m, CH_2CH_2), -0.06 (9 H, s, Me_3Sn), ^{13}C NMR (75 MHz, $CDCl_3$) δ 92.07 (C1), 32.48 (C2), 31.62 (C3), 20.65 (C4), 40.91 (CH_3SO_3), -12.45 (Me_3Sn).

Conductance Kinetics Procedure. Solvolysis rates were measured conductometrically following the proceudure published earlier.[51] For reactions having half-lives of several hours or longer the reactant was dissolved in the solvent, mixed outside the bath, and the solution was added to an unstirred cell of approximately 10-mL volume that was placed in the bath and allowed about 20 min to come to temperature. For faster reactions, 100-mL magnetically stirred cells filled with solvent were allowed to temperature equilibrate in the bath for about 20 min or longer before the reactant was added. Reactant concentrations were about 10^{-3} M. Two- to four-hundred resistance readings were taken at intervals of approximately equal reaction over about 2 half-lives in the range of 10% to 90% reaction. Concentrations derived from the resistance readings using the limiting conductance law with experimentally determined constants for the particular product acid in the particular solvent fit the first-order rate law with standard deviations in the derived rate constants of 0.1% or better.

The resistance residuals were generally in the range of ±0.08% and showed no systematic trends greater than ~0.10% through the course of the reaction; reproducibility of the rate constants was generally ±0.5% or better. Temperatures of the thermostat baths for the reaction rate experiments were determined with a Mueller bridge and a calibrated platinum resistance thermometer with an accuracy of ±0.001 °C. The bath temperature control was also in the range of ±0.001 °C except at the two lower temperatures where control was more difficult and was maintained in the range of ±0.007 °C.

Since 4-(trimethylstannyl)bicyclo[2.2.2]octyl mesylate was too reactive in 97% trifluoroethanol-3% water (97T) for its rate to be measured by our conductance technique at 25 °C, this rate constant was obtained by extrapolation from rates measured at lower temperatures.

Conductance parameters for methanesulfonic acid in 97T at temperatures below 25 °C were determined by the "kinetic" method[52] with 4-(trimethylstannyl)bicyclo[2.2.2]octyl mesylate. The required "infinity" concentrations were determined from the conductance of the cell at 25 °C after the end of the reaction and corrected for the change in density of the sovlent with temperature.

The values for the temperatures, densities, limiting conductances (Λ_0) and slopes (S_α) were as follows: -14.545, 1.4336, 8.06, 34.71; -10.000, 1.4266, 9.96, 57.88; 0.000, 1.4105, 14.27, 66.33; 10.000, 1.3956, 18.75, 69.98; 25.000, 1.3726, 28.5, 119.3; 35.000, 1.3570, 32.67, 130.3. The conductance parameters for the temperatures other than 25 °C are probably accurate to only about ±10% but should be good enough to give satisfactory rate constants. The Arrhenius plot for the trimethylstannyl compound gives a correlation coefficient of 0.99988 and the standard deviation in the rate constant projected to 25 °C is ±5%.

Product Determination. The products of solvolysis of the silyl, germyl, and stannyl mesylates (**1b**: X = $SiMe_3$, $GeMe_3$, and $SnMe_3$, respectively) in perdeuterated 80E, 100E, and 97T were determined by analysis of the proton NMR in the following manner. A solution of the ester (0.1 M) in perdeuterated solvent, buffered with 2,6-lutidine, was put in an NMR tube, capped lightly, and allowed to stand for 10 half-lives after which the NMR spectra were taken. Resonances due to direct substitution were easily identified by comparison to spectra of the authentic alcohols **1** (Y = OH, X = Me_3M). 1,4-Dimethylenecyclohexane was assigned to the resonances at 2.00 and 4.49 ppm (relative area 1:1) in 80E. This is in agreement with the literature values of 2.27 and 4.74 ppm for the same compound in vinyl chloride solution.[53] The destannylation product, $(CH_3)_3SnOR$, was assigned to the singlet at 0.41 ppm (J = 68.4 Hz).

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Simultaneous Hydrogen Bonding and Metal Coordination Interactions in the Two-Point Fixation of Amino Acids with a Bifunctional Metalloporphyrin Receptor[1]

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Abstract: The organometallic acetone-Rh(III) derivative of 5,15-*trans*-bis(2-hydroxy-1-naphthyl)octaethylporphyrin (**1b**) reversibly forms two-point adducts in $CHCl_3$ with *o*-aminobenzoic acid (**2b**, a rigid β-amino acid) and its methyl ester (**2a**) via simultaneous Rh(III)-NH_2- coordination and OH-CO_2R hydrogen bonding (R = H or CH_3). The weaker interaction, hydrogen bonding (HB), was characterized from spectroscopic as well as thermodynamic viewpoints: for adduct **1b**-**2a**, K_{HB} = 9.5 and $\Delta G°_{HB}$ = -1.3 kcal/mol at 288 K ($\Delta H°_{HB}$ = -2.8 kcal/mol and $\Delta S°_{HB}$ = -5.3 cal/mol·K); for adduct **1b**-**2b**, K_{HB} = 107 and $\Delta G°_{HB}$ = -2.7 kcal/mol at 288 K ($\Delta H°_{HB}$ = -3.6 kcal/mol and $\Delta S°_{HB}$ = -3.0 cal/mol·K), where K_{HB} is the selectivity factor due to the hydrogen bonding. α-Amino esters also form similar two-point adducts; for the phenylalanine methyl ester adduct, K_{HB} = 42 and $\Delta G°_{HB}$ = -2.1 kcal/mol at 288 K. The importance of hydrogen bonding, however, sharply decreases in going from flexible β- through γ- to ε-amino ester adducts. The intermolecular hydrogen bonding of **1b** and methyl acetate (K_{HB} = 0.38 M^{-1} and $\Delta G°_{HB}$ = 0.56 kcal/mol at 288 K) ($\Delta H°_{HB}$ = -2.4 kcal/mol and $\Delta S°_{HB}$ = -10.2 cal/mol·K) is a weak interaction. On the other hand, the hydrogen bonding in adduct **1b**-**2a** is essentially intramolecular in nature and takes place much more readily owing to a less unfavorable entropy change; it thus makes a significant contribution to the stability and selectivity of the resulting adduct. Such α-amino acids as phenylalanine, leucine, isoleucine, and 2-aminohexanoic acid (norleucine) are readily extracted from neutral aqueous solutions into $CHCl_3$ upon formation of similar two-point **1b**-(amino acid) adducts, in marked contrast to alanine, serine, and 6-aminohexanoic acid, which are not extractable; sufficient lipophilicities of amino acids as well as intramolecular hydrogen bonding in the adducts play crucial roles. Selective transport of lipophilic α-amino acids through a $CHCl_3$ liquid membrane was also achieved with **1b** as a carrier.

Multipoint interaction plays an essential role in the functions of proteins as biological catalysts, receptors, and carriers. Much recent interest in the host-guest associations[4] has been directed to the multipoint molecular recognition of polar organic compounds

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of biological significances;[5-8] in the case of amino acids, not only two-point interaction but also three-point chiral recognition has been sought.[6a,6d,9] Rebek et al. have presented a general structure that allows convergent arrangements of functional groups working on multifunctional substrates.[10] We have been using Rh(III) porphyrin **1** having trans 2-naphthol moieties at the 5- and 15-meso positions, where the central Rh(III) ion and a OH group are fixed in proximity and in a convergent manner (direction of their actions is shown by arrows), but not so closely as to allow their direct interaction.[11a] In fact, compound **1** promotes certain reactions[11] and binds amino acids in a bifunctional manner.[12] A high degree of rigidity,[13] involvement of two different types of interactions that are independently characterizable spectroscopically, and, most importantly, availability of electronic spectroscopy for precise determinations of binding constants can be taken as advantages of the present system[14] as compared with earlier systems. We present here a full account of the bifunctional binding of amino acids in nonionic forms. The object of this work is to reveal an essential aspect of the multipoint interactions by characterizing the weaker interaction, hydrogen bonding, on a thermodynamic basis so as to allow a deeper insight into the selectivity derived therefrom.

