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Binding of Amino Acids with a Bifunctional Metalloporphyrin via Concurrent Metal-Coordination and Electrostatic Interactions[1)]

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The Cl-Rh(III) complex of 5,15-bis[2-(N,N-dimethylaminomethyl-1-phenyl]octaethylporphyrin undergoes intermolecular coordination to give the dimer in $CDCl_3$, which, upon treatment with an aqueous amino acid solution, readily forms a monomeric amino acid adduct via a two-point interaction involving the metal coordination and electrostatic interaction or salt formation.

Multi-point binding of polar organic compounds constitutes a rapidly growing area in molecular recognition.[2-4)] We have recently shown[2a)] that amino acids can be fixed with a naphthol-functionalized Rh(III) porphyrin via a two-point interaction involving the Rh(III)-NH_2- coordination and the OH-CO_2H hydrogen bonding. In the present work, we investigated the ligand binding properties of a tertiary-amine functionalized Rh(III) porphyrin. We wish to report here that amino acids can also be bound by concurrent metal coordination and electrostatic interaction or salt formation.

5,15-Bis[2-(N,N-dimethylaminomethyl)-1-phenyl]octaethylporphyrin (1, in a schematic representation) was prepared by the acid catalyzed condensation of 3,3',4,4'-tetraethyl-2,2'-dipyrromethane and 2-(N,N-dimethylaminomethyl)benzaldehyde[5)] followed by oxidation of the resulting porphyrinogen under similar conditions as applied for the preparation of related 5,15-diaryl porphyrins.[6,7)] The atropisomers were separated by means of chromatography on alumina, one (TLC R_f 0.5, using CH_2Cl_2-$CH_3CO_2CH_2CH_3$ as eluant) being eluted with CH_2Cl_2 and the other (R_f 0.05) with CH_3OH. Both isomers showed almost identical ^1H NMR spectra, and the less polar isomer was assigned as 1[8)] having trans configuration since this polarity-configuration relationship holds for all known examples of related atropisomers.[6,7)] The insertion of Rh(III) into 1 was carried out under standard conditions.[7,9)] The ^1H NMR spectrum of the resulting Cl-Rh(III) porphyrin in $CDCl_3$ showed two sets of signals of equal intensities for both the CH_3 and CH_2 groups attached to nitrogen atoms, one being considerably upfield shifted due to the porphyrin ring current effect (δ -4.1 (6H) and -3.15 (6H) for CH_3 and -3.25 (2H) and -1.8 (2H) for CH_2) and the other exhibiting normal chemical shifts (δ

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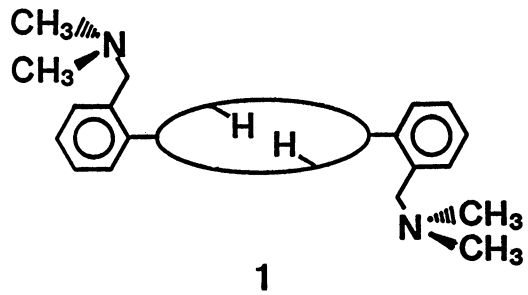

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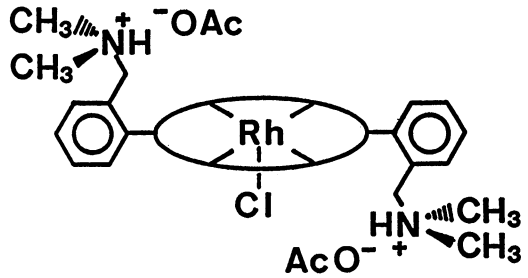

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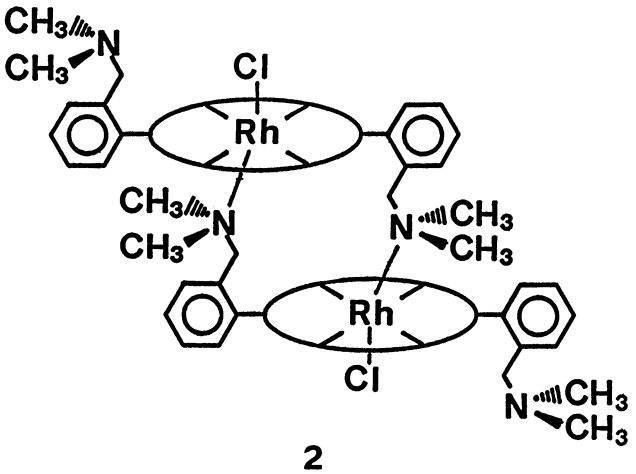

