CHEMISTRY LETTERS, pp. 303-306, 1994.

Induced Assembly of Aromatic Rings Caused by a CH···π Interaction

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The bis-(N-pyridoxy-L-phenylalaninato)cobalt(III) complex exhibiting an anomalous assembly of aromatic rings around the pyridoxy 2'-methyl group has been synthesized and characterized by ^{1}H-NMR spectroscopy and X-ray analysis. The ^{1}H-NMR spectrum of the complex in D_2O, methanol-d_4 and dimethylsulfoxide-d_6 revealed peculiar upfield shift in 2'-methyl group. The detailed examination of the crystal structure demonstrated that the two C-H bond vectors of 2'-methyl group were directed toward the planes of the pyridoxy pyridine and phenylalanyl benzene rings, respectively. These findings indicate the induced assembly of aromatic rings through a CH···π interaction

The non-covalent interactions are the keystone of molecular recognition and are also much interested from a view point of important biological processes relating to the regulation of metabolism.[1] CH···π interaction, one of them, has long been known to spectroscopists and crystallographers,[2] but the definite evidence for their structural significance has never been given yet. We have currently been studying the site-specific N/O recognition of amino acids[3] and dipeptides[4] by the Co(III) complexes with tetradentate ligands through the non-covalent ligand-ligand interactions. In the work on the recognition of dipeptides, the Co(III) complex has been discovered to specifically recognize the dipeptide containing L-phenylalanine for its C-terminal side through a CH···π interaction.[4] Also, in the complexation of N-pyridoxy-L-phenylalanine ligand with the Co(III) ion, it has been found that the pyridoxy 2'-methyl group strongly gives rise to inductive CH···π interaction with pyridoxy pyridine and phenylalanyl benzene rings. Here, we report the ^{1}H-NMR spectroscopic and X-ray structural studies of the bis-(N-pyridoxy-L-phenylalaninato)cobalt(III) complex.

The complex was prepared by the following procedure. To 2.5 mL of a 0.5 M aqueous solution of $K_3[Co(CO_3)_3]$ (1.25 mmol) was added N-pyridoxy-L-phenylalanine (0.79 g, 2.5 mmol), and the resulting mixture, after stirring at room temperature for 12 hr and filtration, was poured onto a QAE Sephadex A-25 column (Cl^- form), which gave a single band of the product (0.4 mmol). The adsorbed band was eluted with an aqueous 0.1 M NaCl solution, and dark brown crystals suitable for X-ray analysis were obtained from the filtrate after several days.

The ^{1}H-NMR spectrum of the complex in D_2O has shown a peculiar upfield shift in the 2'-methyl group of N-pyridoxy-L-phenylalanine (at 0.84 ppm) in comparison with that in the metal-free ligand (at 2.28 ppm), which is significantly large on the basis of the fact that all other peaks of the ligand entirely exhibit downfield shift (0.2 - 1.0 ppm) by the complexation with metal ion. This large upfield shift seems to result from an intramolecular ring

current effect by the phenyl and/or pyridoxy rings. On the basis of the ^{1}H-NMR data, the distance between aromatic ring and 2'-methyl carbon has been estimated to be ~3.6 Å by the computation.[5] Similar upfield shifts have been observed even in methanol-d_4 or dimethylsulfoxide-d_6 solutions, indicating that the interaction between them is rather strong for simple hydrophobic one.

