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Molecular Recognition of α-Amino Acid Esters with Arylporphyrin Zinc Complexes

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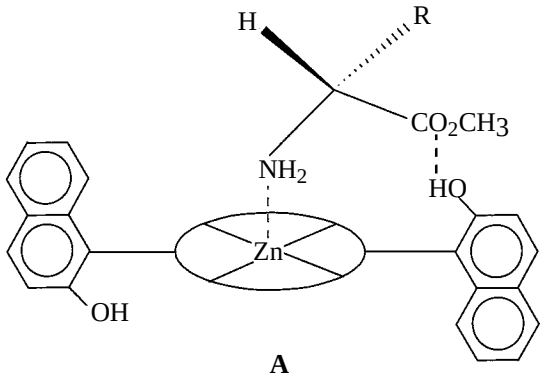
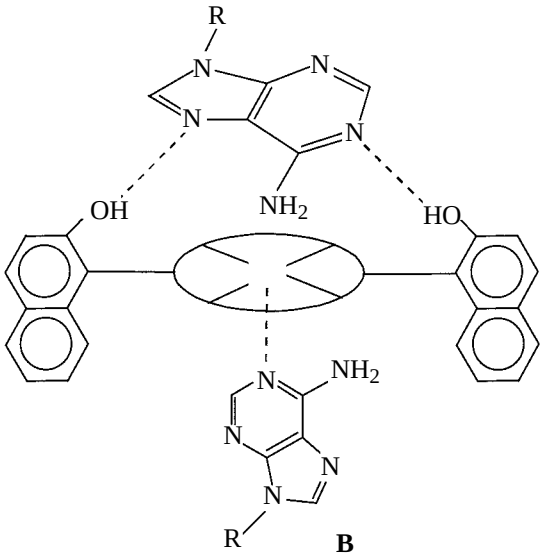
Abstract — The recognition ability of 10 arylporphyrin zinc complexes with respect to glycine, α-alanine, and leucine methyl esters in toluene at 20°C was studied by spectrophotometric titration. The formation of amino acid–porphyrin associates, depending on the substitution pattern in the macroring, was examined by ^{1}H NMR spectroscopy. The zinc complex with diarylporphyrin having hydroxy groups in the *para* positions of the benzene rings was found to be the best recognizing agent with respect to glycine methyl ester, while leucine methyl ester was recognized best by the complex with hydroxy groups in the *ortho* positions of the benzene rings.

Molecular recognition can be defined as a process including binding of two or more molecules into associates according to the guest–host pattern and selection of a guest molecule by a given host molecule. A distinguishing feature of molecular recognition is a considerably higher host–guest association constant (k_{as}) as compared to complex formation (association) constants with other molecules. First publications on the recognition ability of porphyrins appeared in the early 1990s. The set of compounds which can be recognized by porphyrins is fairly large. It includes amino acids [1–3], nucleic acid bases [4, 5], sugars [6–8], morphine [9], etc. Below are shown two examples of molecular recognition with porphyrin zinc complexes [1, 4].

In the first case (structure **A**) [1], recognition of amino acids is based on their coordination to the metal in the porphyrin complex with simultaneous formation of hydrogen bonds with groups located at the periphery of the macroring (two points of recognition). To avoid formation of hydrogen bonds between the hydroxy oxygen atom of the porphyrin and carboxy proton of the amino acid, the corresponding methyl ester was used instead of the free acid. Associates formed by a series of amino acids with com-



A



B

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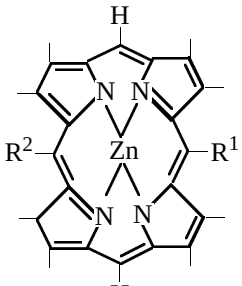
plexes derived from 2,3,7,8,12,13,17,18-octaethyl-*trans*-5,15-bis(2-hydroxy-1-naphthyl)porphyrin, 2,3,7,8,12,13,17,18-octaethyl-*trans*-5,15-bis(2-methoxy-1-naphthyl)porphyrin, and 2,3,7,8,12,13,17,18-octaethyl-*trans*-5,15-bis(1-naphthyl)porphyrin were studied. Analysis of the k_{as} values showed the best recognizing agent is the porphyrin complex having hydroxy groups in the 2 positions of the naphthyl fragments. In the second case (structure **B**), two hydrogen bonds with the peripheral groups are formed, and the substrate coordinates to the metal ion, i.e., the process involves one porphyrin complex molecule and two molecules of a nucleic acid base (three points of recognition) [4]. While studying recognition with porphyrins of amino acid esters capable and incapable of forming hydrogen bonds, Mizutani *et al*. [1] estimated the contributions of the proper extra coordination energy (ΔG_{MC}) and hydrogen bonding (ΔG_{HB}) to the total association energy (ΔG_{tot}).

