Characteristics of Pyrimidine Nucleobases through Inter-base Interactions on the Crystals of the Ternary Copper(II) Complexes

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Characteristics of pyrimidine bases are demonstrated on the crystals of the ternary copper(II) complexes consisting of bpy and pyrimidine-amino acid. Hemiprotonated CH^+:C pair is important for the formation of intermolecular triple hydrogen bonding interaction, mimicking *i*-motif of DNA. The electron-donating effect in thymine ring among pyrimidine bases also promotes intermolecular π–π stacking interaction.

Hydrogen bond in heteroaromatic compound is one of the most versatile interactions for self-assembly systems.[1] Three-dimensional structure of DNA formed through association of two different polynucleotide chains is well known to be stabilized by complementary hydrogen- bond between purine and pyrimidine bases and by π–π stacking interactions.[2] The triple hydrogen-bonding system of the G:C pair in DNA is essential for recognition of each other. As a transition-metal complex is a useful tool for proving interactions of biological compounds,[3] the π–π stacking interactions of nucleobases have been demonstrated on the ternary copper(II) or palladium(II) complexes.[4] In this viewpoint, the ternary complexes containing nucleobase amino acid with purine ring demonstrated intramolecular π–π stacking interaction both in solution and solid state, while those with pyrimidine ring did not show such interaction.[5] In order to clarify the characteristic of the hydrogen-bonding interaction mediated upon nucleobase as well as the π–π interaction, we have carried out the X-ray structural analysis of the ternary copper(II) complexes consisting of bipyridine and pyrimidine bases. Here, two kinds of pyrimidine-amino acid, such as 1-(2-amino-2-carboxyethyl)cytosine (ACEC) and 1-(2-amino-2-carboxyethyl)thymine (ACET), were employed.[6]

The ternary copper(II) complexes, $[\{[Cu(acec)(bpy)]\}_2 \cdot HCl]^{2+}$ (**1**) and $[Cu(acet)(bpy)]^+$ (**2**), were obtained through the complexation with $Cu(ClO_4)_2$, bipyridine (bpy), and ACEC·HCl or ACET in aqueous solution.[5] The crystal structure of **1**, as shown in Figure 1a,[7] reveals formation of the copper complex with square pyramidal geometry containing apical chloride ligand. The chloro-bridged structure of **1** was confirmed by elemental analysis.[8] The bond lengths and angles around copper(II)

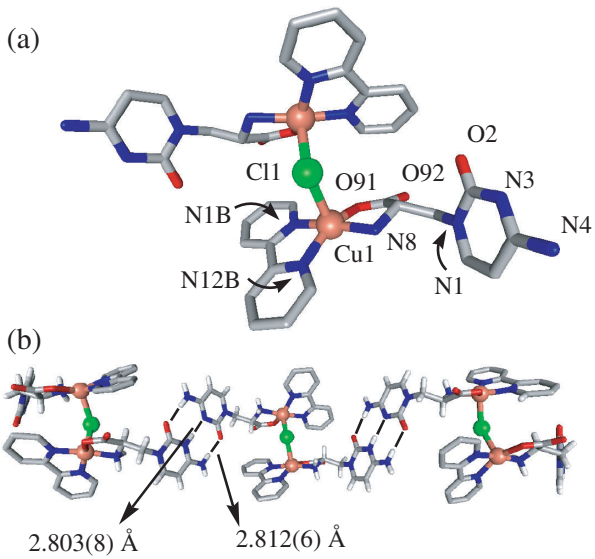

Figure 1. (a) Crystal structure of **1**. Selected bond lengths (Å) and angles (deg) are as follows: Cu1···N1B = 2.020(4), Cu1···N12B = 1.988(3), Cu1···N8 = 2.000(3), Cu1···O91 = 1.949(3), Cu1···Cl1 = 2.5090(8). <N1B···Cu1···O91 = 151.7(2), <N1B···Cu1···N8 = 98.7(1), <N8···Cu1···Cl1 = 95.5(1). (b) Intermolecular triple hydrogen-bonding interaction of **1**.

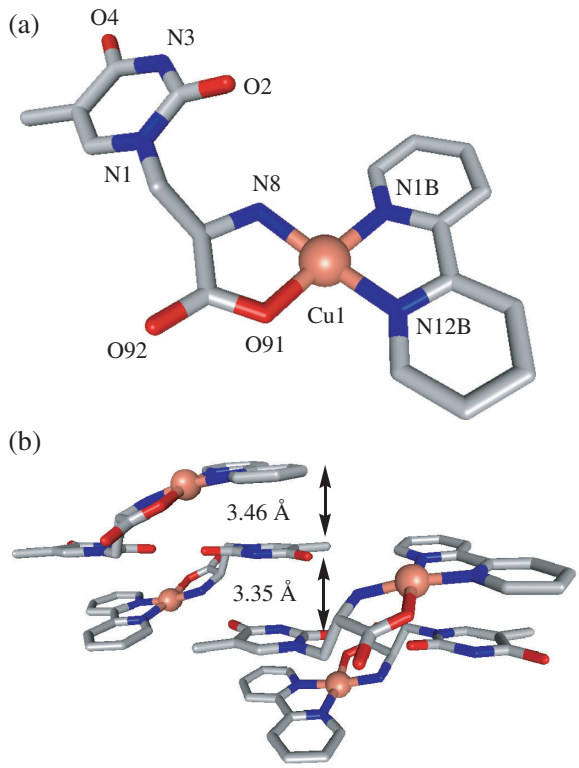

Figure 2. (a) Crystal structure of **2**. Selected bond lengths (Å) and angles (deg) are as follows: Cu1···N1B = 2.000(2), Cu1···N12B = 1.987(4), Cu1···N8 = 1.982(3), Cu1···O91 = 1.922(2). <N1B···Cu1···O91 = 169.3(1), <N1B···Cu1···N8 = 99.5(1). (b) Intermolecular π–π stacking interaction of **2**.