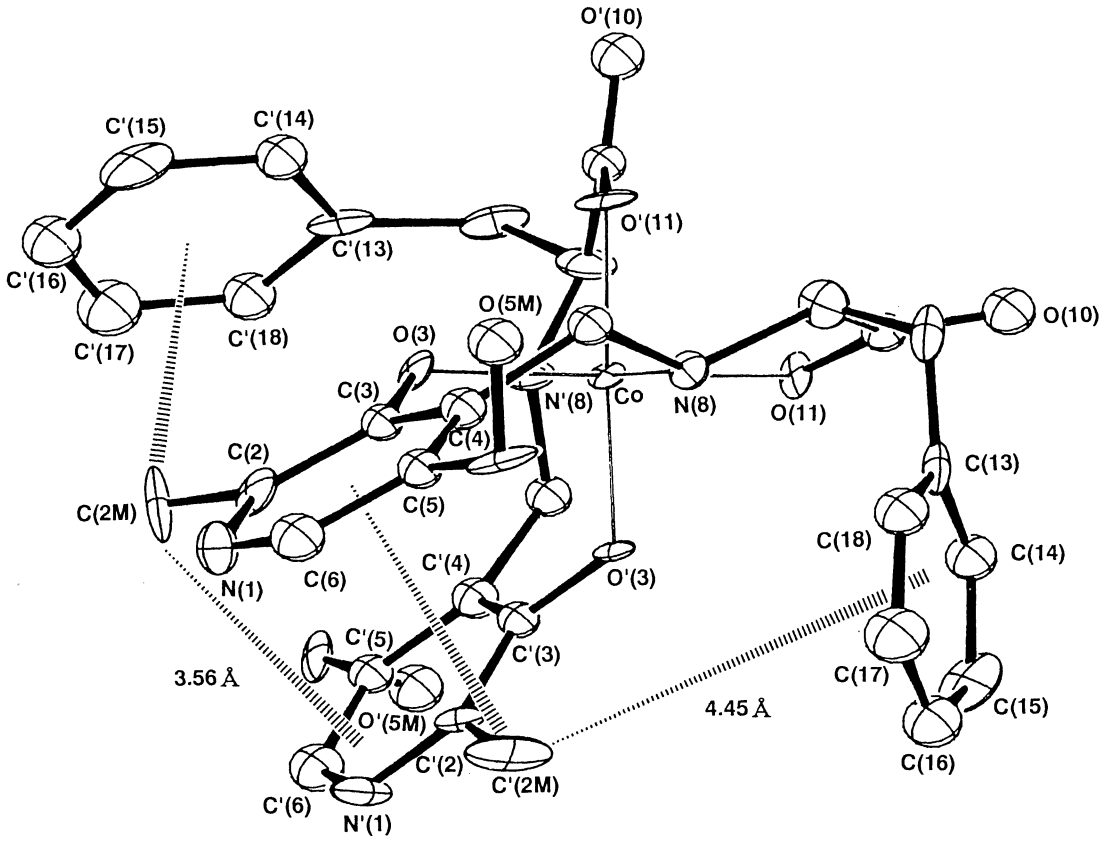

Fig. 1. Molecular structure of the [Co(pyridoxy-L-phenylalaninato)$_2$]$^-$ anion with atomic numbering (ORTEP, 50% probability ellipsoids, hydrogen atoms omitted for clarity). The anion has a crystallographic two-fold axis around the Co(III) atom and the primed atoms are related by a two-fold axis. Important bond lengths: Co-N(8), 1.934(2); Co-O(3), 1.890(3); Co-O(11), 1.903(3) Å.

The crystal structure of the complex[6] consists of two discrete [Co(pyridoxy-L-phenylalaninato)$_2$]$^-$ anions (Fig. 1), two sodium ions and four water molecules in a unit cell, in which the Co(III) ion is coordinated by two N-pyridoxy-L-phenylalanine ligands in meridional form. Interestingly, 2'-methyl group and pyridoxy pyridine ring have been firmly stacked on another pyridine ring and 2'-methyl group, respectively, as was expected from the ^{1}H-NMR spectrum. This is particularly noteworthy because such a conformation causes great stress on the basis of CPK model considerations and because it is possible to form the complex with different conformation. The separations between the mean plane of pyridoxy pyridine ring and the carbon atom of 2'-methyl group, 3.56 Å, were very short. Several shorter distances between 2'-methyl carbon and pyridoxy carbon atom, 3.76, 3.69, and

3.76 Å for C(2M)···N(1), C(2M)···C(2), and C(2M)···C(3), respectively, are comparable to the sum (3.7 Å) of the van der Waals radii of methyl group (2.0 Å) and aromatic carbon (1.7 Å).[7] In addition, benzene ring also approached to the 2'-methyl group, although the distance, 4.45 Å, is slightly long. Such an additional interaction has also been supported from the fact that the upfield shift of 2'-methyl protons in ^{1}H-NMR spectrum of the complex is larger by 0.34 ppm than that in the binary Co(III) complex of N-pyridoxy-L-alanine without phenyl group (at 1.18 ppm). Similar upfield shift has been observed also in methanol-d_4 or dimethylsulfoxide-d_6 solutions. The accurate analysis of X-ray structure of the complex revealed the location of the three hydrogen atoms of 2'-methyl group, whose two C-H bond vectors were significantly directed and fixed toward the planes of the pyridoxy pyridine and phenylalanyl benzene rings of another ligand, respectively, as shown in Fig. 2. This detection has also been confirmed by the low-temperature X-ray analysis (at 173 K).[8] The anomalous assembly of aromatic rings established in this paper may be an experimental evidence for the presence of CH···π interaction and indicate that the pyridoxy 2'-methy group inductively brings about very strong CH···π interaction with aromatic rings.