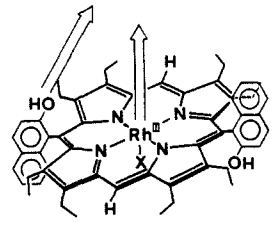
Table I. Binding Constants of Rh(III) Porphyrins with Amino Esters and Amino Acids in $CHCl_3$[a] and Associated Thermodynamic Parameters

	amino ester or amino acid			
	2a	**3a**	**2b**	**3b**
	Rh(III) Porphyrin **1b**			
K, M^{-1}				
273 K	4.06×10^4	4.69×10^3	2.97×10^5	5.32×10^3
288 K	1.77×10^4	2.92×10^3	1.20×10^5	3.13×10^3
303 K	7.61×10^3	1.73×10^3	5.10×10^4	1.88×10^3
318 K			2.54×10^4	1.20×10^3
$\Delta G°$, kcal/mol[b]	−5.5	−4.5	−6.7	−4.6
$\Delta H°$, kcal/mol	−9.1	−5.7	−9.4	−5.6
$\Delta S°$, cal/mol·K	−12.5	−4.0	−9.3	−3.5
	Rh(III) Porphyrin **6**			
K, M^{-1}				
273 K	2.94×10^3	4.42×10^3	1.42×10^3	3.85×10^3
288 K	1.57×10^3	2.46×10^3	7.74×10^2	2.16×10^3
303 K	8.73×10^2	1.49×10^3	4.40×10^2	1.29×10^3
318 K			2.93×10^2	8.07×10^2
$\Delta G°$, kcal/mol[b]	−4.2	−4.5	−3.8	−4.4
$\Delta H°$, kcal/mol	−6.2	−5.5	−6.2	−6.0
$\Delta S°$, cal/mol·K	−6.9	−3.6	−8.4	−5.4

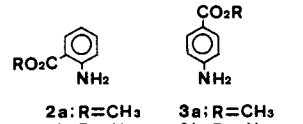
[a] $[\text{Rh porphyrin}]_{total} = 5.0 \times 10^{-5}$ M. Errors in K's are ≤6% for adducts **1b–3a**, **1b–3b**, **6–2a**, **6–2b**, **6–3a**, and **6–3b** and ≤10% for **1b–2a**, and ≤15% for **1b–2b**. [b] At 288 K.

Results and Discussion

Spectroscopic Characterization of Two-Point Fixation of Amino Acids and Amino Esters. The chlororhodium(III) complex of *trans*-5,15-bis(2-hydroxy-1-naphthyl)octaethylporphyrin (**1a**)



1a; X = Cl
1b; X = CH_2COCH_3



2a: R = CH_3 **3a**: R = CH_3
2b: R = H **3b**: R = H

4a: R = CH_3
4b: R = H

5

forms stable 1:1 adducts, in a practically irreversible manner,[15] with methyl *o*-aminobenzoate (methyl anthranilate, **2a**) as well as methyl *p*-aminobenzoate (**3a**) as a reference in $CHCl_3$. The ^{1}H NMR and IR spectra of the adducts for $CDCl_3$ or $CHCl_3$ solutions showed (^{1}H NMR) $\delta(NH_2)$ −1.82 (2 H), (OH) 5.39 (1 H), and 7.28 (1 H), (IR) ν(OH) 3448 and ν(CO) 1696 cm^{-1} for adduct **1a–2a**; and (^{1}H NMR) $\delta(NH_2)$ −3.29 (2 H), (OH) 5.36 (1 H), and 5.09 (1 H), (IR) ν(OH) 3516 and ν(CO) 1720 cm^{-1} for adduct **1a–3a**. The highly upfield-shifted NH_2 proton resonances as a result of the porphyrin ring current effect[16] indicates that both adducts contain a Rh(III)–NH_2– coordination bond. On the other hand, a large (~2.2 ppm) downfield shift of one OH proton in the naphthol moieties and significant shifts to lower wavenumbers in ν(OH) (~70 cm^{-1}) and ν(CO) (11 cm^{-1})[17] for adduct **1a–2a** as compared with those for adduct **1a–3a** indicate that **1a–2a** contains an intramolecular hydrogen bond between OH and CO_2CH_3 groups in addition to a common Rh(III)–NH_2– coordination bond. Such a dual interaction has been demonstrated

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(17) The **2a** and **3a** adducts of the chlororhodium(III) complex of tetraphenylporphyrin (TPP) in $CHCl_3$ showed ν(CO) at 1707 and 1720 cm^{-1}, respectively. Thus, the shifts in ν(CO) for adducts **1a–2a** and **1a–3a** are 11 and 0 cm^{-1}, respectively, as compared with the TPP complexes as references.

Table II. Equilibrium Constants for the Metal Coordination (MC) and Hydrogen-Bonding (HB) Processes in the Formation of Adducts **1b–2a** and **1b–2b** in $CHCl_3$[a] (Refer to Scheme I)

adduct formed		T, K			
		273	288	303	318
1b–2a	K_{MC}, M^{-1}	3.12×10^3	1.86×10^3	1.01×10^3	
	K_{HB}	13.0	9.50	7.51	
1b–2b	K_{MC}, M^{-1}	1.97×10^3	1.12×10^3	6.42×10^2	4.36×10^2
	K_{HB}	151	107	79.5	58.3

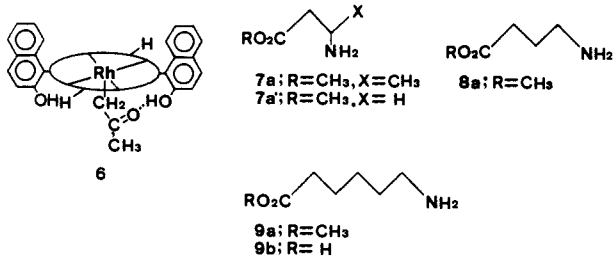
[a] $K_{MC} = K/K_{HB}$. $K_{HB} = [K_{1b}(2)/K_{1b}(3)]/[K_6(2)/K_6(3)] = [K_{1b}(2)/K_6(2)]/[K_{1b}(3)/K_6(3)]$.

for **1a** adducts of α-amino esters (**4a**); e.g., phenylalanine methyl ester adduct (**1a–4a**, X = $CH_2C_6H_5$) showed somewhat more pronounced shifts in δ(OH) (~3 ppm), ν(OH) (~100 cm^{-1}), and ν(CO) (14 cm^{-1}),[12] suggesting that the hydrogen bonding is more effective in the adducts with α-amino esters than with **2a**, a β-amino ester.

