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Interligand Interactions Controlling the μ-N7,N9-Metal Bonding of Adenine (AdeH) to the *N*-Benzyliminodiacetato(2–) Copper(II) Chelate and Promoting the N9 versus N3 Tautomeric Proton Transfer: Molecular and Crystal Structure of $[Cu_2(NBzIDA)_2(H_2O)_2(\mu\text{-N7,N9-Ade(N3)H})]\cdot 3H_2O$

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The reaction in water of the *N*-benzyliminodiacetate–copper(II) chelate ([Cu(NBzIDA)]) and the adenine:thymine base pair complex (AdeH:ThyH) with a Cu/NBzIDA/AdeH/ThyH molar ratio of 2:2:1:1 yields $[Cu_2(NBzIDA)_2(H_2O)_2(\mu\text{-N7,N9-Ade(N3)H})]\cdot 3H_2O$ and free ThyH. The compound has been studied by thermal, spectral, and X-ray diffraction methods. In the asymmetric dinuclear complex units both Cu(II) atoms exhibit a square pyramidal coordination, where the four closest donors are supplied by NBzIDA in a *mer*-tridentate conformation and the N7 or N9 donors of AdeH, which is protonated at N3. The μ-N7,N9 bridge represents a new coordination mode for nonsubstituted AdeH, except for some adeninate(1–)–[methylmercury(II)] derivatives studied earlier. The dinuclear complex is stabilized by the Cu–N7 and Cu–N9 bonds and N6–H(exocyclic)···O(carboxyl) and N3–H(heterocyclic)···O(carboxyl) interligand interactions, respectively. The structure of the new compound differs from that of the mononuclear compound $[Cu(NBzIDA)(Ade(N9)H)(H_2O)]\cdot H_2O$, in which the unusual Cu–N3-(AdeH) bond is stabilized by a N9–H···O(carboxyl) interligand interaction and where alternating benzyl-AdeH intermolecular π,π-stacking interactions produce infinite stacked chains. The possibility for ThyH to be involved in the molecular recognition between [Cu-(NBzIDA)] and the AdeH:ThyH base pair is proposed.

Metal−ion interactions with nucleic acids and their constituents are a matter of an extensive research[1]. Recently, attention has been paid to explore possibilities for developing metal chelates able to display specific or selective molecular recognition patterns with nucleobases.[2−6] Advances reveal that such a recognition process can be "outer-spherical"[6] or can be due to the formation of a metal−nucleobase coordination bond, which may be favored by π,π-stacking[4,5] and/or hydrogen-bonding interligand interactions.[2−5] Such interactions are operative in the control of various DNA conformations.

Studies of native or modified DNAs are now a prominent research field, and many of their viable possibilities arise from the knowledge of the behavior of fragments of these biomolecules. A long time ago, studies of base-pair complexes were carried out, and some of them concerned adenine-like:thymine-like examples.[7−11] Very recently we have reported three new modes of adenine−copper(II) coordination and attempted to explain these findings on the basis of interligand interactions in mixed-ligand complexes of N-substituted iminodiacetato−Cu(II) chelates (with *N*-alkyl, *N*-benzyl, or *N*-phenethyl substituents for A, B, and C IDA-like chelating ligands, respectively; phenethyl = $C_6H_5CH_2CH_2-$).[4,5]

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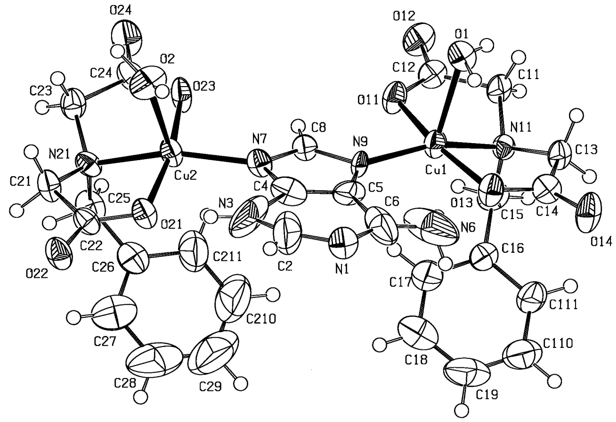

