Three-Point versus Two-Point Attachment of (*R*)- and (*S*)-Amino Acid Methyl Esters to a Cobalt(III) Chiroporphyrin: Implications for the Analysis of Amino Acid Enantiomers by ^{1}H NMR Spectroscopy

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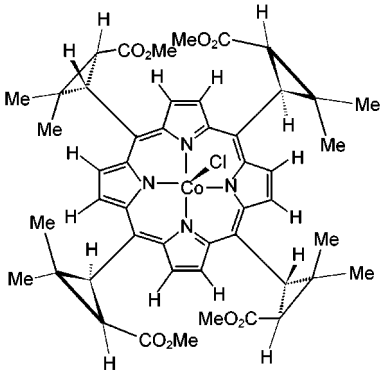
Recently we have proposed chlorocobalt(III) tetramethylchiroporphyrin CoCl(TMCP) **1** as a novel chiral shift reagent which effects quantitative in situ derivatization of amines[1] and allows both their spectral assignment and the determination of their enantiomer excess (ee) by ^{1}H nuclear magnetic resonance spectroscopy.[2] In this communication we describe the stereochemistries of several adducts of (*R*)- and (*S*)-amino acid methyl esters with **1**, which explain the large diastereomeric dispersions observed in their ^{1}H NMR spectra. Our data illustrate the potential of **1** as a derivatizing agent in the chiral analysis of amino acids, and they suggest a possible utility in ee determinations of extraterrestrial amino acids.[3−5]



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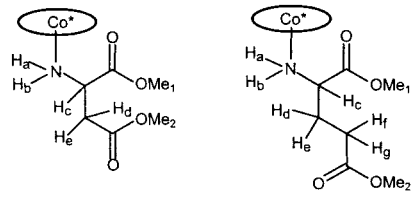
A 3 mg sample of **1** in $CDCl_3$ solution in a NMR tube strongly binds 2 equiv of amino acid methyl ester L* at room temperature without any detectable kinetic resolution. The influences of the chiral cavity and of the porphyrin ring current of **1** on the protons of L* can be seen in the high-field region of the NMR spectrum of the bis-adduct $[Co(L^*)_2(TMCP)]^+Cl^-$.[6] The (*R*) and (*S*) ligands give well-resolved spectral signatures at 200 MHz, and their relative concentrations can be readily determined by peak integration. Good agreement is found with values obtained by chiral chromatography for standard solutions of (*R*)- and (*S*)-phenylalanine methyl esters with ee's in the range 5−95%. Signal attributions have been obtained by ^{1}H−^{1}H and ^{1}H−^{13}C COSY NMR experiments, and relevant data for the methyl esters of aspartic and glutamic acids as representative examples are collected in Table 1. A remarkable feature of the spectra is the large value of the diastereomeric dispersion $\Delta\delta = |\delta_R - \delta_S|$ observed for equivalent protons of (*R*) and (*S*) ligands, which can be as high as 0.5 ppm, as shown for H_d in Table 1. The spectral simplicity observed for 16 of the 20 biogenic amino acids indicates that the amino ester ligand adopts a single, well-defined conformation within the cavity of **1**. The other four biogenic amino acids (Arg, Cys, His, Lys) give complex spectra reflecting the presence of several regioisomeric bis-adducts, which probably result from a second N- or S-donating function besides the α-amino group.[7]

Table 1. ^{1}H NMR Chemical Shifts of Axial Ligand Protons in the Bis-Adducts of **1** with the Methyl Esters of (*R*)- and (*S*)-Aspartic and Glutamic Acids



	aspartic acid		glutamic acid	
	(*R*)	(*S*)	(*R*)	(*S*)
H_a	−5.28 (t)	−4.95 (m)	−5.81 (dd)	−5.48 (m)
H_b	−4.72 (m)	−4.72 (m)	−5.23 (dd)	−4.97 (m)
H_c	−2.48 (m)	−2.79 (t)	−3.39 (m)	−2.93 (m)
H_d	−1.28 (q)	−0.79 (m)	−3.24 (m)	−2.79 (m)
H_e	−0.55 (dd)	−0.79 (m)	−1.77 (m)	−1.26 (m)
H_f	-	-	−1.26 (m)	−1.14 (m)
H_g	-	-	0.05 (m)	0.17 (m)
OMe_1	2.73 (s)	2.59 (s)	2.63 (s)	2.57 (s)
OMe_2	2.82(s)	2.83 (s)	3.40 (s)	3.33 (s)

Single crystals of suitable quality were obtained for the adducts of the enantiopure methyl esters of (*R*)-Ala **2**, (*R*)-Ile **3**, (*R*)-Thr **4**, (*R*)-Tyr **5**, and (*S*)-Glu **6** by slow diffusion of hexane in the $CDCl_3$ solutions used in NMR studies,[8] and their structures were solved by X-ray diffraction methods.[9] The stereochemistries of

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(8) The crystals of the (*S*)-Glu adduct were obtained after several weeks, whereas those of all the (*R*)-adducts were formed in a few days.

