[Chem. Pharm. Bull. 34(9)3553—3562(1986)]

Crystal Structure of Copper(II) Complex with Tryptamine–Pyridoxal Schiff Base and Conformational Study of Tryptophan in Pyridoxal-Catalyzed Reactions[1)]

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(Received February 27, 1986)

An X-ray structural analysis of the 1 : 2 complex between copper(II) and pyridoxylidenetryptamine Schiff base has shown that the copper atom is co-ordinated to phenolic oxygen and imino nitrogen atoms of two ligands related by a pseudo twofold symmetry, forming a tetrahedrally distorted square plane. Conformational analysis using the classical empirical potential energy function and CNDO/2 methods provided reasonable conformers accounting for the metabolic pathway of tryptophan→tryptamine→indoleacetoaldehyde.

Keywords——pyridoxal–tryptamine Schiff base; tryptophan metabolic pathway; X-ray analysis; conformational analysis

Introduction

Pyridoxal phosphate–amino acid Schiff bases are key intermediates in many metabolic reactions of amino acids such as decarboxylation, racemization, transamination and C–C bond cleavage.[2)] These reactions usually proceed by the labilization of one of the three bonds to the amino acid α-carbon atom. Dunathan[3)] has suggested that the bond to be labilized must be oriented perpendicular to the π system of the Schiff base as the result of minimization of the energy of the transition state for bond breaking by allowing maximum σ–π overlap, and that the enzymes govern reaction specificity by controlling the conformation of the N–Cα bond.

It is well known that a part of tryptophan is metabolized to tryptamine, and further to indoleacetoaldehyde. These two reactions, *i.e.* decarboxylation and oxidative deamination, are catalyzed by aromatic L-amino acid decarboxylase and monoamine oxidase, respectively.[4)] Both enzymes require pyridoxal phosphate as a coenzyme.

In order to elucidate the stereochemical aspects of tryptophan metabolism, we have prepared the copper(II) complex of pyridoxylidenetryptamine Schiff base. This compound should be a usuful model for studying both the decarboxylation and the oxidative deamination reactions. The copper(II) ion was selected for the following reasons: 1) it shows the highest overall activity in catalyzing pyridoxal-mediated reactions of amino acids in model systems[5)] and 2) it is required for the effective catalysis of monoamine oxidase.[4)]

This paper describes the crystal structure of the above complex and discusses the stable conformations suitable for both reactions, based on the results of energy calculations. Since the Schiff base complexes derived from pyridoxal and amines are less well-known, knowledge of the crystal structure should improve our understanding of the stereochemistry involved in the metabolism of biologically important amines.

Experimental

Materials and Preparation——Pyridoxal hydrochloride and tryptamine were obtained from commercial sources

and used after verification of their purities by high performance liquid chromatography (HPLC). All solvents used were of reagent grade. Copper(II) complex of pyridoxylidenetryptamine Schiff base was prepared as follows by reference to the reported methods[6,7]: a solution of pyridoxal HCl (254 mg, 1.2 mM) and tryptamine (192 mg, 1.2 mM) in ethanol (20 ml) was heated with stirring for about 10 min. Then AcONa (204 mg, 1.5 mM) and $Cu(OAc)_2$ (120 mg, 0.6 mM) were added, and the mixture was refluxed for 3 h, and reduced to a volume of about 5 ml. Salts were precipitated by adding isopropanol and removed by filtration. The product was obtained by evaporation of the filtrate (5 ml) and by the addition of ether (50 ml), and subjected to thin layer chromatography (TLC), ultraviolet (UV) measurement, and elemental analysis: *Anal.* Calcd for Cu $(C_{18}H_{18}N_3O_2)_2$: C, 63.56; H, 5.33; N, 12.35. Found: C, 63.31; H, 5.55; N, 12.12.

X-Ray Crystal Structure Analysis——Dark green platelet crystals suitable for X-ray analysis were obtained by slow evaporation of a methanol–acetone (1 : 1) solution (12 mM) of the complex after a few weeks at room temperature. Preliminary X-ray photographs revealed that the crystals belong to the monoclinic system. At first we considered the space group to be $C2/c$ having an equivalent point at (3/4, 1/4, 0) or (3/4, 1/4, 1/2) because of the systematic absences of $h+k=2n+1$ and $k+l=2n+1$ for $(h\,k\,l)$ reflections. This implies that the complex molecule itself has a center of symmetry and the copper ion lies at a special position. However, long exposure to X-ray irradiation revealed very weak spots corresponding to reflections of $k+l=2n+1$. Therefore we finally determined the space group to be Cc. The crystallographic data are presented in Table I. The cell constants were obtained from a least-squares refinement from 22 2θ values measured with an automatic Rigaku diffractometer (AFC-5). Intensities were recorded on the diffractometer by using the ω–2θ scan technique with graphitemonochromated MoK_α radiation (scan speed = 2°/min). A total of 3421 independent reflections were collected at 20 °C up to $2\theta(\mathrm{Mo})=49°$. Among these data, only 1758 reflections having $F_o^2 > 3\sigma(F_o^2)$ were used in the structure analysis and refinement.