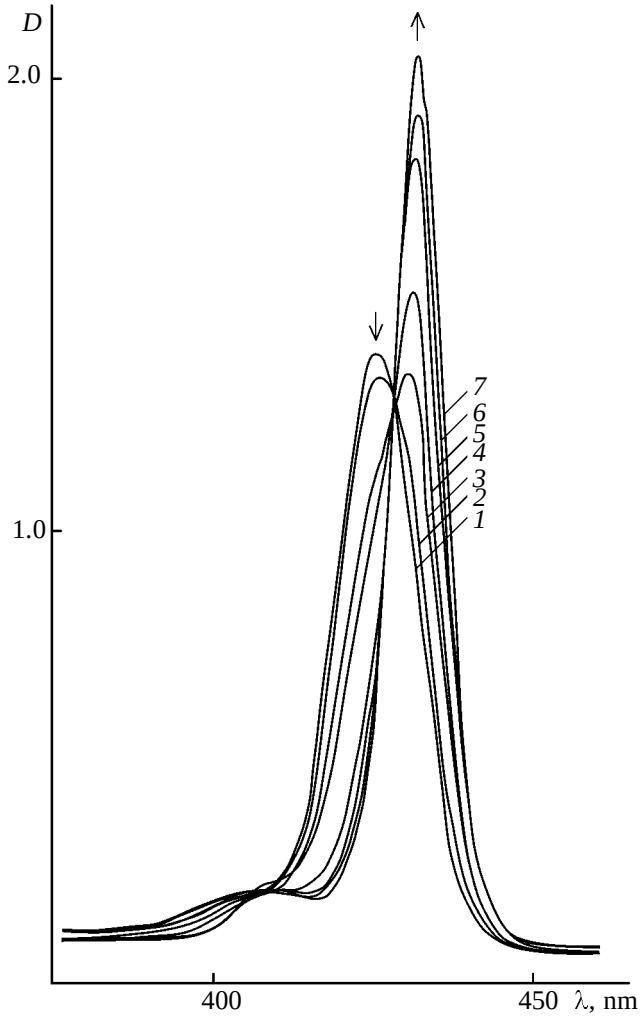
The goal of the present work was to study formation of amino acid–porphyrin associates using glycine, α-alanine, and leucine methyl esters and a series of phenylporphyrins **I**–**X** differing by the position of hydroxy (methoxy) group in the benzene rings and by the number of 2-hydroxyphenyl rings.



I–**X**

I, R^1 = H, R^2 = Ph; **II**, R^1 = H, R^2 = 2-$CH_3OC_6H_4$; **III**, $R^1 = R^2$ = 2-$CH_3OC_6H_4$ (*trans*); **IV**, $R^1 = R^2$ = 3-$CH_3 \cdot OC_6H_4$; **V**, $R^1 = R^2$ = 4-$CH_3OC_6H_4$; **VI**, $R^1 = R^2$ = 4-HOC_6H_4; **VII**, R^1 = H, R^2 = 3-HOC_6H_4; **VIII**, $R^1 = R^2$ = 2-HOC_6H_4 (*trans*); **IX**, $R^1 = R^2$ = 3-HOC_6H_4; **X**, $R^1 = R^2$ = Ph.

The figure shows changes in the electronic absorption spectrum occurring upon addition of glycine methyl ester to porphyrin **IV**. The presence of several isosbestic points indicates formation of a 1 : 1 complex between the porphyrin and amino acid ester. The calculated values of k_{as} are given in Table 1. The association constants determined for porphyrins **I**–**V** and **X** are in fact extra coordination constants which characterize the stability of the porphyrin–extra ligand complex with a single binding point [via coordination to Zn(II)]. Insofar as extra coordination of various



Electronic absorption spectra of solutions of [2,8,12,18-tetrabutyl-5,15-bis(4-hydroxyphenyl)-3,7,13,17-tetramethylporphyrinato]zinc (**VI**) in the presence of (*1*) 0, (*2*) 7.2×10^{-5}, (*3*) 1.4×10^{-4} (*4*) 3.6×10^{-4} (*5*) 6.5×10^{-4}, (*6*) $7.2 \times 10{-}3$, and (*7*) 8.6×10^{-2} mol/l of glycine methyl ester; toluene, 20°C.

