Nucleobase Stacking Evidenced on Ternary Metal (Palladium(II), Copper(II)) Complexes with Nucleobase Amino Acids and Aromatic Diimines

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The three-dimensional structure of DNA is controlled by the noncovalent interactions between the nucleobases: the vertical $\pi-\pi$ stacking interactions and the planar hydrogen bonding interactions.[1−7] An important issue in molecular biophysics arises in attempts to provide a reliable description for such base−base interactions. The relative importance of these two types of interactions and conformational variability of DNA is still not known. The hydrogen bonding interactions are believed to be governed mainly by the electrostatic term. The stacking interactions are thought to be controlled by the dispersion and electrostatic terms, but also details are open to further studies. For the case of the $\pi-\pi$ stacking interaction, the calorimetric and spectroscopic investigations were previously carried out in solution by use of the Pt(II) ternary complexes with nucleotides, which revealed that purine bases attractively associate with the nucleotides stronger than the pyrimidine bases.[8,9] Recently, some theoretical studies have also been performed for nature of the base-stacking interactions. Hunter et al. suggested the importance of the electrostatic interactions between partial atomic charges for the G···C base pairs.[6,10] On the other hand, Sponer et al.[11] deduced that the stability of the stacked base pairs is dominated by the dispersion energy originating in the electron correlation and concluded that the most stable stacked pair is the guanyl dimer, and the least stable one is the uracil dimer. These contradictory situations require direct and structural elucidation of the nature of the $\pi-\pi$ stacking interactions in which nucleobases play an important role.

To obtain direct evidence for the specificity of the $\pi-\pi$ interactions in nucleobases of DNA, we prepared two nonnatural amino acids with nucleobases different in ring structure as their residues, 1-(2-amino-2-carboxyethyl)adenine (acea) and 1-(2-amino-2-carboxyethyl)uracil (aceu),[12] and we investigated the interactive nature of the nucleobases through the aromatic interaction in the ternary metal (M = Cu(II), Pd(II)) complexes with nucleobase amino acid, acea or aceu, and aromatic diimine, 2,2′-bipyridine (bpy) or 1,10-phenanthroline (phen), by use of the X-ray diffraction and ^{1}H NMR methods. The conclusion is that the purine ring with a fused ring structure affords the $\pi-\pi$ stacking interaction both in solution and in solid states but that the pyrimidine ring with a monocyclic ring structure has no interactions in solid state or in solution.

Aqueous solutions of $CuCl_2{\cdot}6H_2O$ or $Cu(ClO_4)_2{\cdot}6H_2O$ (0.55 mmol), nucleobase amino acids (0.55 mmol), and aromatic diimines (0.55 mmol) were mixed and neutralized (pH 7) to make the final volume of 150 mL. Two green crystals, Cu-acea-bpy (**1**)[13] and Cu-aceu-phen (**2**) systems,[14] suitable for X-ray diffraction studies separated from the aqueous solution after several days. The molecular structures of the complexes **1** and **2** are shown in Figures 1 and 2, respectively. The central copper ions in both complexes, five-coordinated, have an approximately square-pyramidal geometry, where the two nitrogen atoms of diimine and one carboxylate oxygen and one amino nitrogen of amino acid constitute the square planar base. The apical positions are located by chloride and water molecules for the complexes **1** and **2**, respectively. The most important is the fact that the complex **1** has an intramolecular aromatic stacking, whereas the complex **2** does not have any aromatic stacking interaction. The former revealed three outstanding structural features. First, the purine ring of acea is located on and approximately parallel to the bpy ring with the mean separation of 3.28 Å (Figure 1), which are comparable with those for ternary copper complexes reported hitherto, $[Cu(\text{L-tryptophan})(bpy)]^+$ (3.67 Å),[15] $[Cu(\text{L-tryptophan})(phen)]^+$ (3.51 Å),[16] $[Cu(\text{L-tyrosine})(bpy)]^+$ (3.35 Å),[17] $[Cu(\text{L-tyrosine})(phen)]^+$ (3.27, 3.38 Å),[18] and $[Cu(\text{L-aminophenylalanine})(bpy)]^+$ (3.46 Å).[18] The aromatic stacking was also found out in an intermolecular fashion with the separation of 3.44 Å between adenines in the crystal. Such nucleobase stacking comparable with these stackings appeared in DNA B-form[19] and in some Pt(II)