As already stated, the position of the copper atom was thought to be near either (3/4, 1/4, 0) or (3/4, 1/4, 1/2). The structures of two Schiff bases were located in a Fourier map in which the copper position of (3/4, 1/4, 1/2) was used for phase calculations. These Schiff bases were nearly related by a twofold symmetry (as mentioned later). This result clearly showed that the space group of this crystal is Cc, not $C2/c$ where these two Schiff bases must be related by a center of symmetry. The nonhydrogen atoms of the Schiff base, along with the copper atom, were refined by the block-diagonal least-squares technique with anisotropic thermal parameters. The ideal positions of hydrogen atoms were calculated and verified by locating the density peaks in a difference Fourier map. These hydrogen atoms were included for the calculations of structure factors, but were not included for refinements. The minimized quantity was $\Sigma w(|F_o|-|F_c|)^2$. In the final refinement, the following weighting scheme was used: $w=[\sigma^2(F_o)+a|F_o|+b|F_o|^2]^{-1}$, where $\sigma(F_o)$ is the standard deviation on counting statistics and a and b are -0.13793 and 0.01317 Å, respectively.

TABLE I. Crystal Data for Bis(pyridoxylidenetryptamine) Copper (II) Complex

Compound	$(C_{18}H_{18}N_3O_2)_2Cu(II)$
Molecular weight	680.26
Cell constant	
a	23.088 (8) Å
b	6.987 (1)
c	23.641 (8)
β	99.25 (3)°
Volume	3764 (2) Å^3
Z	4
D_m	1.23 (1) g·cm^{-3}
D_x	1.20
μ (MoK_α)	3.789 cm^{-1}
Crystal dimensions	0.3 × 0.4 × 0.2 mm

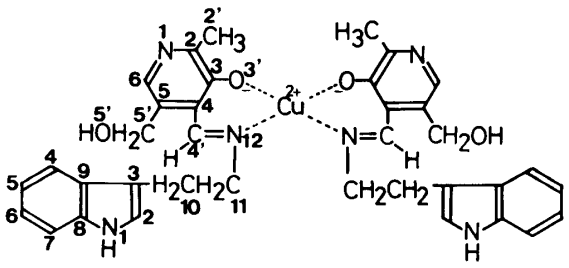


Fig. 1. Atomic Numbering Scheme of Bis(pyridoxylidenetryptamine) Copper(II) Complex

The symbols I and P in the atom designations listed in Table II respectively refer to the tryptamine and pyridoxal moieties of the left-side Schiff base, while the suffixes i and p refer to the respective moieties of the right-side Schiff base.

TABLE II. Positional and Thermal Parameters for the Nonhydrogen Atoms of Bis(pyridoxylidenetryptamine) Copper(II)

Atom	x	y	z	B_{eq} [a)]
N(1)I	0.5897 (6)	−0.249 (3)	0.5984 (5)	5.8 (5)
C(2)I	0.6092 (7)	−0.186 (3)	0.5490 (8)	4.4 (6)
C(3)I	0.5800 (6)	−0.021 (2)	0.5292 (6)	3.5 (5)
C(4)I	0.5040 (7)	0.178 (3)	0.5766 (9)	5.6 (8)
C(5)I	0.4740 (9)	0.174 (4)	0.622 (1)	6. (1)
C(6)I	0.4830 (9)	0.029 (5)	0.662 (1)	7. (1)
C(7)I	0.5193 (8)	−0.123 (3)	0.6587 (8)	5.4 (8)
C(8)I	0.5496 (6)	−0.126 (2)	0.6127 (7)	3.9 (5)
C(9)I	0.5421 (6)	0.021 (2)	0.5708 (6)	3.5 (5)
C(10)I	0.5905 (6)	0.090 (3)	0.4788 (6)	3.8 (5)
C(11)I	0.6182 (5)	0.290 (2)	0.4918 (5)	3.2 (5)
N(12)I	0.6744 (4)	0.271 (2)	0.5296 (4)	3.9 (4)
N(1)P	0.8011 (5)	0.160 (2)	0.7269 (5)	4.4 (4)
C(2)P	0.8152 (5)	0.162 (2)	0.6744 (6)	3.3 (4)
C(3)P	0.7732 (6)	0.198 (2)	0.6243 (5)	3.0 (4)
C(4)P	0.7159 (5)	0.236 (2)	0.6316 (5)	2.8 (4)
C(5)P	0.7021 (5)	0.236 (2)	0.6880 (5)	3.1 (4)
C(6)P	0.7439 (6)	0.197 (2)	0.7325 (5)	3.4 (5)
C(2′)P	0.8775 (6)	0.120 (4)	0.6685 (7)	5.0 (7)
O(3′)P	0.7913 (4)	0.192 (2)	0.5755 (4)	2.7 (3)
C(4′)P	0.6698 (5)	0.272 (2)	0.5837 (5)	2.8 (4)
C(5′)P	0.6396 (6)	0.284 (2)	0.6988 (6)	3.5 (5)
O(5′)P	0.6258 (4)	0.481 (2)	0.6866 (4)	2.9 (4)
N(1)i	0.9103 (6)	−0.249 (3)	0.4016 (5)	5.8 (5)
C(2)i	0.8908 (7)	−0.186 (3)	0.4510 (8)	4.4 (6)
C(3)i	0.9200 (6)	−0.021 (2)	0.4708 (6)	3.5 (5)
C(4)i	0.9960 (7)	0.178 (3)	0.4234 (9)	5.6 (8)
C(5)i	1.0259 (9)	0.174 (4)	0.378 (1)	6. (1)
C(6)i	1.0171 (9)	0.029 (5)	0.338 (1)	7. (1)
C(7)i	0.9807 (8)	−0.123 (3)	0.3413 (8)	5.4 (8)
C(8)i	0.9504 (6)	−0.126 (2)	0.3873 (7)	3.9 (6)
C(9)i	0.9579 (6)	0.021 (2)	0.4292 (6)	3.5 (5)
C(10)i	0.9095 (6)	0.090 (3)	0.5212 (6)	3.8 (5)
C(11)i	0.8817 (5)	0.290 (2)	0.5083 (5)	3.1 (5)
N(12)i	0.8256 (4)	0.271 (2)	0.4704 (4)	3.9 (4)
N(1)p	0.6989 (5)	0.160 (2)	0.2732 (5)	4.4 (4)
C(2)p	0.6848 (5)	0.162 (2)	0.3256 (6)	3.3 (4)
C(3)p	0.7268 (6)	0.198 (2)	0.3757 (5)	3.0 (4)
C(4)p	0.7841 (5)	0.236 (2)	0.3684 (5)	2.8 (4)
C(5)p	0.7979 (5)	0.236 (2)	0.3120 (5)	3.1 (4)
C(6)p	0.7561 (6)	0.197 (2)	0.2675 (5)	3.4 (5)
C(2′)p	0.6224 (6)	0.120 (4)	0.3315 (7)	5.0 (7)
O(3′)p	0.7086 (4)	0.192 (2)	0.4245 (4)	2.7 (3)
C(4′)p	0.8302 (5)	0.272 (2)	0.4163 (5)	2.8 (4)
C(5′)p	0.8604 (6)	0.284 (2)	0.3012 (6)	3.5 (5)
O(5′)p	0.8742 (4)	0.481 (2)	0.3134 (4)	2.9 (4)
Cu	0.7491 (8)	0.2497 (3)	0.5000 (7)	2.82 (5)