molecules to porphyrin metal complexes was the subject of study as long as 40–50 years [10] and was well documented, we shall not consider this topic in detail. By comparing our k_{as} values (i.e., the stability constants of the complexes obtained as a result of extra coordination) with published data for analogous complexes of tetraphenylporphyrin in toluene, we can only note that amino acids are less strong extra ligands than piperidine (k_{as} = 80 900 l mol^{-1}), imidazole (k_{as} = 24 000 l mol^{-1}), and quinoline (k_{as} = 16 900 l mol^{-1}) but considerably stronger than pyrrole (k_{as} = 200 l mol^{-1}), methanol (k_{as} = 5 l mol^{-1}), and other alcohols [10]. Amino acids are most similar to

Table 1. Association constants k_{as} (l mol^{-1}) of porphyrin zinc complexes **I**–**X** with amino acid methyl esters in toluene at 20°C

Porphyrin	GlyOMe	α-AlaOMe	L-LeuOMe
I	1510	920	1220
II	1340	788	1034
III	1400	910	1500
IV	1430	920	1550
V	1420	915	1540
VI	3270	1710	1850
VII	1420	960	1450
VIII	1680	1840	3150
IX	2730	1640	2480
X	1750	1020	1660

pyridine (k_{as} = 5000 l mol^{-1}) in their extra coordination properties. A small increase in k_{as} is observed on raising the number of phenyl substituents in the porphyrin molecule, while introduction of methoxy groups into the phenyl rings leads to a slight decrease in k_{as} (Table 1). An analogous relation was revealed for tetrakis(methoxyphenyl)porphyrin [10]. Some reduction of k_{as} also occurs in going from glycine to α-alanine. This also follows from the data in Tables 2 and 3 (ΔG_{MC} for glycine is greater by 0.6–0.7 kJ mol^{-1} than the corresponding value for α-alanine) and is consistent with those reported in [1].

Table 3. Energies of hydrogen bonds (ΔG_{HB}, kJ mol^{-1}) and extra coordination (ΔG_{MC}, kJ mol^{-1}) and total Gibbs energies of association (ΔG_{tot}, kJ mol^{-1}) for porphyrin zinc complexes with amino acid esters relative to complexes **II**–**V**[a]

Complex	$-\Delta G_{tot}$	$-DG_{MC}$	$-\Delta G_{HB}$	Reference porphyrin
VII–GlyOMe	17.67	17.53	0.14	**II**
VIII–GlyOMe	18.08	17.64	0.44	**III**
IX–GlyOMe	19.26	17.69	1.57	**IV**
VI–GlyOMe	19.70	17.67	2.03	**V**
VII–α-AlaOMe	16.72	16.24	0.48	**II**
VIII–α-AlaOMe	18.31	16.60	1.71	**III**
IX–α-AlaOMe	18.02	16.59	1.43	**IV**
VI–α-AlaOMe	18.13	16.62	1.51	**V**
VII–L-LeuOMe	17.73	16.91	0.82	**II**
VIII–L-LeuOMe	19.61	17.80	1.81	**III**
IX–L-LeuOMe	19.03	17.89	1.14	**IV**
VI–L-LeuOMe	18.32	17.87	0.45	**V**

[a] See note a to Table 2.

Table 2. Energies of hydrogen bonds (ΔG_{HB}, kJ mol^{-1}) and extra coordination (ΔG_{MC}, kJ mol^{-1}) and total Gibbs energies of association (ΔG_{tot}, kJ mol^{-1}) for porphyrin zinc complexes with amino acid esters relative to complexes **I** and **X**[a]

Complex	$-\Delta G_{tot}$	$-DG_{MC}$	$-\Delta G_{HB}$	Reference porphyrin
VII–GlyOMe	17.67	17.67	0	**I**
VIII–GlyOMe	18.08	18.08	0	**X**
IX–GlyOMe	19.26	18.18	1.08	**X**
VI–GlyOMe	19.70	18.18	1.52	**X**
VII–α-AlaOMe	16.72	16.72	0	**I**
VIII–α-AlaOMe	18.31	16.87	1.44	**X**
IX–α-AlaOMe	18.02	16.86	1.16	**X**
VI–α-AlaOMe	18.13	16.87	1.26	**X**
VII–L-LeuOMe	17.73	17.73	0.42	**I**
VIII–L-LeuOMe	19.61	18.05	1.56	**X**
IX–L-LeuOMe	19.03	18.05	0.98	**X**
VI–L-LeuOMe	18.32	18.06	0.26	**X**

[a] $\Delta G_{tot} = -RT\ln k_{as}$; $\Delta G_{HB} = -RT\ln (k'_{as}/k''_{as})$; $\Delta G_{MC} = \Delta G_{tot} - \Delta G_{HB}$.

