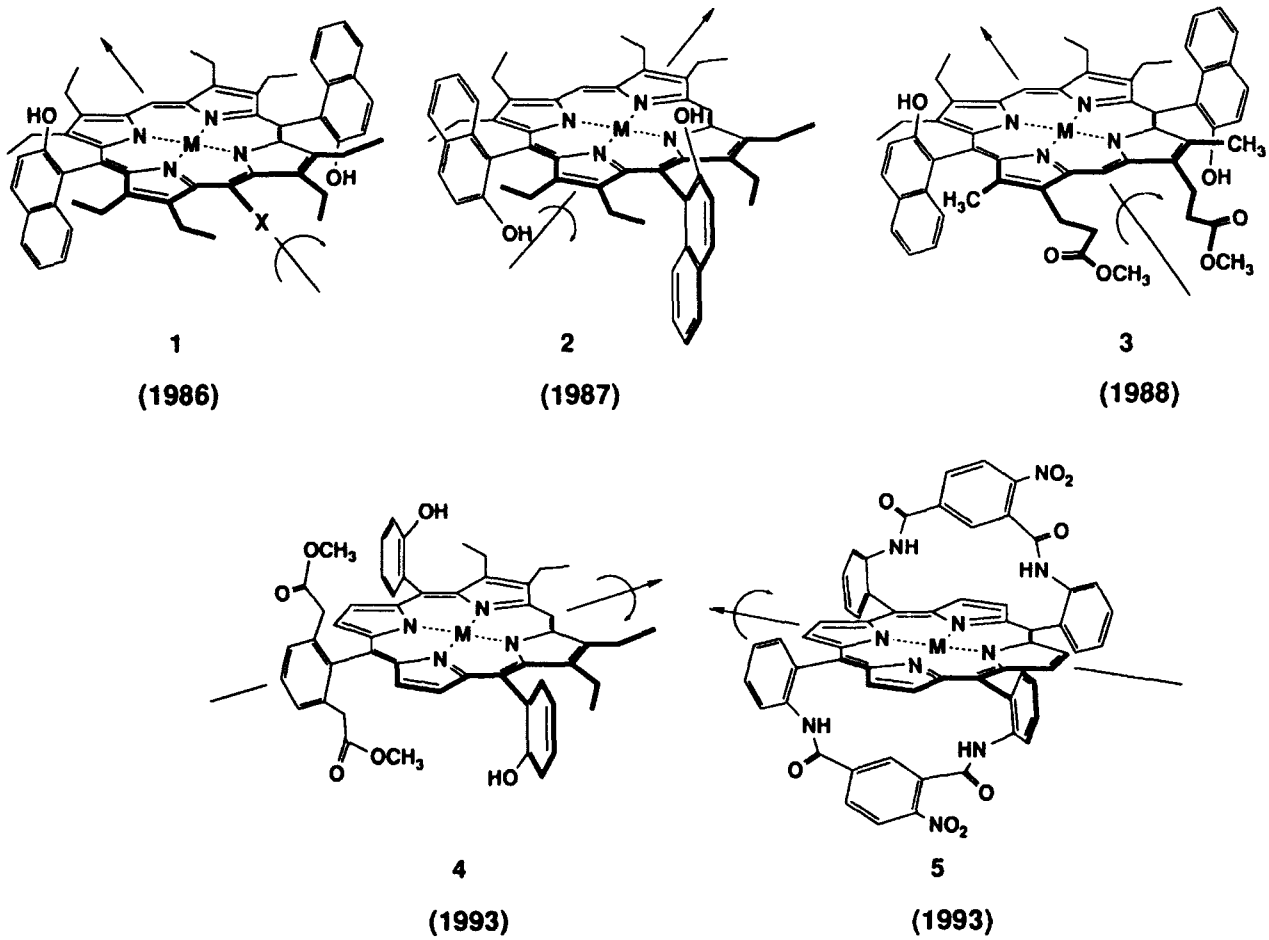


Figure 7 The C_2 symmetric intrinsic chiral porphyrins. The C_2 axis is shown by an arrow.

recognition groups, a zinc ion, a hydroxyl group and a carbomethoxy group. These porphyrins were prepared by the coupling of two dipyrromethane. Host (+)-**6** was designed to bind amino acid derivatives through three interactions: (1) The zinc ion binds the amino group of the guest through coordination interaction, (2) the hydroxyl group bind the carbonyl group of the guest through hydrogen bonding interaction, and (3) the carbomethoxy group interact favorably or unfavorably with the side chain group of the guest. Hosts **7–9** lack some of the recognition groups and are used as reference hosts.