(9) Crystallographic summary for **2**: monoclinic, *P*2(1), $Z = 2$ in a cell of dimensions $a = 11.39840(10)$ Å, $b = 21.2100(4)$ Å, $c = 12.5746(2)$ Å, $\beta = 100.347(1)°$, $V = 2990.60(8)$ Å^3, ρ_{calc} 1.322 g·cm^3, $F(000) = 1262$. 7913 unique reflections collected at 293 K, 6200 with $I > 2\sigma(I)$. Final $R = 0.0975$ and $R_w = 0.2566$, Flack index = 0.01(3). Crystallographic summary for **3**: monoclinic, *C*2, $Z = 2$ in a cell of dimensions $a = 24.378(12)$ Å, $b = 12.601(4)$ Å, $c = 12.280(7)$ Å, $\beta = 113.70(5)°$, $V = 3454(3)$ Å^3, ρ_{calc} 1.381 g·cm^{-3}, $F(000) = 1504$. 5593 unique reflections collected at 193 K, 3620 with $I > 2\sigma(I)$. Final $R = 0.0506$ and $R_w = 0.1094$, Flack index = 0.03(2). Crystallographic summary for **4**: triclinic, *P*1, $Z = 2$ in a cell of dimensions $a = 13.240(3)$ Å, $b = 13.960(3)$ Å, $c = 19.037(4)$ Å, $\alpha = 71.581(4)°$, $\beta = 77.543(4)°$, $\gamma = 75.193(4)°$, $V = 3192.5(10)$ Å^3, ρ_{calc} 1.350 g·cm^{-3}, $F(000) = 1361$. 17167 unique reflections collected at 193 K, 4915 with $I > 2\sigma(I)$. Final $R = 0.0642$ and $R_w = 0.1257$, Flack index = 0.04(3). Crystallographic summary for **5**: orthorhombic, $P2_12_12_1$, $Z = 4$ in a cell of dimensions $a = 11.7375(6)$ Å, $b = 22.5981(13)$ Å, $c = 31.3184(15)$ Å, $V = 8307.1(8)$ Å^3, ρ_{calc} 1.419 g·cm^{-3}, $F(000) = 3664$. 18770 unique reflections collected at 193 K, 7475 with $I > 2\sigma(I)$. Final $R = 0.0644$ and $R_w = 0.1420$, Flack index = −0.02(2). Crystallographic summary for **6**: orthorhombic, $P2_12_12_1$, $Z = 4$ in a cell of dimensions $a = 17.0919(7)$ Å, $b = 19.9345(8)$ Å, $c = 23.5472(8)$ Å, $V = 8023.0(5)$ Å^3, ρ_{calc} 1.437 g·cm^{-3}, $F(000) = 3584$. 18983 unique reflections collected at 193 K, 10127 with $I > 2\sigma(I)$. Final $R = 0.0597$ and $R_w = 0.1473$, Flack index = 0.006(16).

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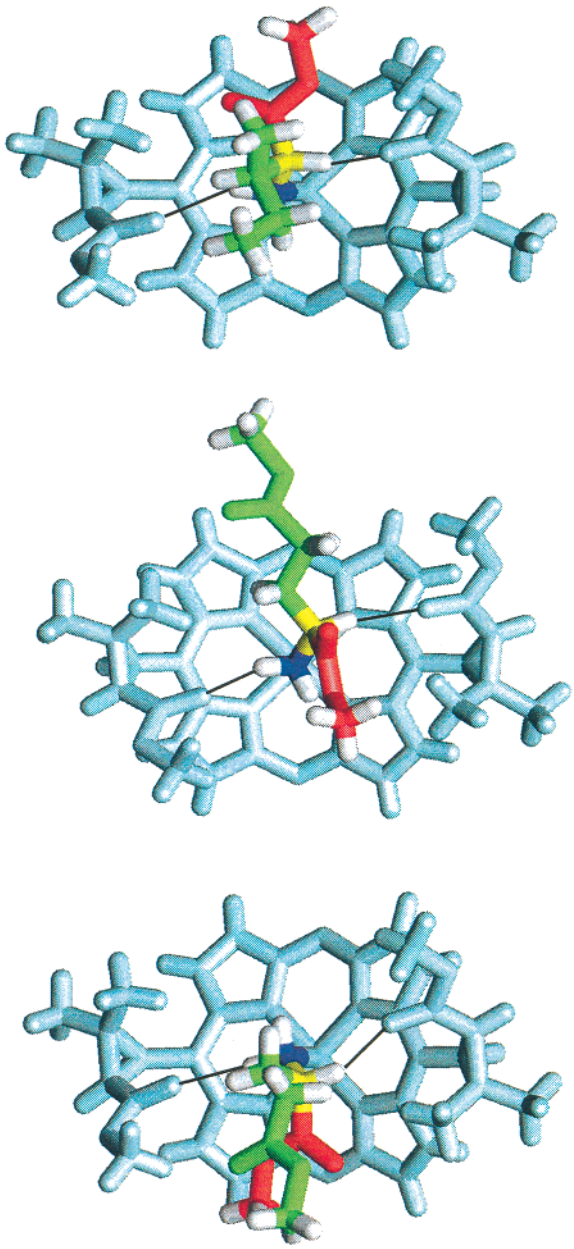