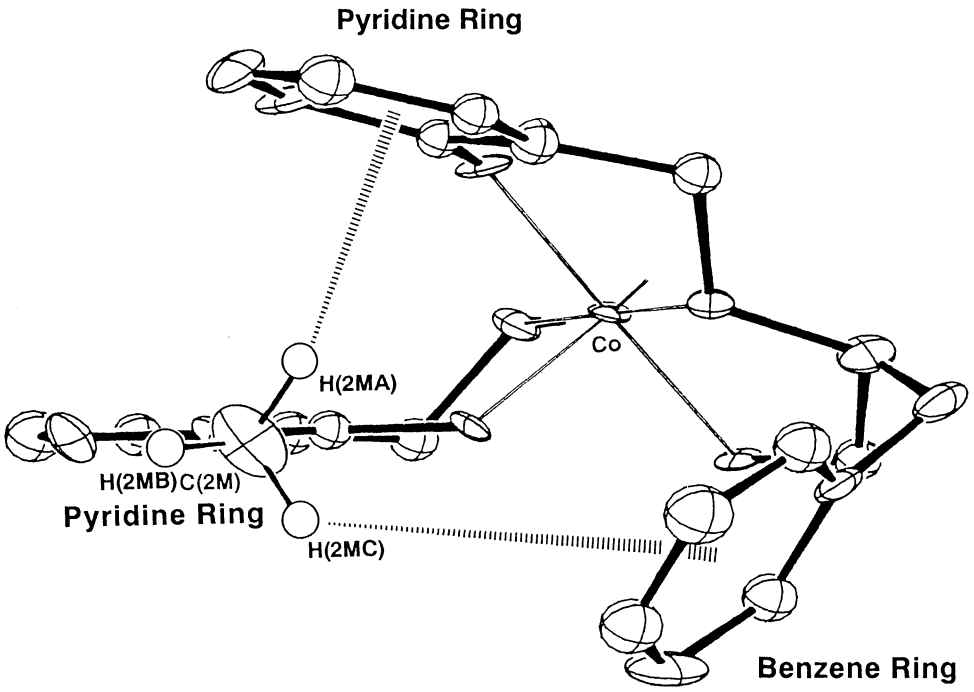

Fig. 2. View of the complex anion showing the manner of CH···π interactions, with atomic numbering (ORTEP, 50% probability ellipsoids, hydrogen atoms except for 2'-methyl group omitted for clarity).

The N-pyridoxy-L-amino acid employed here is a derivative of Vitamin B_6 coenzyme, pyridoxal 5'-phosphate, which plays an important role in amino acid metabolism in biological system, and the significance of some functional groups of pyridoxal, pyridyl 1'-N, 2'-methyl, 3'-oxygen, 4'-azomethine, and 5'-phosphate ester, has long been discussed.[9] However, that of the 2'-methyl group has never been clarified yet. The recent X-ray structure

analysis of aspartate aminotransferase bound with the co-factor pyridoxal-5'-phosphate[10] has demonstrated that the two aromatic rings of tyrosine and tryptophan are close to the 2'-methyl group in the enzyme. The CH···π interactions between 2'-methyl group and aromatic rings, described in this paper, may suggest that 2'-methyl group plays as the recognition group of the active site in the enzyme through the CH···π interaction with the aromatic rings.

Thanks are due to the Instrument Center, the Institute for Molecular Science, for assistance in obtaining the 400 MHz ^{1}H-NMR spectra. This work was supported by a Grant-in-Aid for Specially Promoted Research (No. 04101003) from the Ministry of Education, Science and Culture, Japan.

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6) Crystal data: Monoclinic, space group $C2$, a=15.272(1), b=13.852(1), c=9.200(1) Å, β=116.929(4) °, V=1735.4(2) Å^3, Z=2. Intensities were measured by the ω-2θ scan technique on an Enraf Nonius CAD4-Express automated four-circle diffractometer with graphite monochromatized Mo $K\alpha$ radiation (2θ < 60°). The structure was solved by use of the program SIR88 and refined by the full-matrix least-squares procedure to give the final R and R_w values of 0.041 and 0.045, respectively, for observed 1429 reflections (I_o>3σ(I_o)). Absorption correction was applied with the program DIFABS.
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8) Crystal data: The X-ray crystal structure was analyzed at 173 K by the same method as that described in ref. 6). Monoclinic, space group $C2$, a=15.236(6), b=13.763(9), c=9.151(7) Å, β=116.58(5) °, V=1716(2) Å^3, Z=2, R=0.044, and R_w=0.055 for observed 1557 reflections (I_o>3σ(I_o)).
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(Received November 1, 1993)