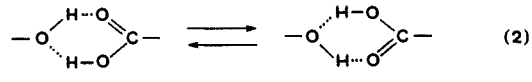
Reversible coordination of amines **2a**, **3a**, and **4a** as well as 4-aminoheptane (**5**) (eq 1) was achieved by using a C-bound

$$\text{Rh(III)} + \text{amine} \overset{K}{\rightleftharpoons} \text{Rh(III)–amine} \qquad (1)$$

acetone–rhodium derivative of *trans*-bis(hydroxynaphthyl)-porphyrin (**1b**) and its cis isomer (**6**, in a schematic representation hereafter);[18] in **6**, the acetone moiety is attached to Rh at the

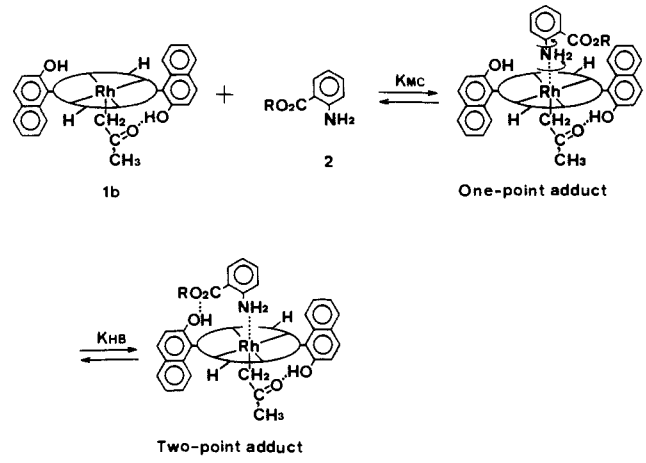


OH-containing side of the porphyrin plane.[11a] The ^1H NMR spectra of adducts **1b–2a** and **1b–4a** showed characteristic downfield shifts of the OH protons due to hydrogen bonding (vide infra) in a manner similar to **1a–2a** and **1a–4a**. For amino acid adducts **1b–2b** and **1b–4b** as well as **1a–2b** and **1a–4b**, on the other hand, both OH and CO_2H resonances could not be detected, presumably because of extensive line broadening due to rapid exchange (eq 2).


(2)

Thermodynamic Characterization of Two-Point Fixation of Amino Acids and Amino Esters. The hydrogen-bonding interactions in the two-point adducts **1b–2a** and **1b–2b** were evaluated by their extra stabilizations as compared with one-point counterparts and were characterized in terms of thermodynamic parameters in light of those for the corresponding intermolecular hydrogen-bonding process. Thus, the coordination of amino esters **2a** and **3a** and amino acids **2b** and **3b** with **1b** and **6** in $CHCl_3$ at various temperatures was followed by well-behaved spectrophotometric titration; a 100% complexation was readily attained in every case and the binding constant (K, eq 1) was obtained from absorbance changes at 20–80% complexation, as summarized in Table I together with associated thermodynamic parameters. Inspection of Table I reveals an extra stabilization in adduct **1b–2a**. Although, at 288 K for example, the para isomer **3a** has similar affinities to **1b** and **6** [$K_{1b}(3a)/K_6(3a) = 1.19$], the ortho isomer **2a** prefers **1b** to **6** by a factor of 11.3 [$K_{1b}(2a)/K_6(2a) = 11.3$]. Although, in a different viewpoint, **6**, whose open coordination site has no nearby OH groups, shows a slight preference for **3a** over **2a** [$K_6(2a)/K_6(3a) = 0.64$], **1b** binds **2a** 6.1 times more strongly than **3a** [$K_{1b}(2a)/K_{1b}(3a) = 6.1$].[19] These results indicate

Scheme I



that the hydrogen bonding (HB) in the two-point adduct **1b–2a** (Scheme I, R = CH_3) gives rise to a selectivity factor of K_{HB} = 11.3/1.19 = 6.1/0.64 = 9.50, corresponding to a stabilization energy of $\Delta G°_{HB} = -RT \ln 9.50 = -1.3$ kcal/mol (288 K). The effect of intramolecular hydrogen bonding is more pronounced in adduct **1b–2b**, which involves bifunctional hydrogen bonds (eq 2). Specifically, change of the functional groups of the para isomer from CO_2CH_3 to CO_2H (i.e., from **3a** to **3b**) resulted in decreases in the binding constants for both **1b** and **6**. In marked contrast, however, similar structural variation for the ortho isomer (i.e., from **2a** to **2b**) led to a significant increase in K of **1b**, while the increase in K of **6** was only slight; the selectivity factor due to the hydrogen bonding in the two-point adduct **1b–2b** (Scheme I, R = H) was thus enhanced to a value of $K_{HB} = [K_{1b}(2b)/K_6(2b)]/[K_{1b}(3b)/K_6(3b)] = 155/1.45 = 107$ ($\Delta G°_{HB} = -2.7$ kcal/mol) at 288 K. Contributions of the metal coordination (MC, Rh(III)–NH_2–) to the overall stabilities of two-point adducts **1b–2a** and **1b–2b** can be evaluated according to $K_{MC} = K/K_{HB}$; $(1.77 \times 10^4)/9.50 = 1.86 \times 10^3$ M^{-1}, corresponding to $\Delta G°_{MC} = -RT \ln K_{MC} = -4.3$ kcal/mol (288 K) for **1b–2a** and $(1.20 \times 10^5)/107 = 1.12 \times 10^3$ M^{-1} ($\Delta G°_{MC} = -4.0$ kcal/mol) for **1b–2b**. Similar treatments of the binding constants for leucine methyl ester (**4a**) and 4-aminoheptane (**5**) as reference led to the following parameters for the two-point adduct **1b–4a** [X = $CH_2CH(CH_3)_2$]; K_{HB} = 42 ($\Delta G°_{HB} = -2.1$ kcal/mol) and $K_{MC} = 1.2 \times 10^5$ M^{-1} ($\Delta G°_{MC} = -6.7$ kcal/mol) at 288 K.[12]

It is reasonable to assume that the two-point adduct formation involves initial Rh(III)–NH_2– one-point adduct formation followed by intramolecular hydrogen bonding (Scheme I); K_{MC} and K_{HB} obtained above are actually the equilibrium constants therein. In Tables II and III are summarized K_{MC} and K_{HB} for the formation of adducts **1b–2a** and **1b–2b** at various temperatures and associated thermodynamic parameters, respectively.[20] The MC processes

(18) The methyl–Rh(III) derivative of **1** (X = CH_3) also forms reversible amine adducts. For the reversible coordination of pyridines with the methyl–Rh(III) derivative of octaethylporphyrin, see: Reference 13.

(19) The formation of two-point adducts **1b–2a** and **1b–2b** is accompanied by larger negative entropy changes (Table I) and is hence more favorable at lower temperatures; the selectivities $K_{1b}(2a)/K_{1b}(3a)$ are 4.4, 6.1, and 8.7, respectively, at 303, 288, and 273 K and $K_{1b}(2b)/K_{1b}(3b)$ are 21, 27, 38, and 56, respectively, at 318, 303, 288, and 273 K. Highly selective binding of **2a** with **1b** at 243 K was directly shown by ^1H NMR spectroscopy; at 243 K, exchange was slow on the NMR time scale and a 1:1:1 mixture of **1b**, **2a**, and **3a** in $CDCl_3$ gave adduct **1b–2a** almost exclusively.

(20) The $\Delta H°_{HB}$ value for adduct **1b–2b** (–3.6 kcal/mol) may be compared with intramolecular hydrogen-bond energy (4.7 kcal/mol) for salicylic acid.

Table III. Thermodynamic Parameters for the Metal Coordination (MC) and Hydrogen-Bonding (HB) Processes in the Formation of Adducts **1b–2a** and **1b–2b** in $CHCl_3$ (Refer to Scheme I)

adduct formed	$\Delta G°_{MC}$[a,b]	$\Delta H°_{MC}$[b]	$\Delta S°_{MC}$[c]	$\Delta G°_{HB}$[a,b]	$\Delta H°_{HB}$[b]	$\Delta S°_{HB}$[c]
1b–2a	−4.3	−5.2	−3.5	−1.3	−2.8	−5.3
1b–2b	−4.0	−6.0	−6.8	−2.7	−3.6	−3.0

[a] At 288 K. [b] Units, kcal/mol. [c] Units, cal/mol·K.