Figure 1. Dinuclear complex molecule of the compound $[Cu_2(NBzIDA)_2(H_2O)_2(\mu\text{-}N7,N9\text{-}Ade(N3)H)]\cdot 3H_2O$. Bond lengths (Å) and *trans*-angles (deg): Cu1−N11 2.024(5), Cu1−O13 1.954(5), Cu1−O11 1.975(5), Cu1−N9 2.005(6), Cu1−O1 2.250(5), O11−Cu1−O13 166.5(2), N9−Cu1−N11 162.4(2); Cu2−N21 1.958(5), Cu2−O23 1.937(5), Cu2−O21 1.958(5), Cu2−N7 1.988(5), O21−Cu2−O23 1.678(2), N7−Cu2−N21 159.8(2). Tetragonality (T) and distortion toward bpt coordination (τ, %) parameters: $T_1 = 0.884$, $T_2 = 0.881$, $\tau_1 = 6.83$, $\tau_2 = 13.33$.

Complexes of the type $[Cu(A)(AdeH)(H_2O)]\cdot H_2O$ have a Cu−N7(AdeH) bond reinforced by an interligand N6−H(exocyclic)···O(A, carboxyl) hydrogen bond, and they display intermolecular π,π-stacking AdeH−AdeH interactions.[4] On the other hand, complexes of the type $[Cu(B)(AdeH)(H_2O)]\cdot H_2O$ exhibit the unusual Cu−N3(AdeH) coordination bond aided by an interligand N9−H(heterocyclic)···O(B, carboxyl) hydrogen bond, whereas the flexible *N*-benzyl arm of ligand B is involved in the alternating AdeH−benzyl π,π-stacking interactions which generate[4,5] infinite complex chains. Surprisingly, the compound $[Cu_4(C)_4(\mu\text{-}AdeH)_2(H_2O)_4]\cdot 2H_2O$ (C = *N*-phenethyliminodiacetato(2−)) shows an unexpected μ-N3,N7-AdeH bridge, but no π,π-stacking interaction.[4]

On the basis of the above findings we explored a broad series of ternary and quaternary metal + chelating ligand + nucleobase systems, using experimental methods similar to those described elsewhere.[4] In a typical experiment, we investigated the reaction of an aqueous solution of the Cu−NBzIDA chelate (100 mL, 10 mM) with an aqueous solution of the "base pair complex" AdeH:ThyH (50 mL, 10 mM) where ThyH is thymine. From this reaction mixture having a 2:2:1:1 Cu(II):NBzIDA:AdeH:ThyH molar ratio, by slow evaporation in a crystallization device (covered with a plastic film) we obtained abundant dark blue parallelepipedal crystals of a compound easily differentiable from $[Cu(NBzIDA)(AdeH)(H_2O)]\cdot H_2O$[4] by the crystal shape, elemental analysis, thermal stability, and FT-IR spectroscopy. However, this experimental information seems consistent with several formulas. We have succeeded in obtaining the crystal structure of the new compound.[12] A plot of the complex molecule with the atom numbering adopted is shown in Figure 1. The numbering system here used for AdeH ligand is that conventionally accepted for chemical and biological purposes. The molecule is an asymmetrical dinuclear copper(II) complex having the unexpected μ-N7,-N9-adenine bridging mode. The copper(II) atoms exhibit a square base pyramidal coordination (type 4 + 1) built up by a NBzIDA ligand in a *mer*-tridentate conformation, a *N*-imidazole-like AdeH donor, and an apical aqua ligand. The difference in the distortion between both copper(II) coordinations does not seem to be particularly relevant (see caption below Figure 1), but the mean AdeH plane defines dihedral angles of 8.4° and 21.8° with the mean basal coordination planes of Cu1 and Cu2, respectively. These Cu(II) atoms deviate by 0.17 and 0.20 Å from the corresponding basal planes, which have deviations of 0.14(1) and 0.15(2) Å of the *trans*-N and *trans*-O donor pairs in the opposite sense (the O atoms toward the apical aqua ligands). To our knowledge this μ-N7,N9-bridging coordination mode is unique, except for some methylmercury(II) metalated adeninato(1−) (Ade^-) derivatives.[13−15] A summary of metal coordination modes for unsubstituted AdeH is given in ref 2. Table 1 provides an updated compilation of Cu(II)−AdeH complexes with known structure. The asymmetry of the new dinuclear Cu(II) complex is consistent with the nonequivalence of the donor atoms N7 and N9. Interestingly, the stability due to the Cu2−N7 and Cu1−N9 bonds of the molecule seems to be reinforced by the interligand hydrogen bonds N6−H6A(exocyclic)···O13(carbonyl) [2.67(1) Å, 148°] and N3−H3(heterocyclic)···O21(carbonyl) [2.65(1) Å, 122°], respectively. This latter H-bonding interaction is a surprising consequence of the bridging μ-N7,N9 coordination mode because the basicity order in AdeH is N9 > N1 > N7 > N3 ≫ N6(exocyclic). Indeed, in the known complex where neutral AdeH only forms a Cu−N9(AdeH) bond, the proton is transferred to N7, but all known structures with the adeninium(1+) cation ($AdeH_2^+$) have H atoms at N9 and N1, showing that N1 is the "normal" protonation site for AdeH.[6]