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(13) Elem. anal. of complex **1**, calcd for $Cu(C_{18}H_{17}ClN_8O_2){\cdot}2.8H_2O$: C, 41.04; H, 4.32; N, 21.27. Found: C, 41.01; H, 3.94; N, 21.29. Crystal data for **1**; $Cu(C_{18}H_{17}ClN_8O_2){\cdot}3H_2O$, M = 530.43, monoclinic, $C2/c$, a = 26.402(1) Å, b = 9.1932(5) Å, c = 21.526(1) Å, β = 120.199(5)°, V = 4515.8(5) Å^3, Z = 8, D_c = 1.553 g cm^{-3}, μ(Mo Kα) = 11.28 cm^{-1}, F(000) = 2184.0. A total of 3490 unique reflections were collected on a Rigaku AFC-5R four-circle diffractometer, of which 2863 reflections with $I > 3\sigma(I_o)$ were used in the structure analysis and refinement using the teXsan program system. Absorption correction was applied by ψ scan method. Final R and R_w factors were 0.064 and 0.090, respectively.
(14) Elem. anal. of complex **2**, calcd for $CuC_{19}H_{18}ClN_5O_9{\cdot}0.5H_2O$: C, 40.15; H, 3.37; N, 12.32. Found: C, 39.97; H, 2.98; N, 12.03. Crystal data for **2**: $CuC_{19}H_{18}ClN_5O_9{\cdot}2H_2O$, M = 595.41, monoclinic, $P2_1/n$, a = 12.862(2) Å, b = 14.352(2) Å, c = 13.004(2) Å, β = 100.54(1)°, V = 2360.1(5) Å^3, Z = 4, D_c = 1.676 g cm^{-3}, μ(Mo Kα) = 11.09 cm^{-1}, F(000) = 1220.0. A total of 9336 unique reflections were collected, of which 2663 reflections with $I > 3\sigma(I_o)$ were used in the structure analysis, in which the teXsan program system was used for the structure analysis and refinement. Absorption correction was applied by ψ scan method. Final R and R_w values were 0.064 and 0.049, respectively.
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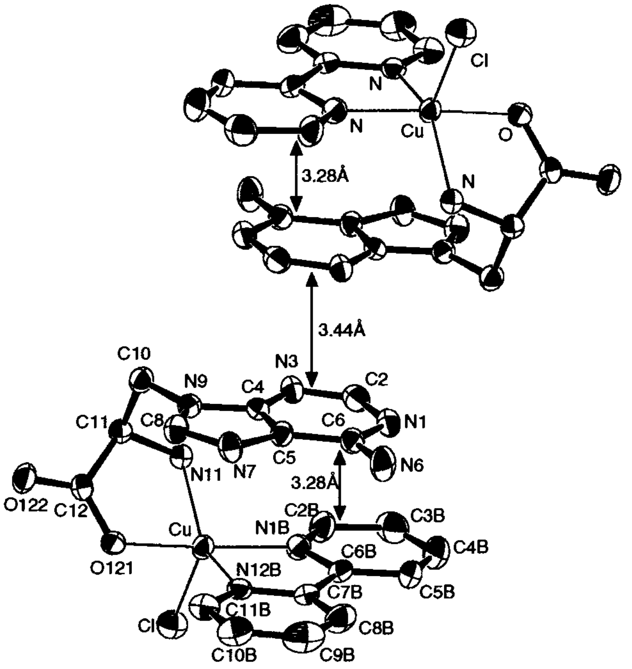

Figure 1. ORTEP drawing of [Cu(bpy)(acea)Cl] (**1**) showing intra- and intermolecular interactions.