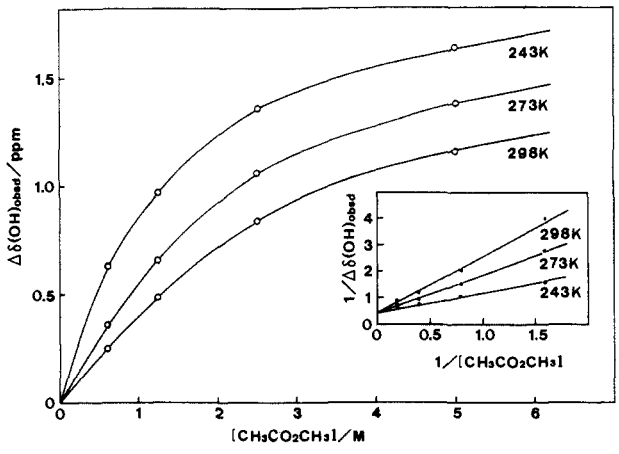


Figure 1. ^1H NMR downfield shifts [$\Delta\delta(OH)_{obsd}$] of the OH proton of **1b** as functions of [$CH_3CO_2CH_3$] at 243, 273, and 298 K. $\Delta\delta(OH)_{obsd} = \delta(OH)_{obsd} - \delta(OH)_{1b}$, where $\delta(OH)_{1b}$ = 5.61, 5.58, and 5.56 at 243, 273, and 298 K, respectively. Inset: analysis of the data according to eq 4, where $\Delta\delta(OH) = \delta(OH)_{com} - \delta(OH)_{1b}$ and $\delta(OH)_{com}$ is the chemical shift for the complex, **1b**–$CH_3CO_2CH_3$.

leading to one-point adducts **1b–2a** and **1b–2b** (Scheme I) are reasonably similar to each other (Table III) and are also related to the one-point MC interactions leading to adducts **1b–3a**, **1b–3b**, **6–2a**, **6–2b**, **6–3a**, and **6–3b** (Table I), especially in respect to $\Delta H°$ values. In order to characterize the intramolecular HB processes in Scheme I, the intermolecular association of **1b** and methyl acetate as reference[21] via hydrogen bonding (eq 3) was investigated

$$\mathbf{1b} + CH_3CO_2CH_3 \overset{K}{\rightleftharpoons} \mathbf{1b}\text{–}CH_3CO_2CH_3 \quad (3)$$

$$\frac{1}{\Delta\delta(OH)_{obsd}} = \frac{1}{K}\frac{1}{\Delta\delta(OH)}\frac{1}{[CH_3CO_2CH_3]} + \frac{1}{\Delta\delta(OH)} \quad (4)$$

by ^1H NMR titration, taking advantage of the ester-induced downfield shifts [$\Delta\delta(OH)_{obsd}$] of the OH proton resonance of **1b** (Figure 1). The binding constants (K) were evaluated by the analysis of the data according to eq 4 (inset of Figure 1);[22] K = 0.75, 0.45, and 0.33 M^{-1}, respectively, at 243, 273, and 298 K, leading to $\Delta H°$ = −2.4 kcal/mol, $\Delta S°$ = −10.2 cal/mol·K, and $\Delta G°$ = 0.56 kcal/mol (288 K).

Comparison of these parameters with those (Table III) for the HB process of the **2a** system (Scheme I) reveals an essential aspect of the present two-point interaction. The enthalpy changes ($\Delta H°$) are reasonably similar to each other (−2.8 and −2.4 kcal/mol). In the intermolecular reaction (eq 3), the favorable enthalpy change is canceled by a very unfavorable entropy change (−10.2 cal/mol·K) and the free energy change is thus positive (0.56 kcal/mol); the equilibrium constant is very small (K = 0.38 M^{-1} at 288 K) as a consequence. In marked contrast, however, the hydrogen bonding in Scheme I is essentially intramolecular in nature, where the associated entropy loss ($\Delta S°_{HB}$ = −5.3 cal/mol·K) is only about half of that for the intermolecular reaction; this gives rise to a net gain in free energy ($\Delta G°_{HB}$ = −1.3 kcal/mol) and thus leads to a significant selectivity due to hydrogen bonding.

(21) Methyl benzoate, probably a better reference, was not used, because strong absorption of this aromatic compound in excess amounts overlaps with the OH proton resonance in concern.

(22) The common intercept [$1/\Delta\delta(OH)$] indicates that $\Delta\delta(OH) \simeq 2.2$ ppm is independent of temperatures.

Table IV. Extents of Intramolecular Hydrogen Bonding in **1b** Adducts of Various Amino Esters and Amine

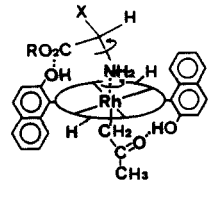
	amino ester or amine							
	4a[a,b]	**2a**	**7a**	**7a′**	**8a**	**3a**	**9a**	**5**[b]
K_{1b}/K_6[c]	31	11	2.6		0.62	1.2	0.70	0.74
$\Delta\delta(OH)_{obsd}$,[d] ppm	1.63	1.57	1.31	0.81	0.38	−0.39[e]	0.36	0.03
K_{HB}[f]	42[g]	9.5[g]	4.1	1.0	0.3		0.3	

[a] X = $CH_2CH(CH_3)_2$. [b] Reference 11. [c] K_{1b} and K_6 are binding constants, respectively, of **1b** and **6** for amino ester or amine in $CHCl_3$ at 288 K. [d] Reference 18. [e] Reference 19. [f] K_{HB}'s for **7a**, **7a′**, **8a**, and **9a** are from $\Delta\delta(OH)_{obsd}$'s; see ref 20. [g] From binding constants at 288 K as detailed in the text.

The present results indicate that the free energy change of an *ideal* two-point interaction is more negative than the sum of those for independent two one-point interactions.

Geometrical Requirements of Hydrogen Bonding. The extent of hydrogen bonding in a **1b** adduct of amino ester (AE) can be evaluated by referring to an appropriate reference amine (RA); $K_{HB} = [K_{1b}(AE)/K_6(AE)]/[K_{1b}(RA)/K_6(RA)]$. Since the correction term $K_{1b}(RA)/K_6(RA)$ is not so much different from unity the ratio $K_{1b}(AE)/K_6(AE)$ provides an approximate measure of intramolecular hydrogen bonding. In Table IV are summarized such ratios based on the binding constants at 288 K for leucine methyl ester [**4a**, X = $CH_2CH(CH_3)_2$] (α-AE), **2a** and methyl 3-aminobutyrate (**7a**) (β-AEs), methyl 4-aminobutyrate (**8a**) (γ-AE), **3a** (δ-AE), and methyl 6-aminohexanoate (**9a**) (ϵ-AE), as well as 4-aminoheptane (**5**) as reference. The intramolecular hydrogen bonding is important for the α- and β-amino ester systems but is not for the γ-, δ-, and ϵ-systems; γ- and ϵ-amino esters **8a** and **9a**, like amine **5**, even show inverse selectivities for **6** over **1b**. In Table IV are also shown the ^1H NMR downfield shifts of the free OH group in **1b** induced by coordination of amino esters [including β-alanine methyl ester (**7a′**)] or amine [$\Delta\delta(OH)_{obsd}$],[23] which can be taken as another measure of the hydrogen-bonding interaction between OH and CO_2CH_3 groups.[24] If it is assumed that the partial downfield shifts for **7a**, **7a′**, **8a**, and **9a** reflect partial two-point adduct formation (referring to the two-step processes similar to that shown in Scheme I), K_{HB}'s can be evaluated directly[25] and are also listed in Table IV.