The surprising tautomeric proton transfer from N9 to N3 in the new compound seems clearly related with the molecular recognition between the Cu2−benzyliminodiacetate moiety and the N9 donor of the bridging AdeH ligand, because such a proton transfer favors the formation of the N3−H···O hydrogen bond. In fact, the referred interligand H-bonds are the two shortest among all interactions of this kind in the crystal packing of the studied compound. Moreover, the analysis of shortest ring−ring interactions, carried out with the program PLATON,[25] shows

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(12) $C_{27}H_{37}Cu_2N_7O_{13}$, fw 794.72, 293(2) K, $\lambda = 0.71073$, triclinic system, space group $P1$, $a = 10.492(2)$ Å, $b = 11.873(3)$ Å, $c = 14.600(3)$ Å, $\alpha = 83.17(1)°$, $\beta = 80°, 19(1)$, $\gamma = 89.23(1°)$, $Z = 2$, $\mu = 1.326$ mm^{-1}, $R = 0.069$, $R_w = 0.142$.

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Table 1. Updated Structural Information on Copper(II) Complexes Having Anionic, Neutral, or Cationic Adenine Forms as Ligand

complex formula[a]	Cu-coord type	adenine form	N-protonation sites	N-binding sites	ref
$[Cu(dien)(Ade)_2]\cdot H_2O$	4 + 1	Ade^-	none	N9	16
$[Cu(tren)(Ade)]Cl\cdot 2H_2O$	3 + 2	Ade^-	none	N9	17
$[Cu(tren)(Ade)]ClO_4$	3 + 2	Ade^-	none	N9	3
$[Cu(\mu\text{-}Ade)_4(H_2O)_2]\cdot 6H_2O$	4 + 2	Ade^-	none	μ-N3,N9	18
$[Cu(glygly)(AdeH)(H_2O)]$	4 + 1	AdeH	N7	N9	19
$[Cu_2(AdeH)_4(H_2O)_2](ClO_4)_2\cdot 2H_2O$	4 + 1	AdeH	N7	μ-N3,N9	20
$[Cu_2(AdeH)_4Cl_2]Cl_2\cdot 6H_2O$	4 + 1	AdeH	N7	μ-N3,N9	21
$[Cu(A)(AdeH)_2(H_2O)]\cdot H_2O$	4 + 1	AdeH	N9	N7	4
$[Cu(B)(AdeH)_2(H_2O)]\cdot H_2O$	4 + 1	AdeH	N9	N7	4,5
$[Cu_4(C)_4(\mu\text{-}AdeH)_2(H_2O)_4]\cdot 2H_2O$	4 + 1 + 1	AdeH	N9	μ-N3,N7	4
$[Cu_2(NBzIDA)_2(H_2O)_2(\mu\text{-}AdeH)]\cdot 3H_2O$	4 + 1	AdeH	N3	μ-N7,N9	this work
$[Cu(AdeH_2)Br_2]Br_2$	Td	$AdeH_2^+$	N1,N7	N9	22
$[Cu(AdeH_2)Cl_2]Cl_2$	Td	$AdeH_2^+$	N1,N7	N9	23
$[Cu_3(AdeH_2)Cl_8]\cdot 4H_2O$	4 + 1 (end) 4 + 2 (central)	$AdeH_2^+$	N1,N7	μ-N3,N9	24