The ratio k'_{as}/k''_{as}, where k'_{as} is the association constant for porphyrin having hydroxy groups, and k''_{as} is the association constant for analogous porphyrin having no hydroxy groups, can be regarded as a quantitative measure of the contribution of hydrogen bond to increase in the association strength. The data in Table 1 show that hydrogen bonds between the oxygen atom of amino acid and hydroxy hydrogen atom of porphyrin are not necessarily formed when amino acid coordinates to metal–porphyrin complex possessing hydroxy groups (compounds **VI**–**IX**). No hydrogen bonds are formed between glycine methyl ester and porphyrins **VII** and **VIII** 2 hydroxy group in the phenyl fragments. Weak hydrogen bonds are formed with 3-hydroxyphenyl-substituted porphyrin **IX**, while the strongest hydrogen bond was found for 4-hydroxyphenylporphyrin **VI**. The reverse pattern is typical of leucine methyl ester (Table 1), which forms the strongest hydrogen bonds with 2-hydroxyphenylporphyrin **VIII**. The strength of H-bonding successively decreases in going to 3- and 4-hydroxyphenyl derivatives **IX** and **VI**. α-Alanine methyl ester gives rise to almost equally strong hydrogen bonds with 4-, 3-, and 2-hydroxy-substituted arylporphyrins (Table 1). The formation of hydrogen bond is possible when the ester group is arranged at a definite angle with respect to the hydroxy group in porphyrin. The magnitude of this angle is determined by steric repulsion between the substituent R in the amino acid [R = H, CH_3, and

$CH_2CH(CH_3)_2$ in glycine, α-alanine, and leucine, respectively] and the porphyrin macroring. Steric repulsion is likely to direct the ester moiety toward the hydroxy group, leading to a conformation favorable for hydrogen bonding. Presumably, the size of the R substituent determines the most favorable position of the hydroxy group in the benzene ring (*para*, *meta*, or *ortho*). The larger the substituent, the shorter the maximal distance between the NH_2 and C=O groups in amino acid, and the more favorable for H-bonding is *ortho* position of the hydroxy group and vice versa. The number of phenyl fragments containing hydroxy groups also affects k_{as}. Probably, this is connected with the probability factor; i.e., the greater the number of hydroxyphenyl groups, the higher the probability for formation of associates like **A**.

The formation of amino acid–porphyrin associates was also studied by ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum of porphyrin complex **VI** in the presence of 5 equiv of glycine, the OH signal shifts downfield by 1.4 ppm. A comparable shift (δ = 1.0 ppm) was observed for porphyrin **VIII** in the presence of leucine. In keeping with published data [1], these findings indicate formation of strong hydrogen bonds between the carbonyl oxygen atom in the amino acid and hydrogen atom of the hydroxy group in the porphyrin. We can conclude that the recognition ability of arylporphyrin zinc complexes with respect to amino acid esters in toluene depends on the position of hydroxy groups in the benzene rings. Hydroxyphenylporphyrin complexes in which the hydroxy group is located in the 4 position recognize glycine methyl ester best. *o*-Hydroxyphenyl-substituted compounds exhibit the greatest recognition ability with respect to leucine methyl ester. α-Alanine methyl ester is approximately equally recognized by porphyrins having *o*-, *m*-, and *p*-hydroxyphenyl substituents. The recognition ability increases in going from porphyrins containing one meso-hydroxyphenyl group to those possessing two such groups. The recognition ability of diphenylporphyrin complexes toward amino acid esters is generally lower than that of analogous dinaphthylporphyrin complexes.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker-200 spectrometer operating at 200 MHz ($CDCl_3$, 20°C). The IR spectrum was obtained in KBr on a Specord M-80 instrument. The electronic absorption spectra were measured on a Specord M-400 spectrophotometer from solutions in chloroform. The zinc complexes of 2,8,12,18-tetrabutyl-3,7,13,17-tetramethyl-5-phenylporphyrin (**I**) and 2,8,12,18-tetrabutyl-5-(2-methoxyphenyl)-3,7,13,17-tetramethylporphyrin (**II**) were synthesized by the procedure reported in [11]. The zinc complexes of 2,8,12,18-tetrabutyl-5,15-bis(2-methoxyphenyl)-3,7,13,17-tetramethylporphyrin (**III**), 2,8,12,18-tetrabutyl-5,15-bis(3-methoxyphenyl)-3,7,13,17-tetramethylporphyrin (**IV**), 2,8,12,18-tetrabutyl-5,15-bis(4-methoxyphenyl)-3,7,13,17-tetramethylporphyrin (**V**), and 2,8,12,18-tetrabutyl-3,7,13,17-tetramethyl-5,15-diphenylporphyrin (**X**) were prepared as described in [12]. Glycine, L-α-alanine, and L-leucine methyl esters were obtained from the corresponding amino acids according to [13].