For the meaning of the symbols I, P, i and p, see the legend to Fig. 1. *a*) B_{eq} values were calculated with anisotropic thermal parameters by using the following equation: $B_{eq}=4/3(B_{11}\boldsymbol{a}^2+B_{22}\boldsymbol{b}^2+B_{33}\boldsymbol{c}^2+\boldsymbol{ac}B_{13}\cos\beta)$.

The final R value [$F_o^2>3\sigma(F_o)^2$] was 0.08. The atomic scattering and anomalous dispersion factors were taken from the usual tabulation.[8] The calculations were carried out using the UNICS programs.[9] The final atomic coordinates are listed in Table II.[10] Figure 1 shows the atomic numbering scheme used.

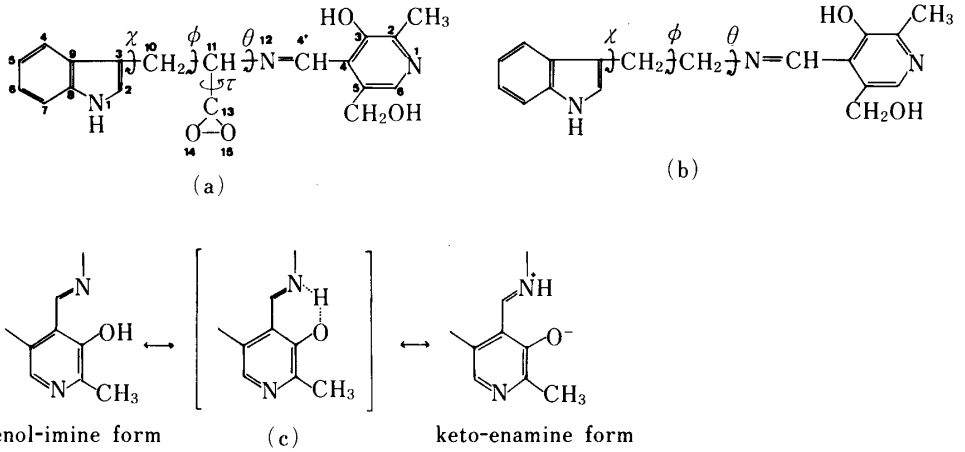


Fig. 2. Variable Torsion Angle Notations of Pyridoxylidenetryptophan (a) and Pyridoxylidenetryptamine (b) Schiff Bases, and Tautomeric Structure (c) of the Schiff Base

The torsion angles of (a) are defined by χ (2-3-10-11), τ (10-11-13-14), ϕ (3-10-11-13) and θ (13-11-12-4'), and those of (b) by χ (2-3-10-11), ϕ (3-10-11-12) and θ (10-11-12-4'), respectively.

Conformational Analyses of Pyridoxylidenetryptophan and Pyridoxylidenetryptamine Schiff Bases——In order to elucidate the stable conformations for pyridoxal-catalyzed reactions of tryptophan, energy calculations for various Schiff base conformers were carried out by using the classical potential energy functions (PPF method) and the semiempirical CNDO/2 method. The atomic coordinates requisite for the calculations were built up from the present X-ray results. We employed the following technique to determine the global and local energy minima of the Schiff bases. Initially the following starting angle set for variable torsion angles (see Fig. 2) was selected, as the most reasonable value, on the basis of the related crystal structure[11] and sp^2–sp^3 bond barrier:

$$\chi = \pm 90,\ 180^\circ,\ \tau = -30^\circ,\ \phi = \pm 60,\ 180^\circ,\ \theta = \pm 30,\ \pm 90,\ \pm 150^\circ$$