Examination of CPK molecular models indicates that rigid β-amino ester **2a** and α-amino esters **4a** fit for the dual interaction [two-point adduct **1b–2a** in Scheme I and structure **10** (R = CH_3),



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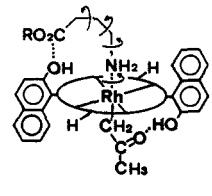


11

respectively]. This is, however, not the case for rigid δ-amino ester **3a**. Flexible β-, γ-, and ϵ-amino esters **7a** and **7a′**, **8a**, and **9a** can form similar two-point adducts by bending their di-, tri-, and pentamethylene backbones, respectively, but practically **8a** and **9a** do not (K_{HB} < 1); this is presumably due to an entropy factor. The formation of two-point adducts **1b–2a** (Scheme I) and **1b–4a** (**10**) requires freezing of rotations around two single bonds, i.e., Rh(III)–N and N–C_α; the associated entropy loss is $\Delta S°_{HB}$ = −5.3 cal/mol·K (Table III) or $-T\Delta S°_{HB}$ = 1.5 kcal/mol. In the case

(23) $\Delta\delta(OH)_{obsd} = \delta(OH)_{obsd} - \delta(OH)_{1b}$, where $\delta(OH)_{obsd}$ and $\delta(OH)_{1b}$ are the chemical shifts of the OH protons for the adduct and **1b**, respectively, at 298 K. See Experimental Section for detail.

(24) The upfield shift observed for adduct **1b–3a** may be due to a ring current effect of the benzene ring of bound **3a**. Examination of CPK models suggests that the benzene ring of **3a** is perpendicular with respect to the two naphthalene rings of **1a**, so as to minimize steric interactions.

(25) $\Delta\delta(OH)_{obsd} = \Delta\delta(OH)(1 + K^{-1}_{HB})$, where $\Delta\delta(OH)$ is the shift for the two-point adduct and is assumed to be the same as that for adduct **1b–4a** (1.63 ppm) and K_{HB} = [two-point adduct]/[one-point adduct].

Table V. Extractabilities (K_{ext}) and Liquid Membrane Transport Rate Constants (k) of Amino Acids (AA) and Their Solubilities in Water (S)

AA	$[AA]_{aq}$, M	(1b–AA)/1b	K_{ext},[a] M^{-1}	S[b]	K_{dis}[c]	k,[d] M^{-1} h^{-1}
4b (X =)						
$CH_2C_6H_5$ (L)	1.53×10^{-1}	0.34	2.2	2.97	4×10^{-8}	1.1×10^{-1}
$CH_2CH(CH_3)_2$ (L)	1.53×10^{-1}	0.28	1.8	2.43	3×10^{-8}	6.8×10^{-2}
$CH(CH_3)CH_2CH_3$ (L)	1.53×10^{-1}	0.13	0.85	4.12	2×10^{-8}	
$(CH_2)_3CH_3$ (DL)	8.77×10^{-2}	0.12	1.4	1.15	3×10^{-8}	5.3×10^{-2}
$CH(CH_3)_2$ (L)	1.53×10^{-1}	0.04	0.27	8.85	5×10^{-9}	
$(CH_2)_2CH_3$ (L)	1.53×10^{-1}	0.04	0.25	10.5[e]	5×10^{-9}	
CH_2CH_3 (DL)	9.70×10^{-1}	0.02	0.02	21.1	4×10^{-10}	3.9×10^{-3}
CH_3 (L)	1.53×10^{-1}	0	0	16.5	0	0
CH_2OH (L)	1.53×10^{-1}	0	0	43.6	0	0
9b	1.53×10^{-1}	0	0	50.5		0

[a] $K_{ext} = (1b–AA)/(1b)[AA]_{aq}$ (eq 6). [b] In g/100 g at 298 K. [c] $K_{dis} = K_{ext}/K_{com} = K_{ext}/(5.5 \times 10^7)$ (eq 11 and ref 30). [d] Reference 32. Reproducibilities are within 15%. [e] At 288 K.

of the hypothetical two-point adduct **1b–8a** (**11**), rotations around two additional C–C bonds must be freezed out with an even larger entropy loss;[26] $\Delta S°_{HB}(8a) < 2 \times (-5.3) = -10.6$ cal/mol·K or $-T\Delta S°_{HB} > 3.1$ kcal/mol.[27,28] If it is assumed that $\Delta H°_{HB}(8a)$ is similar to that for adduct **1b–2a** (−2.8 kcal/mol, Table III), the free energy change for the conversion of **1b–8a** from one-point to two-point adducts can be estimated to be $\Delta G°_{HB}(8a) = \Delta H°_{HB}(8a) - T\Delta S°_{HB}(8a) > -2.8 + 3.1 > 0$ kcal/mol, and hence $K_{HB} < 1$. To summarize, in order for a two-point interaction to occur, the loss in $T\Delta S°$ associated with the weaker interaction, hydrogen bonding, must be more than compensated by the gain in $\Delta H°$. The hydrogen bonding between a phenolic OH group and a CO_2CH_3 group is a weak interaction ($\Delta H° \cong -3$ kcal/mol), so that amino esters having the NH_2 and CO_2CH_3 groups separated by a trimethylene group or a longer alkyl chain practically form only one-point adducts with **1b** without undergoing effective intramolecular hydrogen bonding.

Extraction and Transport of Amino Acids. Reversible amino acid extraction from neutral aqueous solutions was also achieved with **1b**.[29] Thus, vigorous stirring of a $CDCl_3$ solution of **1b** (2.76×10^{-3} M) and an aqueous solution of L-leucine [**4b**, X = $CH_2CH(CH_3)_2$; 1.53×10^{-1} M] at 298 K gave adduct **1b–4b** (**10**, R = H) together with unbound **1b** in a ratio of approximately 1:4 in the organic phase. Variation in $[1b]_{org}$ at constant $[1b]_{aq}$ had little effect on the ratio (**1b–4b**)/**1b**, which in turn was linearly correlated with $[4b]_{aq}$. These results are consistent with an extraction equilibrium as shown in eqs 5 and 6. In Table V are

$$1b_{org} + 4b_{aq} \overset{K_{ext}}{\rightleftharpoons} (1b–4b)_{org} \quad (5)$$

$$\frac{[1b–4b]_{org}}{[4b]_{org}[4b]_{aq}} = K_{ext} \quad (6)$$

summarized the extractabilities as expressed by K_{ext}'s for α-amino acids (**4b**), including L-phenylalanine (X = $CH_2C_6H_5$), L-leucine [X = $CH_2CH(CH_3)_2$], L-isoleucine [X = $CH(CH_3)CH_2CH_3$], DL-2-aminohexanoic acid [norleucine; X = $(CH_2)_3CH_3$], L-valine [X = $CH(CH_3)_2$], L-2-aminopentanoic acid [norvaline; X = $(CH_2)_2CH_3$], DL-2-aminobutyric acid (X = CH_2CH_3), L-alanine (X = CH_3), and L-serine (X = CH_2OH), as well as 6-aminohexanoic acid (**9b**).

All amino acids in Table V are practically insoluble in $CHCl_3$, but an assumption is made here that the extraction equilibrium (eq 5) consists of two elementary processes; the distribution of amino acid (AA) into organic phase with an unmeasurably small equilibrium constant K_{dis} (eqs 7 and 8) and the complexation of

$$AA_{aq} \overset{K_{dis}}{\rightleftharpoons} AA_{org} \quad (7)$$

$$[AA]_{org}/[AA]_{aq} = K_{dis} \quad (8)$$

$$1b_{org} + AA_{org} \overset{K_{com}}{\rightleftharpoons} (1b–AA)_{org} \quad (9)$$

$$[1b–AA]_{org}/[1b]_{org}[AA]_{org} = K_{com} \quad (10)$$

$$[1b–AA]_{org}/[1b]_{org}[AA]_{aq} = K_{dis}K_{com} \quad (11)$$

AA with **1b** in homogeneous organic phase with an equilibrium constant K_{com} (eqs 9 and 10). Combination of eq 8 and 10 leads to eq 11. In connection with eq 6, $K_{ext} = K_{dis}K_{com}$. This treatment is intended not to refer to the actual mechanism of extraction but to show that effective amino acid extraction is subject to two factors. The first is K_{dis} or the lipophilicity of an amino acid,[6b] a measure of which is its solubility in water, as also listed in Table V. This factor controls the extractabilities of α-amino acids, which are expected to have similar K_{com}'s $\cong 5.5 \times 10^7$ M^{-1}, irrespective of side chains.[30,31] Thus, highly hydrophilic serine, alanine, and 2-aminobutyric acid as well as **9b** are hardly extractable, in marked contrast to relatively lipophilic phenylalanine, leucine, isoleucine, and norleucine, which are readily extracted; valine and norvaline provide a borderline case. There is indeed a roughly inverse correlation between extractabilities (K_{ext}) of α-amino acids and their solubilities in water (S). Referring to eq 11 ($K_{com} \cong 5.5 \times 10^7$ M^{-1}) and $K_{ext} = K_{dis}K_{com}$ (Table V), K_{dis} can be evaluated for each α-amino acid and is also shown in Table V.