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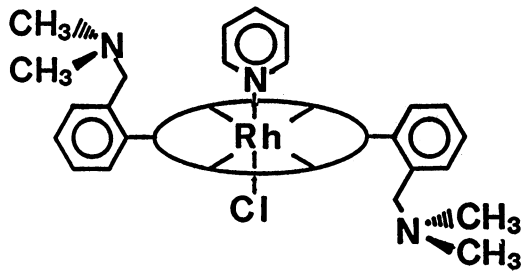

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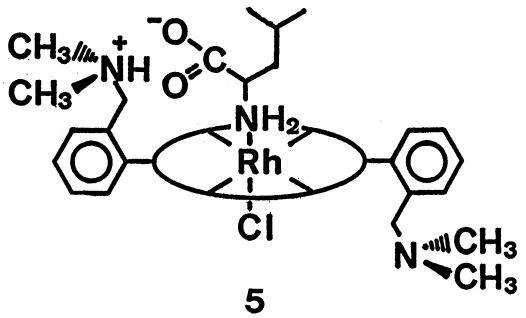

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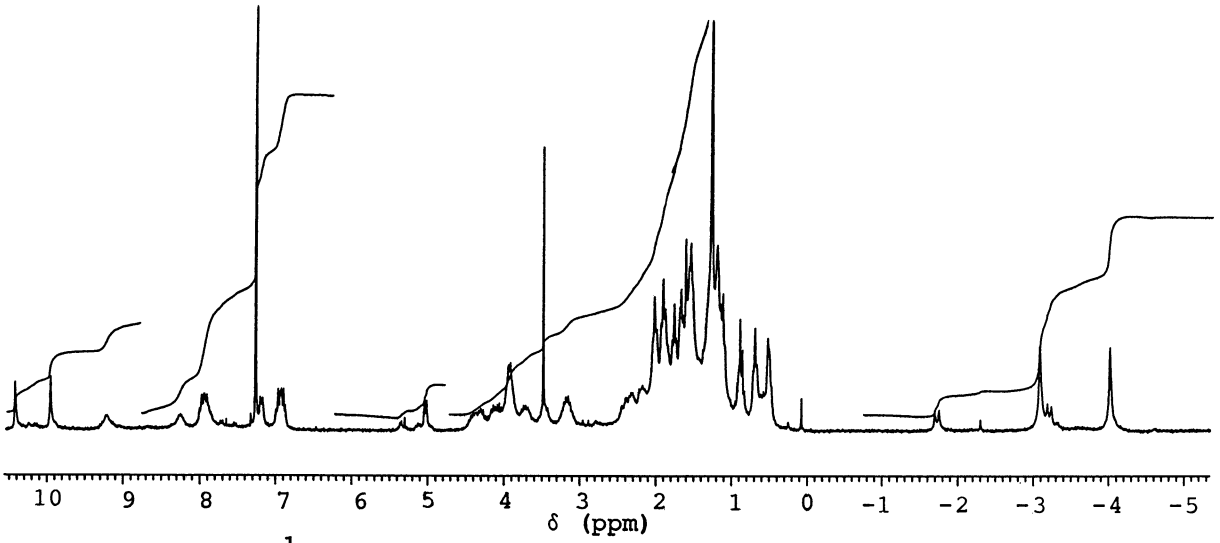

Fig. 1. ^{1}H NMR spectrum of 2 in $CDCl_3$ at room temperature.

1.55 (12H) for CH_3 and 3.45 (4H) for CH_2) (Fig. 1). These results indicate that the product is a dimeric species as schematically shown in 2.[10]

The conversion of 2 into monomeric species in a homogeneous $CHCl_3$ solution was effected either by protonation of the amino nitrogen atoms with acids such as acetic acid or by ligation of the central Rh(III) ion with external amines such as pyridine, giving rise to bis(ammonium acetate) derivative 3 or Rh(III)-pyridine complex 4, respectively.[11] Compound 2 is also capable of extracting amino acids from neutral aqueous solutions to give monomeric adducts. Thus, a $CDCl_3$ solution of 2 (1.7×10^{-3} M, 1 vol) and a saturated aqueous solution of L-leucine (1.8×10^{-1} M, 1 vol) was stirred vigorously at room temperature for 72 h. The ^1H NMR spectrum of the organic phase indicated that it contained adduct 5 and unchanged 2 in a molar ratio of 1:1.9; the former showed upfield shifted resonances for the leucine ligand [δ -5.8 and -4.7 (each 1H, $-NH_2$), -3.7 (1H, $C\underline{H}-NH_2$), -1.6 and -1.35 (each 1H, CH_2), -0.9 (1H, $(CH_3)_2\underline{CH}$), -0.75 and -0.45 (each 3H, CH_3)] in a similar manner as leucine complexes of related Rh(III) porphyrins.[2a,b] The IR spectrum of adduct 5 showed absorptions at 1600 and 2250 cm^{-1}, which could be assigned to ν_{CO} for a CO_2^- moiety and ν_{N^+-H}, respectively; this indicates that the leucine ligand is bound with the porphyrin through an electrostatic interaction or salt formation between ammonium and carboxylate ions, in addition to the Rh(III)-NH_2-coordination (refer to 5).