where the torsion angle, τ, was considered only for the pyridoxylidenetryptophan Schiff base. We fixed the C(4')–C(4) bond so that the C(4')–N(12) bond is coplanar with the pyridoxal ring and has *cis* conformation to the C(3)–O(3') bond, because of the favorable conformation of the Schiff base as was suggested from the literature[12] and the present crystal structure. As possible forms of the pyridoxal moiety, keto-enamine and enol-imine forms (see Fig. 2) were considered, because these two forms have been reported to exist in solution, predominantly.[13] Next, the energies of the 54 different conformers were claculated by using the PPF method: the functions included in calculations were nonbonded, electrostatic and torsional energies. Details of the calculation procedure and the data used were presented in previous papers.[10,14] Each torsion angle, χ, τ, and ϕ, as a variable parameter, was optimized by means of the Powell algorithm[15]: energy minimization was carried out by parabola approximation with 4° intervals, and no angle was permitted to vary by more than 12° at each step. These results provided a coarse, but overall picture of the energetically stable conformation. Thirdly, the conformers having $\theta = 90$, -30, -90, and -150°, which were considered to be energetically stable from the first energy calculations, were further examined at combinations of the following starting angles of χ, τ, and ϕ:

$$\chi = \pm 30,\ \pm 90,\ \pm 150^\circ,\ \tau = \pm 30,\ \pm 90,\ \pm 150^\circ,\ \phi = \pm 60,\ 180^\circ$$

Finally, the total energies of the 30 stable conformers obtained were calculated by the CNDO/2 method[16]: electronic energies were converged by the iterative SCF (self-consistent field) method. We feel this four-step procedure provides the best chance to find the most energetically stable conformation for a molecule possessing freely rotatable bonds.

All numerical calculations were carried out on an ACOS-900 computer at the Computation Center of Osaka University.

Results and Discussion

Molecular and Crystal Structure

The molecular geometry of the present complex is shown in Fig. 3. Bond lengths and angles, and selected torsion angles are summarized in Table III.

TABLE III. List of Bond Lengths, Bond Angles and Selected Torsion Angles with Their Standard Deviations in Parentheses

	Molecule A[a]	Molecule B[a]		Molecule A[a]	Molecule B[a]
a) Bond lengths (in Å)					
N(1)–C(2)	1.39 (3)	1.39 (3)	N(1)–C(2)[b]	1.33 (2)	1.33 (2)
N(1)–C(8)	1.34 (3)	1.34 (3)	N(1)–C(6)	1.37 (2)	1.37 (2)
C(2)–C(3)	1.38 (2)	1.38 (2)	C(2)–C(3)[b]	1.43 (2)	1.43 (2)
C(3)–C(9)	1.45 (2)	1.45 (2)	C(2)–C(2′)	1.50 (3)	1.50 (3)
C(3)–C(10)	1.47 (2)	1.47 (2)	C(3)–C(4)	1.39 (2)	1.39 (2)
C(4)–C(5)	1.38 (4)	1.38 (4)	C(3)–O(3′)	1.29 (2)	1.29 (2)
C(4)–C(9)	1.43 (3)	1.43 (3)	C(4)–C(5)[b]	1.42 (2)	1.42 (2)
C(5)–C(6)	1.37 (5)	1.37 (5)	C(4)–C(4′)	1.45 (2)	1.45 (2)
C(6)–C(7)	1.36 (4)	1.36 (4)	C(5)–C(6)[b]	1.34 (2)	1.34 (2)
C(7)–C(8)	1.39 (3)	1.39 (3)	C(5)–C(5′)	1.54 (2)	1.54 (2)
C(8)–C(9)	1.42 (2)	1.42 (2)	C(5′)–O(5′)	1.43 (2)	1.43 (2)
C(10)–C(11)	1.54 (2)	1.55 (2)	Cu–O(3′)	1.94 (2)	1.92 (2)
C(11)–N(12)	1.46 (2)	1.46 (2)	Cu–N(12)	1.97 (2)	2.01 (2)
N(12)–C(4′)	1.30 (2)	1.30 (2)			
b) Bond angles (°)					
C(2)–N(1)–C(8)	110 (2)	110 (2)	C(11)–N(12)–C(4′)	113 (1)	114 (1)
N(1)–C(2)–C(3)	110 (2)	110 (2)	N(1)–C(2)–C(3)[b]	123 (1)	123 (1)
C(2)–C(3)–C(9)	105 (1)	105 (1)	N(1)–C(2)–C(2′)	118 (2)	118 (2)
C(2)–C(3)–C(10)	125 (2)	125 (2)	C(3)–C(2)–C(2′)	120 (2)	120 (2)
C(9)–C(3)–C(10)	130 (2)	130 (2)	C(2)–C(3)–C(4)	118 (1)	118 (1)
C(5)–C(4)–C(9)	117 (2)	117 (2)	C(2)–C(3)–O(3′)	117 (1)	117 (1)
C(4)–C(5)–C(6)	121 (3)	121 (3)	C(4)–C(3)–O(3′)	125 (1)	125 (1)
C(5)–C(6)–C(7)	125 (3)	125 (3)	C(3)–C(4)–C(5)	119 (1)	119 (1)
C(6)–C(7)–C(8)	117 (2)	117 (2)	C(3)–C(4)–C(4′)	122 (1)	122 (1)
N(1)–C(8)–C(7)	131 (2)	131 (2)	C(5)–C(4)–C(4′)	119 (1)	119 (1)
N(1)–C(8)–C(9)	107 (2)	108 (2)	C(2)–N(1)–C(6)	118 (1)	118 (1)
C(7)–C(8)–C(9)	121 (2)	121 (2)	C(4)–C(5)–C(6)[b]	120 (1)	120 (1)
C(3)–C(9)–C(4)	132 (2)	132 (2)	C(4)–C(5)–C(5′)	121 (1)	121 (1)
C(3)–C(9)–C(8)	108 (1)	108 (1)	C(6)–C(5)–C(5′)	119 (1)	119 (1)
C(4)–C(9)–C(8)	120 (2)	120 (2)	N(1)–C(6)–C(5)	123 (1)	123 (1)
C(3)–C(10)–C(11)	115 (1)	116 (1)	N(12)–C(4′)–C(4)	127 (1)	127 (1)
C(10)–C(11)–N(12)	110 (1)	110 (1)	C(5)–C(5′)–O(5′)	111 (1)	111 (1)
N(12)I–Cu–N(12)i	172 (1)	N(12)I–Cu–O(3′)P	92 (1)		
N(12)I–Cu–O(3′)p	91 (1)	O(3′)P–Cu–N(12)i	90 (1)		
O(3′)P–Cu–O(3′)p	156 (1)	N(12)i–Cu–O(3′)p	91 (1)		
c) Torsion angles (°)					
C(2)–C(3)–C(10)–C(11)	−112 (2)	−112 (2)	C(5)–C(4)–C(4′)–N(12)	−177 (1)	−177 (1)
C(9)–C(3)–C(10)–C(11)	63 (2)	63 (2)	C(4)–C(5)–C(5′)–O(5′)	−68 (2)	−68 (2)
C(3)–C(10)–C(11)–N(12)	59 (2)	58 (2)	C(6)–C(5)–C(5′)–O(5′)	111 (2)	111 (2)
C(10)–C(11)–N(12)–C(4′)	−88 (2)	−88 (2)	C(4)–C(4′)–N(12)–Cu	−8 (2)	−8 (2)
C(11)–N(12)–C(4′)–C(4)	173 (1)	173 (1)	C(4′)–N(12)–Cu–O(3′)	10 (2)	10 (2)
O(3′)–C(3)–C(4)–C(4′)	0 (2)	0 (2)	N(12)–Cu–O(3′)–C(3)	−9 (2)	−9 (2)
C(3)–C(4)–C(4′)–N(12)	2 (2)	2 (2)	Cu–O(3)–C(3)–C(4)	5 (2)	6 (2)