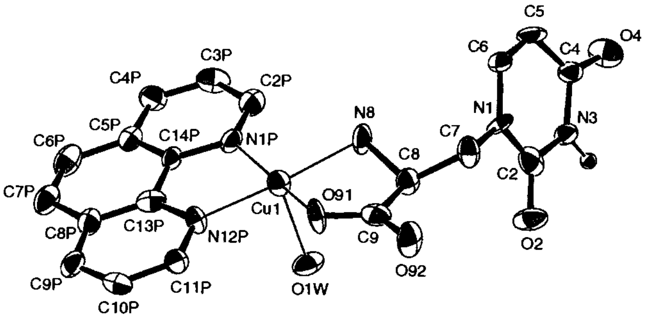

Figure 2. ORTEP drawing of $[Cu(phen)(aceu)(H_2O)]^+$ cation (**2**).

complexes with aromatic diimines and adenosine 5′-monophosphate.[20–22] Second, the basal plane of **1** is tetrahedrally distorted with the bending of the N(12B)–Cu–N(11) angle (140.0(3)°), although that of **2** is almost planar with the N(12P)–Cu–N(8A) angle of 172.5(3)°. This may be attributable to the attractive interaction between the aromatic rings. This tetrahedrally distorted structure of **1** is also supported by the characteristic ESR spectra ($g_\perp = 2.06$, $g_{||} = 2.24$, and $A_{||} = 186.1$ G). Thirdly, the Cu–N bond lengths trans to the carboxylato oxygen are significantly different (the Cu(1)–N(1B) bond in **1**, 1.970(8) Å, is significantly shorter than the corresponding Cu(1)–N(1P) bond in **2**, 2.015(6) Å), but other Cu–N bond lengths are less significantly different for the complexes **1** and **2**. The former evidence may be explained in such a way that the purine ring attractively withdrew the bpy ring through the stacking interaction.

To assess the solution structure of these ternary systems, we prepared the corresponding Pd(II) ternary complexes by use of K_2PdCl_4 in place of $Cu(ClO_4)_2\cdot6H_2O$, [Pd(acea)(bpy)]Cl, and [Pd(aceu)(bpy)]Cl.[23] ^{1}H NMR spectra of the [Pd(acea)(bpy)]Cl (20 mmol/L) in D_2O indicated very interesting spectral behaviors in the two proton peaks of the adenine moiety, 2-H and 8-H; the former detected at 7.61 ppm exhibited a significant upper-field shift in comparison with that of metal free acea (8.00 ppm), although the latter at 8.09 ppm did not show such a shift (8-H of metal-free acea, 8.10 ppm). When we consider the aromatic rings to form the $\pi-\pi$ stacking such as that shown in Figure 1, this upper-field shift is reasonably interpreted as the shielding effect due to these aromatic rings. Their chemical shifts were also affected by solvents: In less polar solution (3:1 dioxane/D_2O), the 2-H proton peak exhibited the reduction of upfield shift to 7.78 ppm, indicating that the $\pi-\pi$ stacking interaction is weakened by hydrophobic solvent. On the other hand, ^{1}H NMR spectra of [Pd(aceu)(bpy)]Cl in D_2O did not show such a shift; 5-H and 6-H peaks of aceu moiety observed at 5.76 and 7.60 ppm were comparable to those of metal-free aceu. The above results indicate that the purine ring with a larger ring size interacts intramolecularly with bpy, but the pyrimidine ring with a smaller ring size has no attractive interaction with bpy.

In summary, it was shown that the purine ring gives rise to a strong $\pi-\pi$ stacking both in solution and in solid states, whereas the pyrimidine ring does not show this sort of attractive interaction. This evidence agrees well with the theoretical ones presented by Sponer et al.[11] Furthermore, the nucleobase specificity of intercalation into DNA by aromatic compounds such as ethidium, actinomycin, 9-amino acridine, and bithiazole in bleomycin, which are specifically incorporated as intercalators into the nucleobase sequence of pyrimidine-(3′,5′)-purine,[24] may also correlate with the above result that purine ring tends to induce the intercalation with aromatic rings. This is a unique, first case that clearly and directly visualizes the discrepancy of stacking interaction in purine and pyrimidine rings from both solution and solid states.

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Supporting Information Available: Tables of atomic coordinates, bond lengths and angles, and thermal parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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