[2,8,12,18-Tetrabutyl-5,15-bis(4-hydroxyphenyl)-3,7,13,17-tetramethylporphyrinato]zinc (VI). A solution of 0.15 ml of boron tribromide in 5 ml of chloroform was added to a solution of 105 mg of complex **V** in 10 ml of chloroform, and the mixture was stirred for 1 h. Methanol, 5 ml, was then added, and the mixture was stirred for 30 min, neutralized with an ammonia solution, and evaporated. The residue was subjected to chromatography on silica gel using chloroform as eluent. Yield 98.5 mg (97%), R_f 0.76 (Silufol, ethyl acetate–heptane, 3 : 1). IR spectrum (KBr), ν, cm^{-1}: 3300 (OH), 1345 [δ(OH)], 1275 (CO). Electronic spectrum, λ_{max}, nm (log ε): 570.7 (3.95), 533.1 (3.60), 403.3 (5.20). ^{1}H NMR spectrum of complex **VI**, δ, ppm: 10.01 s (2H, *meso*-H), 7.86 d (4H, *o*-H), 7.19 d (4H, *m*-H), 4.94 s (1H, OH), 3.85 t (8H, β-C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.42 s (12H, β-CH$_3$), 2.10 quint (8H, β-CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.61 sext (8H, β-CH$_2$CH$_2$C*H*$_2$CH$_3$), 0.99 t (12H, β-CH$_2$CH$_2$CH$_2$·C*H*$_3$). ^{1}H NMR spectrum of glycine methyl ester–complex **VI** associate, δ, ppm: 10.02 s (2H, *meso*-H), 7.89 d (4H, *o*-H), 7.21 d (4H, *m*-H), 6.34 s (1H, OH), 3.82 t (8H, β-C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.40 s (12H, β-CH$_3$), 2.13 quint (8H, β-CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.64 sext (8H, β-CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.02 t (12H, β-CH$_2$CH$_2$CH$_2$·C*H*$_3$). Found, %: C 71.61; H 7.10; N 6.40; Zn 7.43. $C_{52}H_{62}N_4O_4Zn$. Calculated, %: C 71.64; H 7.12; N 6.43; Zn 7.46.

The zinc complexes of 2,8,12,18-tetrabutyl-5-(2-hydroxyphenyl)-3,7,13,17-tetramethylporphyrin (**VII**), 2,8,12,18-tetrabutyl-5,15-bis(2-hydroxyphenyl)-3,7,13,17-tetramethylporphyrin (**VIII**), and 2,8,12,18-tetrabutyl-5,15-bis(3-hydroxyphenyl)-3,7,13,17-tetramethylporphyrin (**IX**) were synthesized in a similar way.

[2,8,12,18-Tetrabutyl-5-(2-hydroxyphenyl)-3,7,13,17-tetramethylporphyrinato]zinc (VII). Yield 92%. Electronic spectrum, λ_{max}, nm (log ε): 571.7 (3.91), 530.1 (3.56), 398.9 (5.11). ^{1}H NMR spectrum, δ, ppm: 10.01 s (1H, *meso*-H), 9.94 s (2H, *meso*-H),

8.26 d (1H, *o*-H), 8.02 m (3H, *m*-H, *p*-H), 5.04 s (1H, OH), 3.99 t (8H, β-CH_2CH$_2$CH$_2$CH$_3$), 2.53 s (12H, β-CH$_3$), 2.18 q (8H, β-CH$_2$CH_2CH$_2$CH$_3$), 1.67 sext (8H, β-CH$_2$CH$_2$CH_2CH$_3$), 1.09 t (12H, β-CH$_2$CH$_2$·CH$_2$CH_3).