The complexation of amino acid esters was studied by ^{1}H NMR. The chemical shift of signals of host (+)-**6** was monitored by addition of L-Leu-OMe. In Figure 9 are shown the spectral changes upon addition of racemic Leu-OMe in $CDCl_3$. The OH proton of host (+)-**6** shifts to downfield (Figure 9b), indicating that the hydrogen bonding between host and guest takes place. Meso protons and the methylene and methyl protons of the carbomethoxy groups split into two sets of signals (Figure 9a, 9c, 9d). This splitting is ascribed to the diastereomeric interaction between chiral host (+)-**6** and L- and D-Leu-OMe. The signal of the methyl protons of the carbomethoxy group shifts downfield for D-Leu-OMe while it shifts upfield for L-Leu-OMe as shown in Figure 9d. Comparison of binding constants among hosts

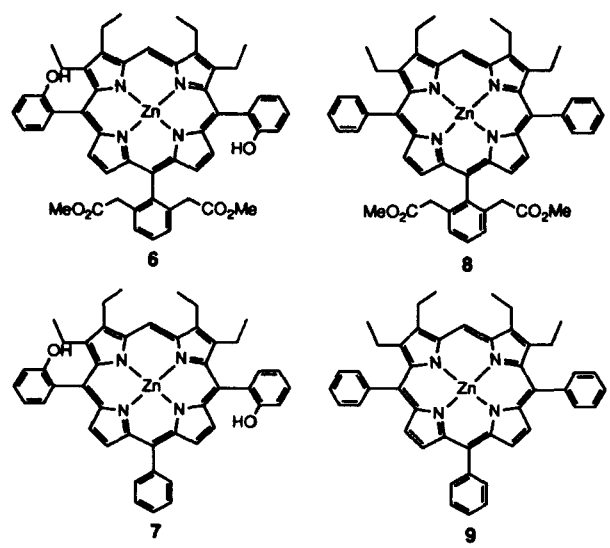


Figure 8 Chiral porphyrin **6** and reference porphyrins **7-9**.