ion were very similar to those in the ternary complexes previously reported.[5,9] Notably, the interatomic distances between cytosine rings (2.812(6) Å in O(2)···N(4′) and 2.803(8) Å in N(3)–N(3′), respectively) in the crystal of **1** were within the hydrogen bonding one, clearly indicating formation of intermolecular triple hydrogen bond (Figure 1b). It is well known that cytosine (C) is easily protonated at N3-position to give CH^+:C base pair under weakly acidic condition, although formation of triple hydrogen bond system seems to be hard in the case of nonprotonated cytosine–cytosine base pair.[10] In the complex **1**, the hemiprotonated CH^+:C pair might be generated in moderate acidic condition and the bridged chloride ligand is an evidence for the hemiprotonation in the cytosine pair. The interatomic distances in **1** above mentioned were very similar to those in the crystal of cytosine hemitrichloroacetate, 2.805(8) Å in O(2)···N(4′), 2.755(8) and 2.858(8) Å in N(3)···N(3′), and 2.866(9) Å in O(4)···N(2′), respectively,[11] and in the crystal of 2′-deoxycytidene hemiperchlorate, 2.801(6) Å in O(2)···N(4′) and 2.800(6) Å in N(3)···N(3′).[12] When the complexation was carried out at more acidic condition (pH < 2), triple hydrogen-bonding system, such as CH^+:C pair, was not formed because the electrostatic repulsion might operate between the both protonated N-3 nitrogen atoms. For the formation of triple hydrogen-bonding system in cytosine–cytosine pair, hemiprotonated CH^+:C formula at N3-position is important. We consider that the complex **1**, involving the CH^+:C pair, is a simple model for binding mode of the *i*-motif, which is a cytosine quadruplex of telomer of DNA involving CH^+:C pair.[13] The crystal structure of the thymine complex, **2** (Figure 2a),[14] with square planar geometry did not show such an intermolecular hydrogen-bonding interaction, which is interpreted by the proton receptivity of cytosine at N3-position ($pKa = 4.4$).[15]

In the crystals of thymine complex **2**, notably, two kinds of intermolecular stacking interactions were demonstrated as shown in Figure 2b. The thymine ring of ACET was located approximately parallel to the neighboring bpy ring with the mean separation of 3.46 Å and to the neighboring thymine ring with that of 3.35 Å, respectively. On the other hand, such an intermolecular interaction was not observed in the crystal of uracil-amino acid complex, $[Cu(aceu)(phen)]^+$ (ACEU, 1-(2-amino-2-carboxyethyl)uracil), even though the larger phenanthroline ligand was used instead of bpy.[5] The electron-donative methyl group attached at 5-position of pyrimidine ring in ACET can promote the π–π stacking interaction,[4] but uracil without such group is unable to stack each other. Although the stacking interaction caused by pyrimidine nucleobase is known to be weaker than that of purine one,[16] we can find that thymine show the interaction.

In summary, characteristics of pyrimidine nucleobases are demonstrated on the crystals of the ternary copper complexes consisting of bpy and pyrimidine-amino acid. Formation of triple hydrogen-bonding interaction upon $[\{[Cu(acec)(bpy)]\}_2 \cdot HCl]^{2+}$ (**1**) mimicked *i*-motif of DNA. The intermolecular hemiprotonated CH^+:C pair is important for the nucleobase pairing. Intermolecular π–π stacking interactions are also explained by the electron-donating effect in thymine ring among pyrimidine nucleobases.

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References and Notes

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7 Crystal data for **1**: $C_{17}H_{19.5}Cl_{1.5}CuN_6O_8$, $M_r = 552.60$, monoclinic, space group $C2/c$ (#15), $a = 34.937(1)$, $b = 5.9443(3)$, $c = 26.045(1)$ Å, $\beta = 126.002(3)^\circ$, $V = 4375.8(4)$ Å^3, $Z = 8$, $\mu(\text{Mo K}\alpha) = 1.240\,\text{cm}^{-1}$, N. of reflections obsd. 4448, N. of reflections used 3431 ($I > 2\sigma(I)$), $R = 0.0464$, $R_w = 0.1431$. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.
8 Elemental analysis for **1**: Calcd for $[\{[Cu(acec)(bpy)]\}_2 \cdot HCl]2ClO_4 \cdot 2H_2O$: $C_{34}H_{35}Cl_3Cu_2N_{12}O_{16}$; C, 37,08; H, 3.20; N, 15.26. Found, C, 36.87; H, 3.28; N, 15.23%.
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14 Crystal data for **2**: $C_{18}H_{20}ClCuN_5O_9$, $M_r = 549.38$, triclinic, space group $P\bar{1}$ (#2), $a = 9.3616(6)$, $b = 10.3484(7)$, $c = 13.235(1)$ Å, $\alpha = 97.592(6)$, $\beta = 109.299(6)$, $\gamma = 111.046(5)^\circ$, $V = 1082.7(2)$ Å^3, $Z = 2$, $\mu(\text{Mo K}\alpha) = 1.195\,\text{cm}^{-1}$, N. of reflections obsd. 4388, N. of reflections used 3496 ($I > 2\sigma(I)$), $R = 0.0421$, $R_w = 0.1263$. Elemental analysis for **2**: Calcd for $[Cu(acet)(bpy)]ClO_4 \cdot 3.75H_2O$: $C_{18}H_{25.5}ClCuN_5O_{11.75}$; C, 36.10; H, 4.28; N, 11.69. Found, C, 35.93; H, 3.94; N, 11.46%.
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