Unusual Intermolecular Short Contacts of C···C = 2.3 Å in Crystal Structure of Copper Complex of Schiff Base of Vitamin B_6 Phosphate Ester; Does It Reveal an Intermediate Structure to σ-Covalent Bond Formation ?

Toshimasa Ishida,* Yasuko In, Hiroomi Nagata, Mitsunobu Doi, and Akio Wakahara*†
Department of Physical Chemistry, Osaka University of Pharmaceutical Sciences, 2-10-65 Kawai, Matsubara, Osaka 580
†Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532

(Received September 8, 1995)

The crystal structure of copper complex of Schiff base of pyridoxal-5-phosphate and pyridoxamine-5-phosphate showed the strikingly short intermolecular C···C contact of ~ 2.3 Å. Since this value corresponds just to a transition state for cycloaddition reaction estimated by *ab initio* calculation, the present result may be the first structural presentation of an intermediate structure from the noncovalent π–π interaction to the σ-covalent bond formation

As far as intermolecular C···C contact is concerned, there is a general agreement that 3.4 Å, which corresponds to the sum of van der Waals radii for aromatic carbon atom, is the minimum separation distance,[1] and special force such as aromatic π···π or C-H···π interaction shortens the distance by 0.1 ~ 0.2 Å at most;[2] the short contact shorter than 3.2 Å has not been observed because of the van der Waals atomic repulsion. In the cyclic addition reaction between the unsaturated compounds, such as Diels-Alder or 1,3-dipolar reaction, however, the intermolecular C···C atoms must be located at distance less than 3.2 Å to form the σ–covalent bond. This means that any specific interaction overcoming such van der Waals repulsion must predominate in an initial step of the reaction. Although such a reaction mechanism has been the subject of the most heated and interestingly controversies in the field of theoretical approach,[3] experimental data on the transition structure are quite lacking. Herein we report the x-ray crystal structure of the copper complex of the Schiff base of pyridoxal-5-phosphate(PLP) and pyridoxamine-5-phosphate (PMP) (**1**), in which the short contact of ~2.3Å observed in the intermolecular C···C atomic pairs may correspond to an intermediate state between the noncovalent π–π short contact and the σ-covalent bond.

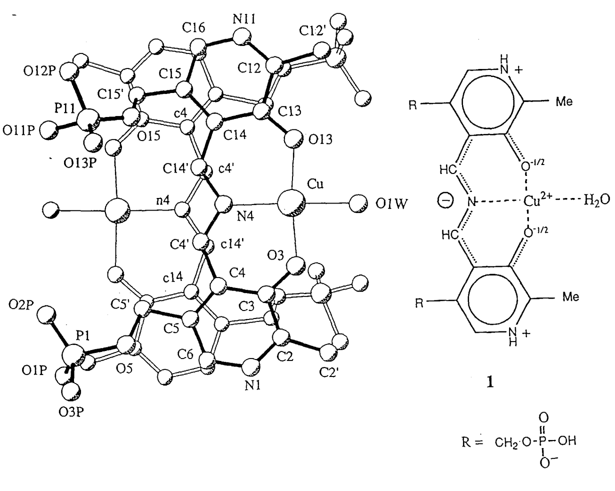

Figure 1. Overlap between two centrosymmetrically-related Cu(II) complexes of **1**, together with the atomic numberings used in this paper. The atoms labeled with small letters represent the translation from the original ones by a center of symmetry. The thin lines represent the coordination bonds. The electronic state of **1** is also illustrated, where the dotted lines represent the resonance state, and the coordination bonds are shown with broken lines.

Table 1. Some structural parameters of **1**

Intramolecular atomic pairs			
C3 – O3	1.30(2) Å	C13 – O13	1.29(2) Å
C4 – C4'	1.46(2)	C14' – C14	1.46(2)
C4' – N4	1.35(2)	N4 – C14'	1.32(2)
C4-C4'-N4	122.1(8)°	C14-C14'-N4	122.3(7)°
C4'-N4-C14'	113(1)		
Centrosymmetry-related intermolecular atomic pairs			
C4 ··· c14 (=C14 ··· c4)	3.22(2) Å		
C4 ··· c14' (=C14' ··· c4)	3.02(2)		
C4' ··· c14 (=C14 ··· c4')	3.01(2)		
C4' ··· c14' (=C14' ··· c4')	2.29(2)		
C4' ··· n4 (=N4 ··· c4')	2.69(2)		
N4 ··· c14' (=C14' ··· n4)	2.73(2)		
N4 ··· n4	2.83(1)		

The Cu(II) complex structure[4] of **1** is shown in Figure 1. Bond lengths and angles indicate that **1** has the structure where the phosphate oxygen is deprotonated and pyridine nitrogen protonated. Characteristically, **1** is in an intermediate state between the aldimine and ketimine structures[5] of the Schiff base by the deprotonation at the C4'-N4-C14' bonding moiety (Table 1), where the total charge of -1*e* is distributed over the entire C4'-N4-C14' moiety through the carbanion structure. On the other hand, each of the two pyridine phenolic oxygens (O3 and O13) has a charge of -1/2*e*, as judged from the partial double-bond character.[7] This may be also interpreted as that two structures, one with the O3 and C14' deprotonated and C4' and O13 nonprotonated state and the other with an opposite state, coexist with equal population in the crystal. As a whole, the electronic state of -2*e* of **1** is neutralized by the coordination of Cu^{2+} ion in the complex crystal.