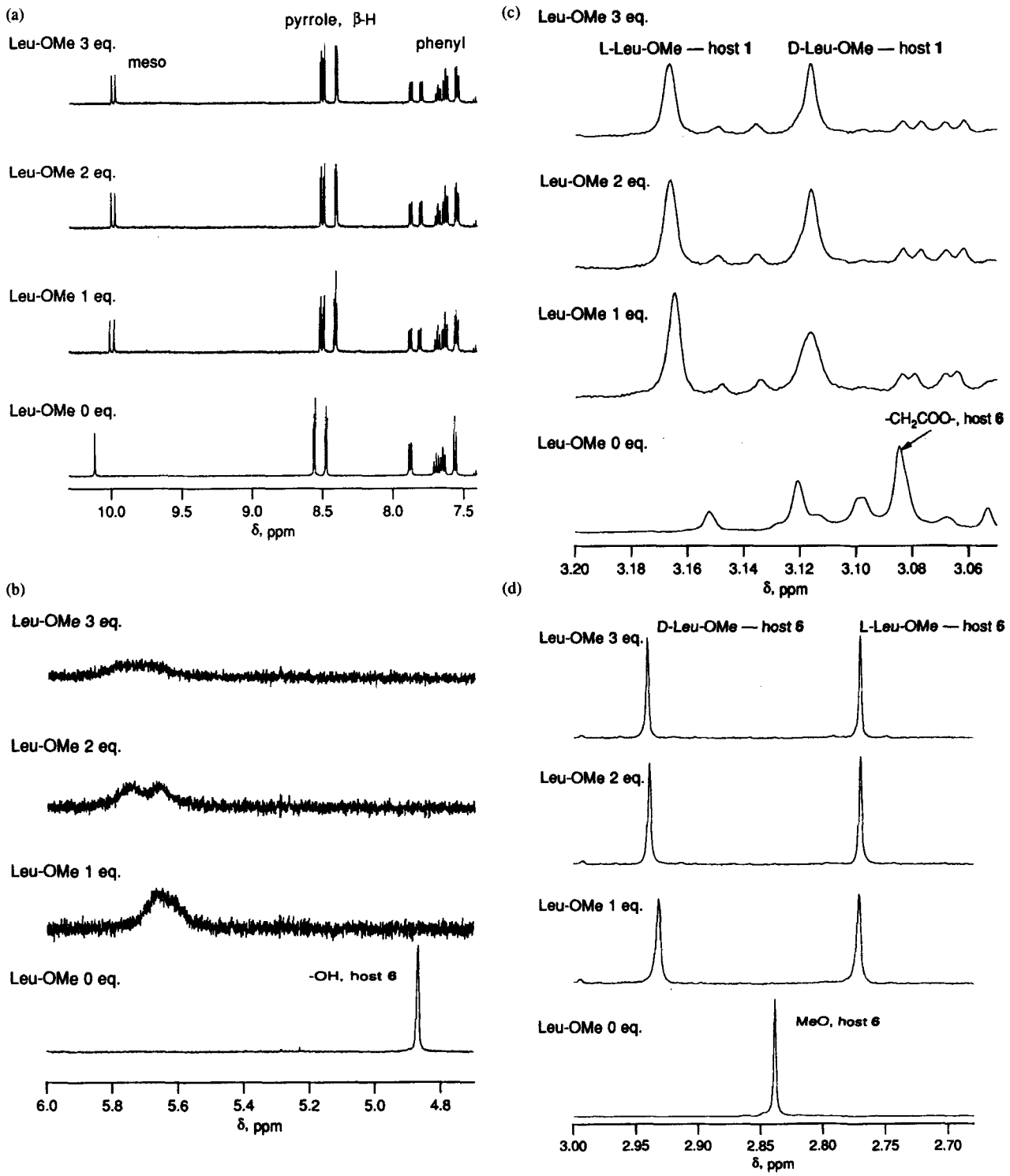


Figure 9 ^{1}H NMR titration of host **6** by racemic Leu-OMe in $CDCl_3$ at 25°C. [**6**] = 2.83×10^{-3} M, [Leu-OMe] = 0 -8.49×10^{-3} M. (a) Meso and phenyl protons. (b) The *OH* protons. (c) The *methylene protons of the carbomethoxy group of host* **6**. (*d*) The methoxy protons of the carbomethoxy group of host **6**.

6–9 suggests that the side chain group of D-guest comes closer to the carbomethoxy group of host (+)-**6** than that of L-guest. The downfield shift of the methyl protons of the carbomethoxy groups for D-Leu-OMe is consistent with this orientation in the complex.

The equilibrium constants determined by UV-vis titration in chloroform containing 1% ethanol as stabilizer are listed in Table 3. The binding constants of host **7** are larger than those of host **9**. This increase in the binding constants can be ascribed to the hydrogen bonding

between the OH group of the host and the carbonyl group of the guest. The binding constants for host (+)-**6** is smaller than those for host **7** except for D-Ser-OBzl. Therefore the carbomethoxy group of host (+)-**6** acts as a repulsive site except for serine benzyl ester. For D-serine benzyl ester, the binding constant for host (+)-**6** is larger than that for host **7**, indicating that the hydrogen bonding between the OH group of serine benzyl ester and the CO_2Me group of host (+)-**6** stabilizes the host-guest complex.