a) Molecules A and B represent the left- and right-side Schiff bases shown in Fig. 1, respectively. *b*) These bond lengths and angles represent the pyridoxal moiety of the Schiff base.

As was supposed from the preliminary data (elemental analysis and crystal data), the Schiff base existed as a bidentate monobasic ligand with an anionic O(3′)P atom. The copper(II) atom is four-coordinated to two phenolic oxygen atoms O(3′)P and O(3′)p and two nitrogen atoms N(12)I and N(12)i with reasonable distances. The coordination mode can

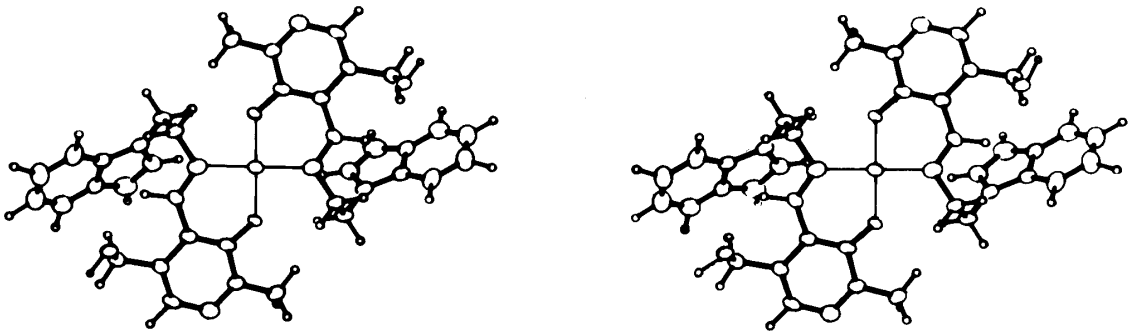


Fig. 3. Stereoscopic Drawing of Bis(pyridoxylidenetryptamine) Copper(II) Complex

Thin lines represent the coordinate bonds.