[2,8,12,18-Tetrabutyl-5,15-bis(2-hydroxyphenyl)-3,7,13,17-tetramethylporphyrinato]zinc (VIII). Yield 94%. Electronic spectrum, λ_{max}, nm (log ε): 573.7 (3.88), 536.1 (3.62), 401.9 (5.16). ^{1}H NMR spectrum, δ, ppm: 10.19 s (2H, *meso*-H), 7.76 d (2H, *o*-H), 7.65 m (6H, *m*-H, *p*-H), 5.14 s (1H, OH), 3.96 t (8H, β-CH_2CH$_2$CH$_2$CH$_3$), 2.51 s (12H, β-CH$_3$), 2.16 quintet (8H, β-CH$_2$CH_2CH$_2$CH$_3$), 1.62 sextet (8H, β-CH$_2$CH$_2$CH_2CH$_3$), 1.02 t (12H, β-CH$_2$CH$_2$·CH$_2$CH_3). ^{1}H NMR spectrum of leucine methyl ester–complex **VIII** associate, δ, ppm: 10.16 s (2H, *meso*-H), 7.80 d (2H, *o*-H), 7.62 m (6H, *m*-H, *p*-H), 6.14 s (1H, OH), 3.93 t (8H, β-CH_2CH$_2$CH$_2$CH$_3$), 2.54 s (12H, β-CH$_3$), 2.12 quint (8H, β-CH$_2$CH_2CH$_2$CH$_3$), 1.60 sextet (8H, β-CH$_2$CH$_2$CH_2CH$_3$), 1.00 t (12H, β-CH$_2$CH$_2$CH$_2$CH_3).

[2,8,12,18-Tetrabutyl-5,15-bis(3-hydroxyphenyl)-3,7,13,17-tetramethylporphyrin (IX). Yield 96%. Electronic spectrum, λ_{max}, nm (log ε): 574.2 (3.91), 531.4 (3.60), 402.3 (5.18). ^{1}H NMR spectrum, δ, ppm: 10.18 s (2H, *meso*-H), 7.61 m (4H, *o*-H), 7.55 m (4H, *m*-H, *p*-H), 5.09 s (1H, OH), 3.93 t (8H, β-CH_2CH$_2$CH$_2$CH$_3$), 2.49 s (12H, β-CH$_3$), 2.14 quintet (8H, β-CH$_2$CH_2CH$_2$CH$_3$), 1.67 sextet (8H, β-CH$_2$CH$_2$CH_2CH$_3$), 1.03 t (8H, β-CH$_2$CH$_2$CH$_2$CH_3).

Association of amino acid esters with porphyrin zinc complexes **I**–**X** was studied by spectrophotometric titration using a Specord M-40 spectrophotometer at descending and ascending wavelengths [1–5, 9]. A quartz cell (l = 1 cm) was charged with a solution of porphyrin complex in toluene with a concentration of $\sim 6 \times 10^{-6}$ M and a solution of amino acid ester with a specified concentration, and the optical density was measured at two wavelengths at 20°C; approximately similar variations in the optical density were observed. The association constants k_{as} were calculated by the formula

$$k_{as} = \frac{[\mathrm{ZnP{\cdot}L}]}{[\mathrm{ZnP}]{\cdot}[\mathrm{L}]} = 1/c_2 \left(\frac{\Delta D_{i,\lambda_1} \Delta D_{0,\lambda_2}}{\Delta D_{0,\lambda_1} \Delta D_{i,\lambda_2}} \right).$$

Here, λ_1 is the descending wavelength, λ_2 is the ascending wavelength, c_2 is the concentration of amino acid ester, D_0 is the maximal variation of the optical density at a given wavelength, and D_i is the optical density at a given wavelength and a given concentration.

Variations in the optical density were monitored in the range of amino acid ester concentrations from $(7–10) \times 10^{-6}$ to $(7–100) \times 10^{-4}$ M, depending on the porphyrin complex and amino acid ester. The narrower the concentration range in which variations of optical density were observed, the greater the recognition ability of the corresponding porphyrin complex.

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