The free energy change of each pair of recognition groups is calculated from the following equations and listed in Table 4. The coordination interaction ($-\Delta G°_{Zn}$) is the largest term and it is appropriate to take this coordination interaction as the first interaction. The choice of the second interaction is arbitrary, but the hydrogen bonding between the OH group of host and the C=O group of the guest is taken as the second pair in the following analysis. As shown in Table 4, the coordination interaction is approximately −3.5 to −4.2 kcal/mol, the hydrogen bonding interaction is approximately −0.9 to −1.4 kcal/mol, and the third repulsive interaction between the carbomethoxy groups of host (+)-**6** and guest is +0.4 to +1.0 kcal/mol except for D-Ser-OBzl. The hydrogen bonding interaction ($-\Delta G_{OH}$) and the chiral interaction ($|\Delta G°$((+)-**6**-L)—$\Delta G°$((+)-**6**-D)|) shows good correlation. As the hydrogen bonding interaction is stronger, the chiral selection becomes better. It is noteworthy that the third interaction becomes attractive for D-Ser-OBzl, namely $\Delta G_{COOMe} < 0$. These observations are consistent with a complex where the carbomethoxy group is close to the side chain of guest for D-guest, whilst distant for L-guest. The hydrogen bonding fixes the internal rotation of the bound guest, thus inducing the third interaction (interaction between the carbomethoxy group and the side chain of the guest) to operate effectively. On the other hand there is poor correlation between the chiral interaction ($|\Delta G°$((+)-**6**-L)—$\Delta G°$((+)-**6**-D)|) and the coordination interaction ($-\Delta G_{Zn}$). Since the coordination interaction is used to bind the guest and not used to restrict the internal rotation, these correla-

$$\Delta G_{Zn} = -RT \ln K(\mathbf{9})$$

$$\Delta G_{OH} = -RT \ln \frac{K(\mathbf{7})}{K(\mathbf{9})}$$

$$\Delta G_{COOMe} = -RT \ln \frac{K(\mathbf{6})}{K(\mathbf{7})}$$

Table 3 Binding Constants (K) between Zinc Porphyrins (**6–9**) and Chiral Amino Acid Esters or Related Amines.[a]

	$K(M^{-1})$			
	(+)-**6**[b]	**7**	**8**	**9**
L-Ile-OMe	6780 ± 40	13700 ± 90	780 ± 30	1420 ± 20
D-Ile-OMe	2420 ± 20			
L-Leu-OMe	6160 ± 40	13300 ± 70	680 ± 20	1130 ± 20
D-Leu-OMe	2460 ± 20			
L-Val-OMe	6130 ± 40	12600 ± 100	650 ± 30	1240 ± 20
D-Val-OMe	2440 ± 30			
L-Ala-OMe	1590 ± 20	3460 ± 20	720 ± 30	740 ± 10
D-Ala-OMe	1420 ± 20			
L-Leu-OBzl	3450 ± 30	10100 ± 60	560 ± 30	1060 ± 20
D-Leu-OBzl	1540 ± 10			
L-Ser-OBzl	1340 ± 10	2400 ± 50	920 ± 20	480 ± 10
D-Ser-OBzl	2840 ± 10			
ethanolamine	5040 ± 30	4500 ± 50	5250 ± 110	2410 ± 20

[a]In $CHCl_3$ at 15°C.
[b]The optical resolution of **6** was performed by means of HPLC, and the first eluted enantiomer (+)-**6** was used.

Table 4 Contribution from Various Recognition Interactions to Total Free Energy Changes upon Complexation (kcal/mol).[a]

	$\Delta G°_{Zn}$	$\Delta\Delta G°_{OH}$	$\Delta\Delta G°_{COOMe}$	$\Delta\Delta G°^{L}_{COOMe}$	$\Delta\Delta G°^{D}_{COOMe}$
Ile-OMe	−4.15	−1.30	+0.35	+0.40	+0.99
Leu−OMe	−4.02	−1.41	+0.29	+0.44	+0.97
Val-OMe	−4.08	−1.33	+0.37	+0.41	+0.94
Ala-OMe	−3.78	−0.89	+0.02	+0.45	+0.51
Leu-OBzl	−3.99	−1.29	+0.37	+0.61	+1.08
Ser-OBzl	−3.53	−0.92	−0.37	+0.33	−0.10
ethanolamine	−4.46	−0.36	−0.45	___b	___b

[a]In $CHCl_3$ at 15°C. [b]$-RT\ln(K$((+)-**6**$)/K(\mathbf{7})) = -0.06$ kcal/mol.

tions are consistent with the mechanism that the hydrogen bonding fix the internal rotation of the guest, induce the third interaction effectively, and chiral selection is achieved. In Figure 10 is shown the complex between host **6** and Ser-OBzl. The geometry was optimized by the PM3 method.