The second factor is K_{com} or the intramolecular hydrogen bonding. When **6** was used in place of **1b**, no extraction of leucine was observed, indicating that, in addition to lipophilicity, the intramolecular hydrogen bonding with an estimated free energy change $\Delta G°_{HB} \cong -3.5$ kcal/mol[30] also plays a crucial role in the extraction of α-amino acids.

Similar extractabilities of phenylalanine and leucine (Table V) suggest that π stacking interaction involving an aromatic amino acid is not so important. This apparently requires some comments in light of recent publications of Rebek et al., demonstrating its

(26) Actual internal rotations are not free but restricted. In one-point adduct **1b–8a**, the rotations around Rh(III)–N and N–C_α bonds must be more restricted due to the presence of the bulky porphyrin macrocycle than those around C–C bonds.

(27) Calculation shows that the entropy of free internal rotation in $(CH_3)_2Hg$ is 2.98 cal/mol·K: Moore, W. J. *Physical Chemistry*, 3rd ed.; Prentice-Hall: Englewood Cliffs, NJ, 1962.

(28) The relationship between rates and conformational flexibilities based on internal rotation for intramolecular reactions has been a subject of considerable studies. Bruice and Pandit, for example, noted that freezing of rotation of one CH_2 moiety requires ca. 3 kcal/mol: Bruice, T. C.; Pandit, U. K. *Proc. Natl. Acad. Sci. U.S.A.* **1960**, *46*, 402. Also see: (a) Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1963**, *85*, 1. (b) Bruice, T. C.; Turner, A. *Ibid.* **1970**, *92*, 3422. (c) Bruice, T. C.; Bradbury, W. C. *Ibid.* **1965**, *87*, 4846. (d) Milstien, S.; Cohen, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1143. (e) Storm, D. R.; Koshland, D. E., Jr. *Ibid.* **1970**, *66*, 445. (f) Bruice, T. C.; Brown, A.; Harris, D. O. *Ibid.* **1971**, *68*, 658.

(29) For a recent study on neutral amino acid transport, see: Reference 6f.

(30) Homogeneous amino acid binding with **1b** in $CHCl_3$ could not be studied directly because of the insolubility of amino acids. The associated free energy change, $\Delta G°_{com} = \Delta G°_{MC} + \Delta G°_{HB}$, can be estimated by assuming that $\Delta G°_{MC}$ is equal to that for amino ester binding (−6.7 kcal/mol)[6g] and $\Delta G°_{HB}$ is approximated to that for amino ester binding (−2.1 kcal/mol)[6g] after correction for the difference (−1.4 kcal/mol) in the hydrogen bonding involving CO_2CH_3 and CO_2H groups ($\Delta G°_{HB} = -1.3$ and −2.7 kcal/mol for adducts **1b–2a** and **1b–2b**, respectively; Table III); $\Delta G°_{HB} = -2.1 + (-1.4) = -3.5$ kcal/mol. Consequently, $\Delta G°_{com} = -6.7 + (-3.5) = -10.2$ kcal/mol and hence $K_{com} = 5.5 \times 10^7$ M.

(31) ^1H NMR analyses of competitive binding of phenylalanine and leucine methyl esters or alanine and leucine methyl esters for **1b** in $CDCl_3$ indicated that these three α-amino esters have similar affinities to **1b**.

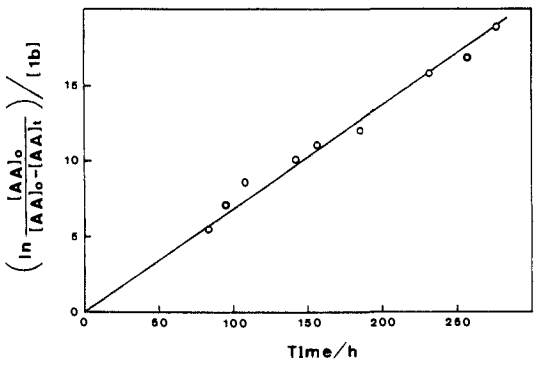
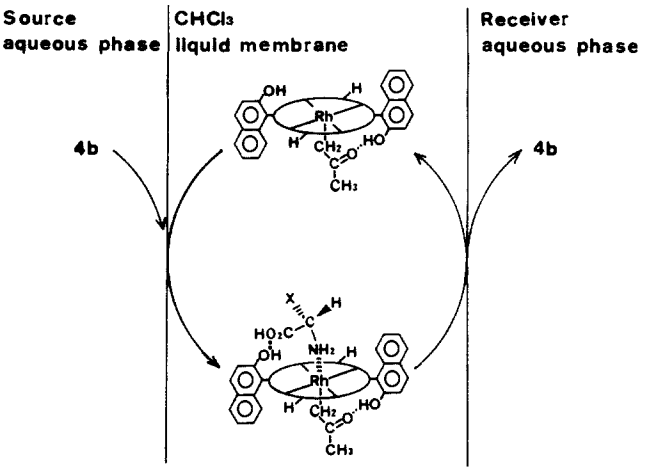


Figure 2. Time course of leucine transport across a $CHCl_3$ liquid membrane containing **1b** as carrier (3.73×10^{-3} M) at 288 K. $[AA]_0 = 7.63 \times 10^{-2}$ M and ($[AA]_0 - [AA]_t$) stand for concentrations of leucine in the source aqueous phase at time 0 and t, respectively, where $[AA]_t$ is the concentration of leucine transported in the receiver phase at time t. For analysis of the data according to the first-order kinetics, see ref 32.

Scheme II



importance.[6e,f] The aromatic stacking interaction in apolar organic media is generally weak as compared with the present metal coordination and hydrogen-bonding interactions ($\Delta G°_{MC} = -6.7$ and $\Delta G°_{HB} \cong -3.5$ kcal/mol).[30] The two stronger interactions thus determine the relative geometry of adduct **1b**–(phenylalanine), where the benzene ring of the amino acid can be located only above the edge of the porphyrin plane or additional naphthalene ring.

The amino acid thus solubilized in $CHCl_3$ could be readily and completely reextracted into H_2O owing to the reversible nature of adduct formation. Liquid membrane transport of amino acids with **1b** as a carrier was carried out by using an H-tube. Figure 2[32] shows a typical time course of leucine transport from a source aqueous phase (10 mL) containing L-leucine (7.63×10^{-2} M) to a receiver aqueous phase (10 mL) through a $CHCl_3$ liquid membrane (10 mL) containing **1b** (3.73×10^{-3} M) in a cylindrical H-tube with an inner diameter of 1.5 cm (section area, 1.8 cm^2) at 288 K under gentle stirring. No transport of leucine was observed in the absence of **1b** or in the presence of **6** instead of **1b**, indicating that the leucine transport is mediated by **1b** via complexation–decomplexation cycles (Scheme II).[6b,e,f] The transport rate constants (k)[32] for selected amino acids are shown in Table V. There is a reasonable parallel between K_{ext} and k.