The Cu(II) complex of **1** exists as a centrosymmetrically-related dimer in the unit cell (Figure 2), in which the Cu(II) ion forms an approximately square-pyramidal coordination with N4, O3, O13 and O1W atoms in-plane (also see Figure 1) and with a centrosymmetrically-translated O3P atom in apical position. The most exciting and novel finding observed in the crystal is the unusual intermolecular short contact [=2.29(2) Å] of C4'···c14' [=C14'···c4'] between the centrosymmetrically-related dimers; it appears noteworthy that this distance agrees well with the values (2.1~2.4 Å) of transition structures calculated for Diels-Alder or 1,3-dipolar cycloaddition reactions.[3] The other atomic pairs between the C4'-N4-C14' regions also show the contacts shorter than the sum of respective van der Waals atomic radii (Table 1). Since the two pyridine rings facing each other deviate significantly from parallel alignment [dihedral angle=30.8(4)°], probably due to van der Waals repulsion, it could be supposed that a certain force operates in the C4'···c14'

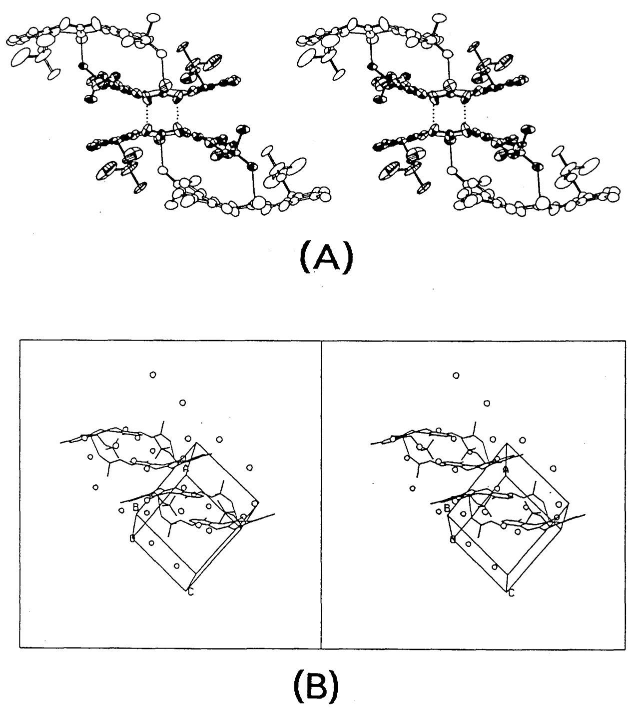

Figure 2. (A) Stereoscopic view of dimer (upper and lower pairs) and unusual short contact (central pair) formations. Dimer formation of **1** is accomplished by the coordination of O3P to the symmetry-related Cu(II) ion. The short contacts of C4'···c14' and C14'···c4' atomic pairs between the centered two molecules with shaded ellipsoids are shown with dotted lines, and the coordinations are shown with thin lines.
(B) Stereoscopic crystal packing of **1**. Water molecules are shown with open circles, and thin lines represent the coordination bonds.

and C14'···c4' atomic pairs. The existence of such a special force can also be supported from the infrared spectral measurement of the complex crystal. The C=N stretching of **1** locates unequivalently at 1612 cm^{-1} and 1592 cm^{-1}, and these peaks are significantly shifted to the low-frequency side, compared with those of PLP–PMP (1640 cm^{-1} and 1633 cm^{-1}) and pyridoxal–pyridoxamine Schiff bases (1631cm^{-1}). This reflects the weakened C=N stretching force of the Schiff base of **1** in the present Cu(II) complex, together with the $\overset{..}{-}\mathrm{CH}\overset{..}{-}\mathrm{N}\overset{..}{-}\mathrm{CH}\overset{..}{-}$ double-bond character by deprotonation.

Since the direction of C4'···c14' [=C14'···c4'] close contact is almost perpendicular to a bent *trans zig-zag* plane of C4–C4'–N4–C14'–C14 moiety [angle=91°], it is obvious that π-orbitals [$=\chi_{2pz}$ orbital] of the C4' and C14' atoms are responsible for this short contact formation. It is important to note that since close contact between the neighboring azomethine carbons has not been observed in the -CH=N–CH_2- chemical bonding,[8] its Cu(II)-mediated deprotonation [$\overset{..}{-}\mathrm{CH}\overset{..}{-}\mathrm{N}\overset{..}{-}\mathrm{CH}\overset{..}{-}$] is indispensable to achieve such closer contacts. The enrichment of electrons in both C4' and C14' π-orbitals, which is caused by deprotonation, increases the resonance and overlap integrals [$\int\chi_{(C4')2pz}H\chi_{(c14')2pz}d\tau$ and $\int\chi_{(C4')2pz}\chi_{(c14')2pz}d\tau$, respectively], thus promoting the σ-covalent bond formation.