Chiral recognition by functionalized chiral porphyrin—II—

More facile synthesis of chiral porphyrin was performed based on the different synthetic strategy. The bridging reaction of tetrafunctionalized porphyrins with an asymmetric difunctionalized reagent gives a mixture of meso and a pair of enantiomers as shown in Figure 11. In this reaction, both porphyrin and a bridging reagent are achiral. Fixation of the bridging reagent on the porphyrin plane alters the symmetry of the molecule and results in chirality. The α,α,β,β atropisomer of tetraarylporphyrin is doubly bridged with a difunctional reagent to yield a mixture of a *meso* porphyrin and a pair of enantiomeric porphyrins with C_2 symmetry **10**, **11**.[10] The difunctional bridging reagents were either nitroterephthaloyl chloride or 4-nitroisophthaloyl chloride. The molecular modeling study indicates that the phthaloyl group of host **10** declined to the porphyrin plane, partially blocking the binding pocket. In contrast to host **10**, the phthaloyl group of host **11** is almost perpendicular to the porphyrin plane and a good binding pocket is formed on the porphyrin plane. The zinc complexes of these porphyrins were investigated as a receptor for amino acid derivatives. Host **10** and host **11** have two recognition groups, a zinc ion and an N-H group. The zinc ion can act as a coordination site to bind the amino group of the guest. The NH group acts as a hydrogen bonding site and binds the carbonyl group of the guest.

Complexation with amino acid esters were studied by UV-vis titration experiments. Table 5 summarizes the binding constants for host **10·Zn**, **11·Zn** and TPP·Zn as a reference host. Clearly, the binding constant for **10·Zn** is

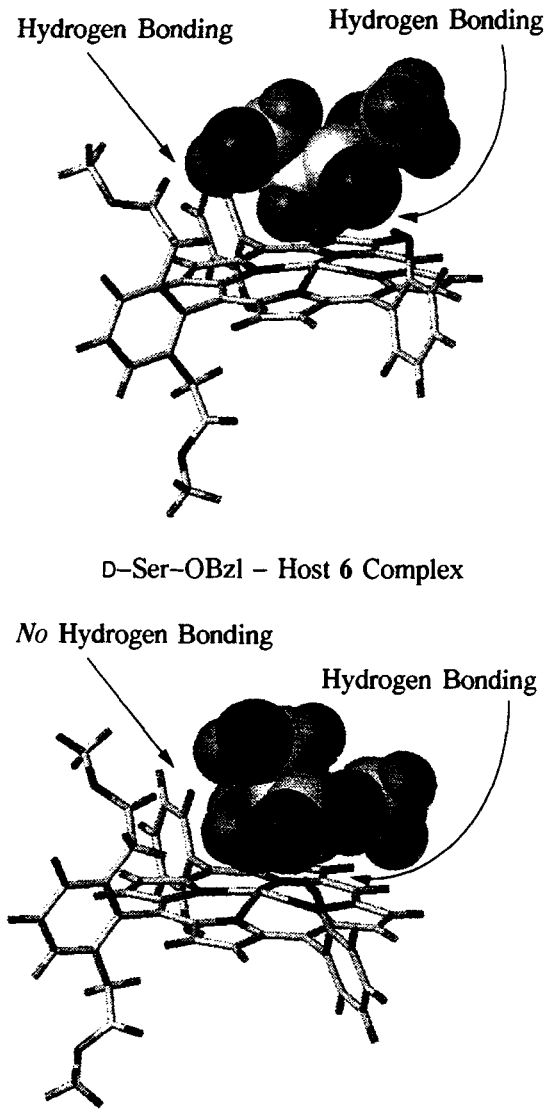


Figure 10 Schematic representation of the complex between host **6** and (a) D-Ser-OBzl and (b) L-Ser-OBzl. For D-Ser-OBzl, the side chain of serine is close to the carbomethoxy group and the hydrogen bonding between host and guest stabilizes the complex. For L-Ser-OBzl, the side chain of serine is too far to make hydrogen bonding to host.