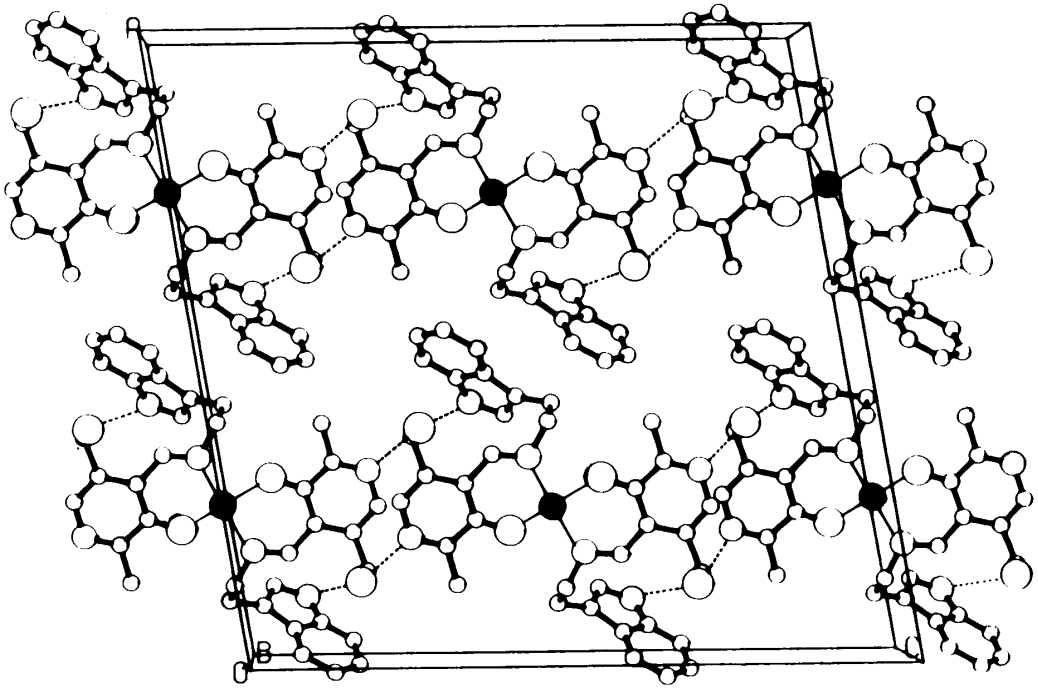


Fig. 4. Crystal Packing of Bis(pyridoxylidenetryptamine) Copper(II) Complex Viewed Down the *b* Axis

Broken lines indicate the hydrogen bonds.

be described as a tetrahedrally distorted square plane. The distortion from an ideal square plane can be defined by the dihedral angle between the two chelating moieties of Cu, N(12)I, O(3′)P and Cu, N(12)i, O(3′)p[17]; in this complex, the value is 26(2)°. Such a distortion has also been observed in the copper complex of the pyridoxalbenzylamine Schiff base,[6] and appears to be a common mode in the copper complexes of pyridoxal–amine Schiff bases. As is obvious from Fig. 3, the two pyridoxylidenetryptamine molecules are almost related to each other by a pseudo twofold symmetry which lies on the central copper atom; a comparison of their bonding parameters shows nearly the same molecular geometry.

Two Schiff bases which are related by a center of symmetry can also form the same coordination environment to the copper ion as one with a twofold symmetry. The reason why only the latter case is observed may be related to the character of copper ion in taking a tetrahedrally distorted coordination structure.

Figure 4 shows a projection of the crystal packing. Four kinds of hydrogen bonds, shown by the broken lines, were formed between N(12) and O(5′) atoms: N(1)I$(x,y,z)\cdots$O(5′)P$(x,-1+y,z)=2.84(2)$ Å, N(1)i$(x,y,z)\cdots$O(5′)p$(x,-1+y,z)=2.84(2)$ Å, O(5′)P$(x,y,z)\cdots$N(1)P$(1.5-x,\ 0.5+y,\ 1.5-z)=2.74(2)$ Å and O(5′)p$(x,y,z)\cdots$N(1)p$(1.5-x,\ 0.5+y,\ 0.5-z)=2.74(2)$ Å. Although no direct interaction of indole and pyridoxal rings is observed in the crystal packing, the molecular conformation for each Schiff base takes a folded form, and the dihedral angle of the rings is 46.5(7)°. This conformation appears to be consistent with the nuclear magnetic resonance (NMR) data of tryptophan–pyridoxal Schiff base in solution[12]: the data suggested intramolecular π–π

TABLE IV. Stable Conformations of Pyridoxylidenetryptophan Schiff Base and Their Energies

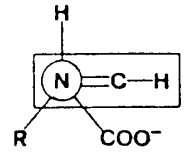
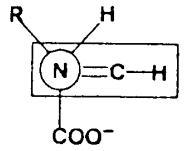
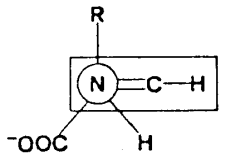
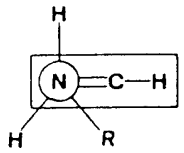
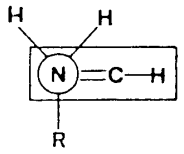
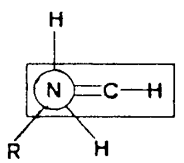
	Conformer	Total energy (in atomic unit)	
		Enol-imine form	Keto-enamine form
 $\theta=-30°$	A1 ($\chi=-90°$, $\tau=49°$, $\phi=184°$)	−257.5917	−257.5315
	A2 ($\chi=-70°$, $\tau=52°$, $\phi=-58°$)	−257.5914	−257.5327
	A3 ($\chi=97°$, $\tau=51°$, $\phi=-67°$)	−257.5903	−257.5291
 $\theta=-90°$	B1 ($\chi=-79°$, $\tau=-27°$, $\phi=-58°$)	−257.5986	−257.5309
	B2 ($\chi=100°$, $\tau=-25°$, $\phi=-61°$)	−257.5961	−257.5274
	B3 ($\chi=-90°$, $\tau=-24°$, $\phi=184°$)	−257.5906	−257.5222
 $\theta=-150°$	C1 ($\chi=92°$, $\tau=-25°$, $\phi=186°$)	−257.5842	−257.5214
	C2 ($\chi=104°$, $\tau=-24°$, $\phi=-67°$)	−257.5818	−257.5190
	C3 ($\chi=-97°$, $\tau=-25°$, $\phi=191°$)	−257.5721	−257.5098