The short contact, which is significantly less than the sum of respective van der Waals radii, has already been observed between N and I atoms (=2.27Å) in the trimethylamine–iodine complex.[9] This could be interpreted as a typical n–σ charge-transfer interaction, where the lone-paired electrons of N atom are transferred into the σ* orbital of I_2 molecule. In contrast, the carbon atom usually does not possess such lone-paired electrons. Therefore, the present "σ-bonding-like" π–π interaction may be the first example that is not explicable with the intermolecular interactions so far accepted.

References and Notes

1 L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, (1940); A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

2 J. C. A. Boeyens and F. H. Herbstein, *J. Phys. Chem.*, **69**, 2160 (1965).

3 R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969); K. N. Houk, Y. Li, and J. D. Evanseck, *Chem., Int. Ed. Engl.*, **31**, 682 (1992); Y. Li and K. N. Houk, *J. Am. Chem. Soc.*, **115**, 7478 (1993); K. N. Houk, J. Gonzalez, and Y. Li, *Acc. Chem. Res.*, **28**, 81 (1995).

4 To an aqueous solution dissolving equimolar PLP and $Cu(NO_3)_2$ (10 mM), an excess of L-alanine (~15 mM) was added. Greenish platelet crystals were precipitated from the reaction solution kept at 20 °C within a few week. The crystals consisted of the Cu(II) complex of PLP–PMP Schiff base; PMP would be produced from PLP as a result of Cu(II)-mediated transamination of L-alanine.[5] A single crystal with dimensions of 0.2 × 0.1 × 0.05 mm was sealed in a glass capillary containing some mother liquid. Crystal data of **1**: $C_{16}H_{18}N_3O_{10}P_2\cdot Cu\cdot 8H_2O$, Mr=681.96, triclinic, $P\overline{1}$, a= 10.894(1)Å, b=13.603(1)Å, c= 9.776 (1)Å, α=95.00(1)°, β= 92.87(1)°, γ=67.61(1)°, V= 1334.2(3)$Å^3$, Z=2, D_{calcd}=1.698, D_{obsd}=1.613(5)g.cm^{-3}, λ(Cu Kα)=1.5418 Å, μ(CuKα)=3.10 mm^{-1}, F(000)=708. A total of 4201 independent reflections collected within 2θ=124°(*Rint*= 0.033) at 15°C were corrected for the Lorentz and polarization factors and the absorption effect. The statistical distribution of normalized structure factors suggested the centrosymmetric space group for **1**. The structure was solved by the heavy atom method and all heavy atoms were refined with the use of anisotropic temperature factors (SHELXL-93[6]); all H atoms in ideal positions, except for water molecules, were used only for the calculation of structure factors. The refinements *versus* Fo^2 led to R_1=0.112 for 2651 reflections with $|Fo| > 4\sigma(|Fo|)$. Because of the small size and thin-layered crystal, the analysis is less accurate than usual. However, the bonding parameters all lie within the acceptable region[7]. The coordination parameters to Cu(II) ion are also reasonable, compared with the Cu(II) complex of pyridoxal–tryptamine Schiff base[8]: Cu-O3, 1.90(1)Å;Cu-N4, 1.979(9)Å; Cu-O13, 1.894(9)Å; Cu-O1W, 1.99(1)Å; Cu-O3P (at 1-*x*, -*y*, 1-*z*), 2.385(9)Å; O3-Cu-N4, 92.6(4)°; O3-Cu-O13, 164.9(4)°; O3-Cu-O1W, 86.7(4)°; O3-Cu-O3P, 95.8(4)°; N4-Cu-O13, 92.4(4)°; N4-Cu-O1W, 176.9(4)°; N4-Cu-O3P, 92.0(3)°; O13-Cu-O1W, 87.5(4); O13-Cu-O3P, 98.3(4)°; O1W-Cu-O3P, 91.1(4)°.

5 A. E. Martell, in *Advances in Enzymology*, ed by A. Meister, John Wiley & Sons, New York, (1982), Vol.53 p163.

6 G. M. Sheldrick, SHELXL-93, a program for the refinement of crystal structures from diffraction data, University of Göttingen, 1993.

7 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc., Perkin Trans.2*, **1987**, S1.

8 T. Ishida, K. Hatta, S. Yamashita, M. Doi, and M. Inoue, *Chem. Pharm. Bull.*, **34**, 3553 (1986).

9 K. O. Strømme, *Acta Chem. Scand.*, **13**, 268 (1959).