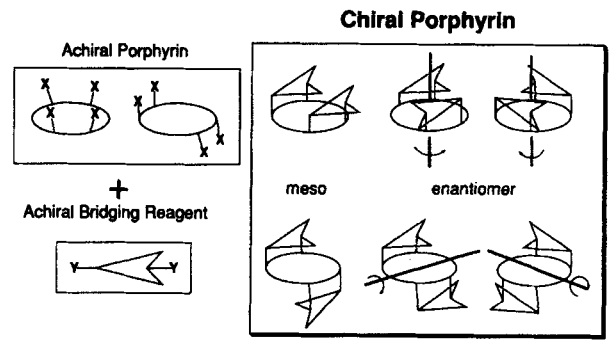
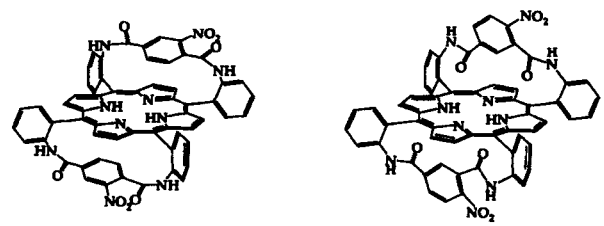


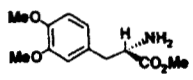
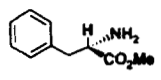
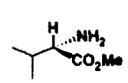
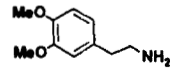
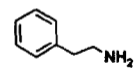
Figure 11 Synthetic strategy for intrinsic chiral porphyrins. Achiral porphyrin and an achiral bridging reagent are reacted to give a mixture of a meso porphyrin and C_2 symmetric chiral porphyrins.



10 **11**

Figure 12 Chiral porphyrin hosts **10** and **11**.

Table 5 Binding Constants (K_a, M^{-1}) for the Host-Guest Complex at 288K in $CHCl_3$

	L -DOPA-OMe	L -Phe-OMe	L -Val-OMe	Homoveratrylamine	Phenylethylamine
					
10-meso · Zn	1100 (100)	900 (100)			
11-meso · Zn	14000 (500)	10000 (500)	14000 (500)	4100 (100)	3000 (200)
TPP · Zn	2500 (100)	2600 (100)			
11-chiral(+)·Zn	5400 (500)	2800 (200)	3900 (100)		
11-chiral(−)·Zn	24000 (600)	15000 (1000)	22000 (800)		

( ): Standard deviation

smaller than TPP·Zn. This is consistent with the partially blocked binding pocket as suggested by the molecular modeling study. On the other hand, host **11·Zn** shows stronger binding to amino acid esters, indicating that the binding pocket produced by the phthaloyl group helps stabilize the host-guest complex. This binding enhancement is ascribed to the hydrogen bonding between the N-H group of host **11·Zn** and the carbonyl group of the guest. ^1H NMR and IR studies also support the complex formation with coordination and hydrogen bonding interactions stabilizing the host-guest complex. Schematic representation of the complex between host **11·Zn** and amino acid ester is shown in Figure 13. The ratios of the binding constants of **11-chiral(+)·Zn** to **11-chiral(-)·Zn** were in the range of 4.4 to 5.6. It should be noted that the two N-H groups of host **11·Zn** should have different hydrogen bonding ability to exhibit chiral selectivity. This chiral selection can be ascribed to the host-guest complex with controlled geometry, where coordination interaction, hydrogen bonding interaction takes place in a confined binding pocket.

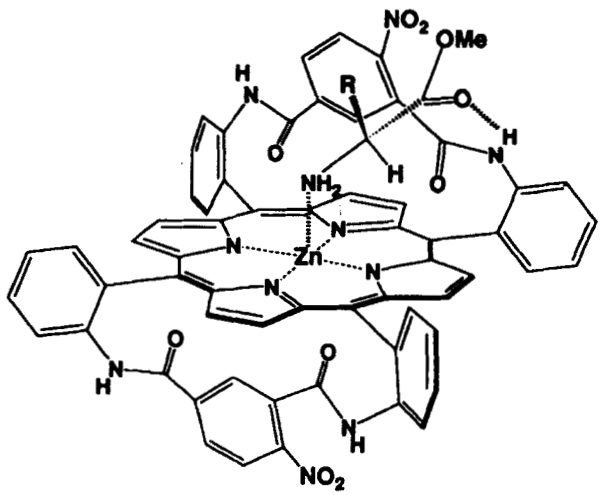


Figure 13 Schematic representation of a complex between host **11-chiral·Zn** and amino acid esters.

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