TABLE V. Stable Conformations of Pyridoxylidenetryptamine Schiff Base and Their Energies

	Conformer	Total energy (in atomic unit)	
		Enol-imide form	Keto-enamine form
 $\theta=-30°$	D1 ($\chi=89°$, $\phi=207°$)	−214.4833	−214.4332
	D2 ($\chi=-94°$, $\phi=207°$)	−214.4830	−214.4341
	D3 ($\chi=45°$, $\phi=103°$)	−214.4741	−214.4231
 $\theta=-90°$	E1 ($\chi=-100°$, $\phi=-58°$)	−214.4827	−214.4314
	E2 ($\chi=-112°$, $\phi=51°$)	−214.4777	−214.4254
	E3 ($\chi=109°$, $\phi=59°$)	−214.4768	−214.4249
 $\theta=-150°$	F1 ($\chi=-84°$, $\phi=55°$)	−214.4880	−214.4379
	F2 ($\chi=-86°$, $\phi=-51°$)	−214.4863	−214.4374
	F3 ($\chi=93°$, $\phi=56°$)	−214.4856	−214.4346

interaction of the aromatic rings.

Conformational Analyses of Tryptophan– and Tryptamine–Pyridoxal Schiff Bases

1) Pyridoxylidenetryptophan Schiff Base——According to Dunathan's hypothesis,[3] the conformation of $\theta = 90$ or $-90°$ must be the most suitable form for the decarboxylation of L-tryptophan to tryptamine. Table IV summarizes the result of energy calculations. Although the conformation about the Cα–N bond of general pyridoxal–amino acid Schiff bases in solution can be considered as a dynamic equilibrium of various rotamers ($\theta = \pm 30$, ± 90, $\pm 150°$), the most important conformations for tryptophan were those of $\theta = -30°$ (conformer A), $-90°$ (conformer B), and $-150°$ (conformer C); it is of interest to note that the conformations having $\theta = 30$, 90 or 150° were energetically unstable. The preference for conformers A, B and C in solution has also been suggested by NMR and circular dichroism (CD) studies of pyridoxal–amino acid Schiff bases.[12,18] The most energetically stable conformation belonging to each conformer (A1, B1 and C1) is shown in Fig. 5. Conformer C was significantly more unstable than conformers A and B. The energy differences between A1 and B1, A1 and C1, and B1 and C1 were 3.58, 4.71 and 9.04 kcal/mol,

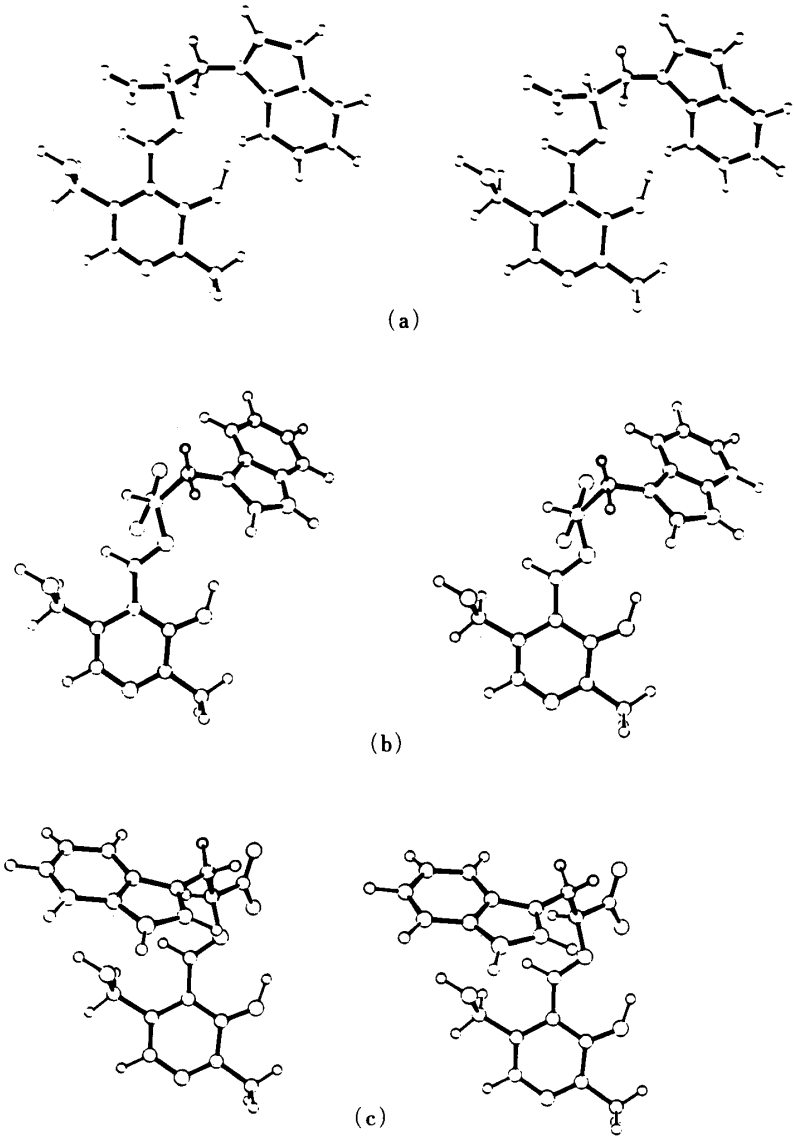


Fig. 5. Stereoscopic Drawings of Conformers A1 (a), B1 (b) and C1 (c)