Lipophilic α-amino acids can thus be separated from hydrophilic α-amino acids such as alanine and "remote" amino acids such as **9b**.[33]

Conclusion

This work provides a novel example of detailed thermodynamic studies on the two-point binding of amino acids and esters in nonionic forms. The use of metalloporphyrin as a bifunctional binder is significant in that the binding constants are readily determined by spectrophotometric titration so as to allow the weaker interaction, hydrogen bonding, to be well characterized. The intermolecular hydrogen bonding is a weak interaction, where favorable enthalpy change is cancelled by unfavorable entropy change. However, the intramolecular nature of the hydrogen bonding in the present two-point interactions renders associated entropy changes less unfavorable; this results in considerable net gains in free energy in cases of α- and rigid β-amino acids and esters. The hydrogen bonding thus brings about significant selectivities for homogeneous binding of these and also plays a crucial role in the extraction of relatively lipophilic α-amino acids from neutral aqueous solutions.

Experimental Section

General Procedures. ^1H NMR spectra at 270 MHz were taken for $CDCl_3$ solutions of Rh complex ($\sim 5 \times 10^{-3}$ M) on a JEOL-GX 270 spectrometer. The OH and NH proton resonances were identified by deuteriation. IR spectra were obtained for $CHCl_3$ solutions with a Jasco IR-810 spectrophotometer. Electronic spectra were recorded with a Hitachi 320 spectrophotometer. Chlororhodium(III) complexes of *trans*-5,15-bis(2-hydroxy-1-naphthyl)octaethylporphyrin (**1a**), acetone–Rh(III) derivative of **1a** (**1b**), cis isomer of **1b** (**6**), and tetraphenylporphyrin (TPP) were prepared as described.[11a,34] Amino acids used here are commercial products of the highest grades. Amino acid methyl esters were also commercially available either as free bases [methyl esters of *o*-aminobenzoic acid (**2a**) and *p*-aminobenzoic acid (**3a**)] or as hydrochlorides [methyl esters of α-amino acids (**4a**) and β-alanine (**7a'**)], which were converted to free bases on treatment with aqueous K_2CO_3 if necessary. Methyl esters of 3-aminobutyric acid (**7a**), 4-aminobutyric acid (**8a**), and 6-aminohexanoic acid (**9a**) were prepared by esterification of the corresponding amino acids with methanol in the presence of HCl.

Amino Ester and Amino Acid Adducts of 1a. Amino ester adducts of **1a** were prepared either by stirring of a homogeneous solution of **1a** and a slightly excess amount of amino ester (**2a** or **3a**) in $CHCl_3$ or by stirring of a two-phase mixture of a solution of **1a** in $CHCl_3$ (1 vol) and an aqueous solution (10 vols) of a hydrochloride salt of amino ester (**4a**, **7a**, **8a**, and **9a**; 0.1 M) for 15–24 h. Amino acid adducts of **1a** were also conveniently obtained by extracting amino acids in water into a $CHCl_3$ solution of **1a**. All the adducts could be isolated by chromatography on silica (Wakogel C-200) and the yields were nearly quantitative in all cases. Adduct **1a**–**4a** (X = $CH_2C_6H_5$) in a $CHCl_3$ solution underwent neither amino ester exchange in the presence of a large excess amount of the second amino ester nor decomplexation upon treatment with 6 N aqueous HCl for 24 h. These results indicated that the adduct formation with **1a** is practically irreversible. Consistent with this, all the adducts gave sharp ^1H NMR signals for coordinated amino ester or amino acid ligands. Their characteristic upfield shifts due to the porphyrin ring current effect facilitated the assignments and identifications; ^1H NMR integration readily established the 1:1 stoichiometry (**1a** to amino ester or amino acid). For the spectroscopic data for adducts **1a**–**2a**, **1a**–**3a**, **1a**–**4a** (X = $CH_2C_6H_5$), and **1a**–**4b** (X = $CH_2C_6H_5$), see text and ref 6g. The ^1H NMR data for coordinated **4a** [X = $CH_2CH(CH_3)_2$] and **9a** ligands as other representative examples are as follows. For **1a**–**4a**: δ −4.33 and −5.46 (both 1 H, diastereotopic NH_2), −3.51 (1 H, $CHNH_2$), −1.47 (2 H, $CH_2CH(CH_3)_2$), −0.89 (1 H, $CH(CH_3)_2$), −0.23 and −0.68 (both 3 H, $CH(CH_3)_2$), 3.03 (3 H, CO_2CH_3). For **1a**–**9a**: δ −5.48 (2 H, NH_2), −3.53 (2 H, CH_2), −1.48 (2 H, CH_2), −0.66 (2 H, CH_2), 0.32 (2 H, CH_2), 3.42 (3 H, CO_2CH_3).

Amino Ester and Amino Acid Adducts of 1b. Amino ester adducts of **1b** were obtained by stirring of a $CHCl_3$ or $CDCl_3$ solution of **1b** (5×10^{-3} M) and an amino ester in an equimolar (in case of **4a**) or a slightly excess amount to allow nearly complete conversion of **1b** to its adduct. *o*- and *p*-Aminobenzoic acid adducts **1b**–**2b** and **1b**–**3b** were obtained in

(32) The transport rate $d[AA]_r/dt = k_2[\mathbf{1b}\text{–}AA]_{org}$, where AA stands for amino acid, subscript r refers to the receiver aqueous phase, and k_2 is the rate constant for reextraction of AA into one of aqueous phases upon decomplexation of **1b**–AA. The electronic spectrum of the organic phase during transport of AA was that of **1b**, indicating that $[\mathbf{1b}\text{–}AA]_{org}$ was very small. If a steady-state approximation is applied to $(\mathbf{1b}\text{–}AA)_{org}$, $d[\mathbf{1b}\text{–}AA]_{org}/dt = k_1[\mathbf{1b}]_{org}[AA]_s - 2k_2[\mathbf{1b}\text{–}AA]_{org} = 0$ at an early stage of transport, where subscript s refers to the source aqueous phase and k_1 is the rate constant for bimolecular complexation of AA_s and $\mathbf{1b}_{org}$. Thus, the transport rate $d[AA]_r/dt = -d[AA]_s/dt = (k_1/2)[\mathbf{1b}]_{org}[AA]_s$ and the experimentally obtained rate constant k (as the slope of Figure 2) is actually $k_1/2$.

(33) The present system can also be modified so as to allow three-point interaction with amino acids:[9] (a) Reference 6h. (b) Aoyama, Y.; Saita, K.; Toi, H.; Ogoshi, H. *Tetrahedron Lett.* **1987**, *28*, 4853. Chiral discrimination in the amino acid extraction and transport will be reported soon.

(34) Sadasivan, N.; Fleisher, E. B. *J. Inorg. Nucl. Chem.* **1968**, *30*, 591.