Leucine in water has pKa's of 9.60 ($-NH_3^+ \rightleftharpoons -NH_2 + H^+$) and 2.36 ($-CO_2H \rightleftharpoons -CO_2^- + H^+$) and it exists as a zwitterion ($^-O_2C-CHR-NH_3^+$) in the pH range 3 - 9. The extraction of leucine from an aqueous solution at pH 3.5 took place readily in a similar manner as above, leading to a molar ratio of 5:2 = 1:0.9 in the organic phase. In marked contrast, however, no extraction of ethylamine (pKa = 10.63) as a reference from an aqueous solution at pH 3.5 was observed under otherwise identical conditions. The ligand binding behavior of the Cl-Rh(III) complex of octaethylporphyrin (OEP) was also investigated. This reference complex has an open coordination site and it extracts not only leucine but also ethylamine with a 100% efficiency at pH 3.5. Thus, the pentaco-ordinate Rh(III) ion is apparently a stronger acid than H^+ so that amine coordination takes place even with simple ammonium salts [$-NH_3^+$ (aq) + Rh(III)(OEP) (org) $\longrightarrow$ Rh(III)-NH_2- (org) + H^+ (aq)]. This is, however, not the case for 2, which is already hexaco-ordinate; in order to break its stable, self-dimerized structure, a bifunctional amino acid (leucine) is required so as to allow dual interaction with both the acidic and basic centers (Rh(III) and tertiary amino group, refer to 5). Homogeneous leucine binding was achieved in acetic acid. When dissolved in this solvent, 2 underwent dissociation into 3 (vide supra). Addition of leucine (8.4×10^{-2} M) to this solution resulted in facile generation of the leucine adduct. Ethylamine could also be bound under similar conditions. However, competition between leucine and ethylamine ([leucine] = [ethylamine] = 8.4×10^{-2} M) for 3 in CD_3CO_2D led to almost exclusive binding of the former, as revealed by ^1H NMR spectroscopy.

This work presents a novel example of acid-base cooperative binding of amino acids. One of the fundamental problems of bifunctional acid-base systems is "neutralization". Amino acids in water are intramolecularly neutralized to give zwitterions. On the other hand, the present amino acid receptor in organic media

undergoes intermolecular neutralization to give 2. It is significant that the formation of adduct 5 as a consequence of two-point molecular recognition of these two bifunctional substrate and receptor competes favorably with their self-neutralization processes. Further work is now under way to shed more light on the thermodynamics and selectivity of the present two-point interaction. Molecular recognition of various biological anions, especially phosphates, along the present line is also an interesting application of this work.

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8) 1: yield 6% after recrystallization from CH_2Cl_2-hexane; ^1H NMR ($CDCl_3$) δ -2.0 (2H, s, NH), 1.2 and 1.85 (each 12H, t, $CH_2\underline{CH_3}$), 1.8 (12H, s, N-CH_3), 2.5 (4H), 3.05 (4H), and 4.0 (8H) (q, $\underline{CH_2}CH_3$), 2.75 (4H, s, N-CH_2), 7.6, 7.8, 7.95, and 8.3 (each 2H, d or t, Ar-H), 10.2 (2H, s, meso-H); UV-vis (CH_2Cl_2) λ_{max} 415, 512, 544, 581, 634 nm. Very slight blue shifts by 1-2 nm were observed when the spectrum was taken for a CH_3OH-CH_2Cl_2 (10:1) solution.
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10) 2: yield 31% after chromatography on silica gel; UV-vis (CH_2Cl_2) λ_{max} 415, 532, 561 nm.
11) The monomeric nature of 3 and 4 was confirmed by the lack of highly upfield shifted NMR resonances. 3: IR 1600 (ν_{CO}) and 2250 cm^{-1} (ν_{N^+-H}). 4: UV-vis ($CHCl_3$) λ_{max} 422, 535, 563 nm.

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