respectively. For the pyridoxylidenetryptophan Schiff base, the stable conformation appears to depend on the tautomeric structure of the Schiff base; in the comparison of conformer A1 with B1, the former is more stable for the keto-enamine form, while the enol-imine form shows the reverse. The enol-imine form of conformer B1, which is the most energetically stable form among many conformers surveyed, could be considered as the most suitable conformation for the pyridoxal-catalyzed reaction (decarboxylation) from tryptophan to tryptamine. This conformer was also the most energetically stable form in relation to the protonation of the pyridine nitrogen atom N(1), which is considered to be an important intermediate form for the strong electron withdrawal from the Cα atom of amino acids in the metabolic process.[19] The same conformation may be applicable to the synthesis of serotonin from 5-hydroxytryptophan.

NMR studies[12] have shown that the conformation about Cα–Cβ bond preferentially takes *trans* form ($\phi = 180°$) as the result of π–π interaction between the aromatic ring of the amino acids and the pyridoxal system. In the present results, some of the stable conformers show ring stacking interaction between the aromatic rings. Conformers C1 and C3 listed in Table IV have this interaction.

2) Pyridoxylidenetryptamine Schiff Base——Since the conformations of $\theta = 0$—$180°$ gave the same stereostructural environment as those of $\theta = 0$——$180°$, respectively, because there

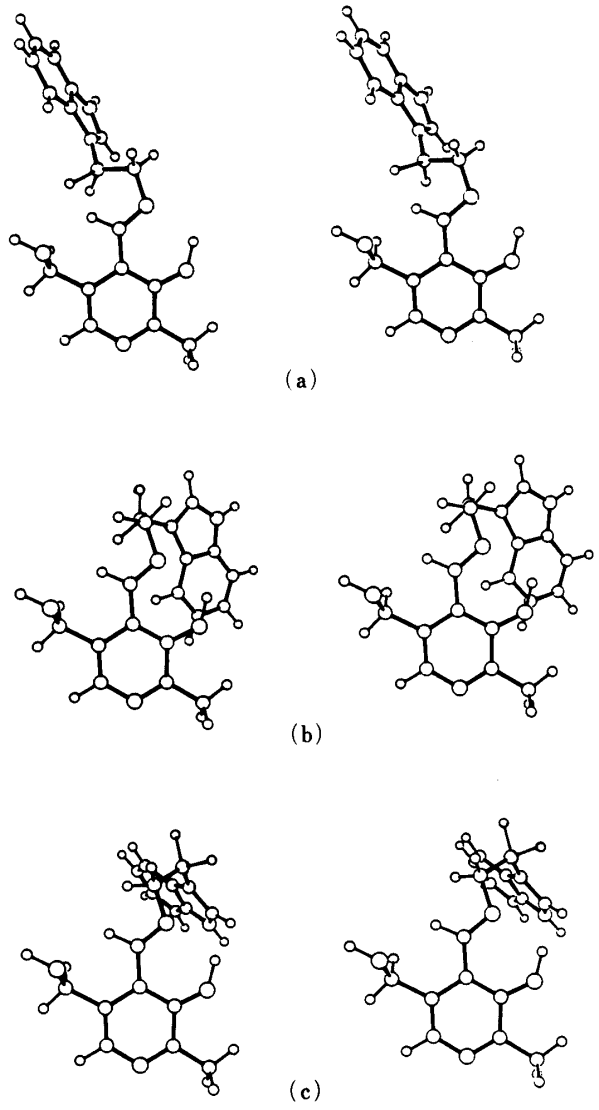


Fig. 6. Stereoscopic Drawings of Conformers D1 (a), E1 (b) and F1 (c)

is no asymmetric atom and because of the planarity of the pyridoxal–imine plane, we dealt only with the conformations of $\theta = -30$, -90 and $-150°$. The results of the energy calculations are summarized in Table V. The most stable conformations with respect to conformers D($\theta = -30°$), E($\theta = -90°$) and F($\theta = -150°$) are shown in Fig. 6. Although conformer E is rather less stable than the other two conformers, the energy difference is not large, compared to the case of pyridoxylidenetryptophan Schiff base. This implies that conformational rotation about the C(11)–N(12) bond is feasible and an equilibrium state among these conformers may exist in solution. As with the pyridoxylidene–tryptophan Schiff base, the stacking interaction of the aromatic rings appears to give stable forms as observed in conformer E1, E2 or E3. The conformation observed in the crystal structure has a total energy of -214.2796 a.u. and belongs to conformer E.

The metabolism from tryptamine to indoleacetoaldehyde, which is catalyzed by monoamine oxidase, can proceed *via* C(11)-H cleavage of the Schiff base according to Dunathan's hypothesis.[3] Conformer F1 would be the most suitable conformation as an intermediate of this enzymatic reaction (oxidative deamination). This conformer was also the most energetically stable form in the protonation of the pyridine nitrogen atom.

In summary, the energy calculation studies provided the reasonable conformations of the Schiff base in relation to the synthesis and metabolism of tryptamine. These conformations may also be applicable to the case of serotonin.

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