[a] A, B, or C = *N*-alkyl, *N*-benzyl, or *N*-phenethyliminodiacetato(2−) ligand.

that no π,π-stacking interaction is operative in the new mixed-ligand Cu(II) complex as it occurs in $[Cu_4(C)_4(AdeH)_2(H_2O)_4]\cdot 2H_2O$.[4]

The studied compound $[Cu_2(NBzIDA)_2(H_2O)_2(\mu\text{-}N7,N9\text{-}Ade(N3)H)]\cdot 3H_2O$, where Ade(N3)H is neutral adenine with its dissociable H atom at N3 instead of at N7 or N9, initiates its thermal decomposition in an air-dry flow with an "actual" TG-formula of the type $[Cu_2(NBzIDA)_2(H_2O)_2(\mu\text{-}N7,N9\text{-}AdeN3{-}H)]\cdot 1.03H_2O$, in five steps (55−390 °C). Steps I (55−125 °C) and II (125−180 °C) correspond approximately to the loss of 2.03 and 1 H_2O, showing a partial discrimination of noncoordinated and apical-coordinated water. Step III (180−225 °C) is mainly due to NBzIDA pyrolysis with production of abundant CO_2 and water plus CO (and probably N_2O). Steps IV and V correspond to AdeH pyrolysis (mp > 360 °C) and produce CO_2, H_2O, CO, N_2O, and NO.

The FT-IR spectrum shows characteristic bands of AdeH, NBzIDA, and H_2O. The electronic spectrum has an asymmetrical band with ν_{max} 14 575 cm^{-1} and a baricenter of intensity near 13 400 cm^{-1}, due to the chromophore $CuN_2O_2 + O$. The ESR spectrum of a polycrystalline sample at room temperature is quasi-isotropic ($g = 2.10$) and consistent with a $d_{x^2-y^2}$ ground state in a crystal with a misaligned local molecular axis. At room temperature, $\mu_{Cu} = 1.73\ \mu_B$.

Finally, we should add that the specific role of thymine in the solution mixture, which affords the title compound, is unknown at present, but it probably displays an active role in the molecular recognition between Cu−NBzIDA chelate and AdeH. An aqueous solution with a molar ratio Cu(II)/NBzIDA/AdeH = 2:2:1 produces [Cu(NBzIDA)] (light blue) and $[Cu(NBzIDA)(AdeH)(H_2O)]\cdot H_2O$[4] (dark blue). This latter product is now regularly prepared by some of our students in the laboratory sessions of the course "Inorganic Aspects of Biological Processes". We have observed that thymine increases the solubility of the mother liquor that produces crystals of the title compound even though this nucleobase itself is unable to produce a mixed-ligand complex of the type $Cu(NBzIDA)(ThyH)\cdot nH_2O$ (and similar derivatives). This latter observation is in accordance with results of Aoki et al.[2,3] and ourselves,[4,5] suggesting that the molecular recognition of Cu(II) chelates with nucleobases is favored if the metal−nucleobase coordination bond is reinforced by an interligand chelating-base H-bonding interaction. These findings mean that the Cu−NBzIDA chelate reacts with the AdeH:ThyH base pair complex in such a way that breaks it. ThyH is released by also modifying the molecular recognition process with AdeH which is definitively used in the bridging mode μ-N7,N9-Ade(N3)H. As an extrapolation, we could consider that "complementary base pair" in double (or higher) stranded DNAs should influence platination reactions including mechanisms of Pt-based anticancer drugs and other DNA−metal binding processes.

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Supporting Information Available: Synthesis and properties of $[Cu_2(NBzIDA)_2(H_2O)_2(\mu\text{-}N7,N9\text{-}Ade(N3)H)]\cdot 3H_2O$ and FT-IR, electronic (reflectance), and electron spin resonance spectra. Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 190082 for the title compound. Structural files and information on the thermal stability and spectral properties of the studied compound can be supplied by the authors or from the deposited data.

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