a similar manner. The adducts could not be isolated because of their reversible nature (eq 1), but were readily characterized by means of UV–vis (vide infra), IR, and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra at 298 K of $CDCl_3$ solutions prepared as above gave a single signal, at δ 7.19 in the case of adduct **1b–4a** [X = $CH_2CH(CH_3)_2$], for the otherwise free OH proton of **1b** (δ 5.56 at 298 K). The downfield shifts, 1.63 ppm in this case, are listed in Table IV for various amino ester adducts. The NMR spectra at 298 K, on the other hand, gave no distinct signals for coordinated amino ester ligands as a result of exchange between bound and free amino ester molecules due to reversibility of the adduct formation (eq 1). Sharp signals, however, were observed at 243 K; ^{1}H NMR integration showed the 1:1 (**1b** to amino ester) stoichiometry. The selectivity in the competitive binding with **1b** of two amino esters [**2a** vs **3a**, **4a** (X = $CH_2CH(CH_3)_2$) vs **4a** (X = $CH_2C_6H_5$), or **4a** (X = $CH_2CH(CH_3)_2$) vs **4a** (X = CH_3)] was based on direct ^{1}H NMR integration of the characteristic and distinct upfield-absorptions for the two adducts in the spectrum taken at 243 K for an equimolar mixture of **1b** and two amino esters. It was notable that in the chiral α-amino ester adducts (**1b–4a**) the two CH_2 protons in the Rh–CH_2COCH_3 moiety, like two NH_2 protons, were rendered diastereotopic and gave split signals. For the spectroscopic data for adducts **1b–4a** [X = $CH_2CH(CH_3)_2$], **6–4a** [X = $CH_2CH(CH_3)_2$], and **1b–5** 4-aminoheptane adduct), see ref 6g. The characteristic ^{1}H NMR absorptions in the high-field region for other amino ester ligands are as follows. For **1b–2a**: δ −0.08 and −3.37 (NH_2). For **1b–3a**: δ −3.01 (NH_2). For **1b–4a** (X = $CH(CH_3)_2$): δ −4.66 and −5.64 (NH_2), −3.53 ($CHNH_2$), −1.24 and −1.31 ($CH(CH_3)_2$), −0.23 ($CH(CH_3)_2$). For **1b–4a** (X = CH_3): δ −4.42 and −5.72 (NH_2), −2.88 ($CHNH_2$), −1.13 (CH_3). For **1b–4a** [X = $(CH_2)_3CH_3$]: δ −4.61 and −5.48 (NH_2), −3.35 ($CHNH_2$), −1.27 (CH_2), −1.00 and −0.48 (CH_2), −0.03 (CH_2), 0.15 (CH_3). For **1b–7a**: δ −4.91 and −5.37 (NH_2), −2.42 (CH_3CHNH_2), −2.08 ($CHNH_2$), −1.62 and −0.14 (CH_2). For **1b–7a′**: δ −5.18 (NH_2), −2.25 (CH_2), −0.88 (CH_2). For **1b–8a**: δ −5.42 (NH_2), −3.02 (CH_2), −1.11 (CH_2), 0.59 (CH_2). For **1b–9a**: δ −5.58 (NH_2), −3.11 (CH_2), −1.42 (CH_2), −0.47 (CH_2), 0.45 (CH_2).

Spectrophotometric Titration. Compound **1b** (λ_{max} 410, 526, and 557 nm for $CHCl_3$ solution) and **6** (λ_{max} 410, 525, and 557 nm) underwent a considerable red-shift of their absorption maxima upon adduct formation with amines (**2–5** and **7–9**); e.g., λ_{max} for **1b–2a** 422, 532, and 562 nm and λ_{max} for **1b–4a** [X = $CH_2CH(CH_3)_2$] 421, 537, and 567 nm. Spectra in the region of 500–600 nm for solutions of **1b** or **6** (5.0×10^{-5} M) and varying amounts of **2a**, **3a**, **2b**, or **3b** in a thermostated cell set in the spectrophotometer were recorded at various temperatures, where isosbestic points were observed at 523, 544, and 561 nm in the case of titration of **1b** with **2a**. A 100% or saturation binding was readily attained in every case with a sufficiently large excess amount of amine. The binding constants (K) were obtained from absorbance changes (ΔA) at 557 nm, a λ_{max} for **1b** and **6**, according to K = [complex]/[**1b** or **6**][amine], where [amine] = $[\text{amine}]_{total}$ − [complex], [**1b** or **6**] = $[\textbf{1a}$ or $\textbf{6}]_{total}$ − [complex], and [complex] = $(\Delta A_{obsd}/\Delta A_{sat})[\textbf{1a}$ or $\textbf{6}]_{total}$. The K values listed in Table I are averages of those obtained at about five different amine concentrations, which cover 20–80% binding, i.e., $\Delta A_{obsd} = 0.2\Delta A_{sat}$–$0.8\Delta A_{sat}$. The errors in K's are within 6% in the case of adducts **1b–3a**, **1b–3b**, **6–2a**, **6–2b**, **6–3a**, and **6–3b**, within 10% in the case of **1b–2a**, and within 15% in the case of **1b–2b**. ΔA_{sat} observed and amine concentration ranges used are as follows: 0.66 and 3.3×10^{-5}–3.3×10^{-4} M for **2a**; 0.66 and 1.0×10^{-4}–1.0×10^{-3} M for **3a**; 0.70 and 2.1×10^{-5}–1.0×10^{-4} M for **2b**; and 0.66 and 2.5×10^{-4}–2.0×10^{-3} M for **3b**. Thermodynamic parameters were evaluated from the usual ln K vs $1/T$ plots according to the equations, $K = \exp(-\Delta G°/RT)$ and $\Delta G° = \Delta H° - T\Delta S°$.

^{1}H NMR Titration of 1b with Methyl Acetate. A series of $CDCl_3$ solutions of **1b** with and without varying amounts of methyl acetate were prepared. The ^{1}H NMR spectra taken at 243, 273, and 298 K showed a single absorption for the otherwise free OH proton of **1b** (δ 5.61, 5.58, and 5.56 at 243, 273, and 298 K, respectively), indicating that the exchange between **1b** and **1b**–$CH_3CO_2CH_3$ (eq 3) is rapid even at 243 K.

Extraction and Transport of Amino Acids. A $CDCl_3$ solution of **1b** (2.76×10^{-3} M, 0.6 mL) was stirred vigorously with an aqueous solution of L-leucine [**4b**, X = $CH_2CH(CH_3)_2$; 1.53×10^{-1} M, 10 mL] in a sealed test tube at 298 K for 72 h. Stirring for 72 h was independently shown to be sufficient for the equilibrium (eq 5) to be attained. The ^{1}H NMR spectrum at 243 K of the organic phase separated from the aqueous phase showed the presence of unbound **1b** and adduct **1b–4b**; the latter gave sharp and characteristic signals for the leucine ligand in a manner similar to adduct **1b–4a**. The molar ratio of (**1b–4b**)/**1b** = 0.28 was determined from the ratio of ^{1}H NMR integration of the CH_3 signals for coordinated **4b** at δ −0.13 and −0.98 to that of the CH_3 signal for the CH_3COCH_2–Rh moiety of unbound **1b** at δ −1.90. The extractabilities of other amino acids were evaluated similarly by referring to ^{1}H NMR integration of the methine proton ($CHNH_2$) at δ −2.39 (L-phenylalanine adduct; **1b–4b**, X = $CH_2C_6H_5$) or that of characteristic CH_3 resonances; δ −0.33 and −1.33 [L-isoleucine adduct; **1b–4b**, X = $CH(CH_3)CH_2CH_3$], 0.16 [DL-norleucine adduct; **1b–4b**, X = $(CH_2)_3CH_3$], −1.23 and −1.38 [L-valine adduct; **1b–4b**, X = $CH(CH_3)_2$], −0.48 [L-norvaline adduct; **1b–4b**, X = $(CH_2)_2CH_3$], and −1.36 (DL-2-aminobutyric acid adduct; **1b–4b**, X = CH_2CH_3). Control runs with lower concentrations of aqueous leucine indicated that the extractabilities, (**1b–4b**)/**1b**, are nearly proportional to $[\textbf{4b}]_{aq}$, and no extraction of leucine was observed when **6** was used in place of **1b**.

Liquid membrane transport of amino acids was carried out by using an H-tube composed of two test tubes (inner diameter, 1.5 cm) connected with a glass tube (length, 2.5 cm; inner diameter, 0.6 cm) at the point 2 cm from the bottoms. The source and receiver solutions were stirred at 600 rpm, as measured by a digital tachometer. Analysis of amino acids transported into the receiver phase was performed by means of HPLC on a Shimadzu ODS-H column using CH_3CN–H_2O as eluant, and the components eluted were detected by either UV absorption at 254 nm (in the case of phenylalanine) or RI change (in the case of nonaromatic amino acids). The transport rate constants (k) listed in Table V are averages of those for two or more runs and the reproducibilities were within 15%.

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