Figure 1. Conformations and hydrogen-bond patterns of amino acid ligands in the bis-adducts of (*R*)- and (*S*)-amino acid methyl esters with **1**, as seen in their crystal structures. (Top) (*R*)-Ile. (Middle) (*S*)-Glu (conformation A). (Bottom) (*S*)-Glu (conformation B). Only the top faces are shown; the second ligand and meso-substituents on the bottom faces have been omitted for clarity. Hydrogen bonds are indicated by black lines. Color code for the asymmetric carbon (yellow) substituents: blue, amine group; red, methyl ester group; green, alkyl group.

the four (*R*) bis-adducts show a number of conserved features (see (*R*)-Ile **3** in Figure 1, and (*R*)-Ala **2**, (*R*)-Thr **4**, and (*R*)-Tyr **5** in the Supporting Information). Two hydrogen bonds connect the amino ester to the carbonyl groups of opposite meso substituents of the porphyrin (shown light blue): N−H···O, always with the same hydrogen of the amine (blue), and C−H···O[10] with the hydrogen on the asymmetric carbon (yellow). The methyl ester group (red) of the axial ligand lies on the porphyrin macrocycle, nearly parallel to its mean plane, at a distance of 3.5−3.7 Å, suggesting a weakly bonding $\pi-\pi$ interaction. Thus, the weak bonds which involve three substituents of the (*R*) asymmetric carbon of the axial ligand impose a unique conformation of this guest within the cavity of the host and project the fourth substituent (green) outward. This observation led us to anticipate that in an (*S*) adduct at least one of the three weak interactions is necessarily lost; if the two hydrogen bonds are maintained, the ester and alkyl substituents must exchange places as a consequence of the (*S*) absolute configuration of the asymmetric carbon.

The crystal structure of the adduct of (*S*)-Glu dimethyl ester **6** (Figure 1) confirms this expectation. Interestingly, a different conformation of the coordinated amino ester is found on each of the two faces of the chiroporphyrin complex. One face shows a stereochemistry (A) similar to that of the (*R*) adducts, with exactly the same pattern of opposite N−H···O and C−H···O hydrogen bonds; the expected permutation of the alkyl (green) and ester (red) substituents of the asymmetric carbon is indeed observed, and the π-stacking interaction is therefore lost. The conformation (B) found on the other face is totally different: while the three intermolecular bonds which were present in the (*R*) adducts are observed, the N−H···O interaction surprisingly involves the other amine hydrogen. This has required a ca. 120° turn around the Co−N bond; this rotation allows the ester group to π-stack on the ring, and it projects the fourth (alkyl) substituent outward. The C−H···O hydrogen bond is as usual. We relate the (B) conformation to the changes in NMR spectrum which are seen in aged samples of **6** after several weeks,[8] and we conclude that both (*S*) ligands in a fresh sample of the bis-adduct exhibit the (A) conformation. The permutation of ester and alkyl substituents of the asymmetric carbon seen in (A) puts the alkyl protons at very different elevations above the porphyrin, where they are subject to significantly different ring current effects. This explains the exceptionally large diastereomeric dispersion which is seen for protons such as H_d.

In summary, the hydrogen-bonding capabilities of **1** allow the conformation of coordinated amino esters to be uniquely defined within the chiral cavity on the time scale of NMR analysis, and the porphyrin ring current amplifies the chemical shift differences between the diastereomeric adducts. Taken together, these structural features make **1** a very powerful derivatizing agent for the chiral analysis of amino acid derivatives. The possibility of amino acid enantio-discrimination on the basis of a configuration-dependent π-stacking interaction is also appealing.

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Supporting Information Available: Stick representations of the X-ray structures for the bis-adducts of (*R*)-Ala **2**, (*R*)-Thr **4**, and (*R*)-Tyr **5** methyl esters (PDF). Tables of crystal data, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for the complexes **2**−**6** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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