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Review

Interligand interactions involved in the molecular recognition between copper(II) complexes and adenine or related purines

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Contents

Abstract

The available crystal structure information in the CSD database on ternary species prepared by the reaction of diverse copper(II) complexes (CuL) and purine, adenine and guanine or related purine derivatives is considered in order to deepen the intra-molecular interligand interactions affecting the molecular recognition patterns of the ‘metal complex + purine nucleobase’ and closely related systems. The degree of protonation and the possibilities of different tautomeric forms in the purine-like moieties are taken into account. The main conclusion is a general trend to form a Cu─N(purine-like) coordination bond which can be reinforced by an intra-molecular interligand H-bonding interaction. N─H(purines)· · ·A (O or Cl acceptor) or N─H(amino ligand L)· · ·O6(oxo-purines) are commonly observed. In addition, selected examples revealed that the presence of a variety of non-coordinating groups in L or in the purine-like nucleobases can significantly influence the structurally observed molecular recognition pattern. Moreover, examples are known where binuclear cores of the types $Cu^{II}_2(\mu_2\text{-}N3,N9\text{-adeninate})_4(\text{aqua})_2$ or $Cu^{I}_2(\mu_2\text{-}N3,N9\text{-adeninate})_2(\text{aqua})_2$ recognise CuL chelates by means of the expectable pattern (Cu─N7 coordination bond + N6─H· · ·O(L) interaction).

Keywords: Interligand interactions; Molecular recognition; Crystal structures; Copper; Mixed-ligand complexes; Purine; Adenine; Guanine; Nucleobase

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Abbreviations: acv, acyclovir; ade^-, adeninate(1−) ion; dien, bis(2-aminoethyl)amine; 9Egua, 9-ethylguanine; EIDA, *N*-ethyliminodiacetate(2−) ion; en, ethylenediamine; gly, glycinate(1−); $glygly^{2-}$, glycylglycinate(2−) ion; gua^{2-}, guaninate(2−) ion; guo, guanosine; Hade, adenine; H_2ade^+, adeninium(1+) ion; H_3ade^{2+}, adeninium(2+) ion; H_4EDTA, ethylenediaminetetraacetic acid; Hgua, guanine; H_2gua^+, guaninium(1+) ion; H_3gua^{2+}, guaninium(2+) ion; Hpur, purine; H_2pur^+, purinium(1+) ion; H_3pur^{2+}, purinium(2+) ion; IDA, iminodiacetate(2−) ion; 9Made, 9-methyladenine; 1Mcyt, 1-methylcytosine; 9Mgua, 9-methylguanine; MIDA, *N*-methyliminodiacetate(2−) ion; NBzIDA, *N*-benzyliminodiacetate(2−) ion; *N*-sal,*N*′-M-en, *N*-salicylidene,*N*′-methyl- ethylenediamine(1−) ion; oda, oxydiacetate(2−) ion; ox, oxalate(2−) ion; pheida, *N*-phenethyliminodiacetate(2−) ion; tren, tris(2-aminoethyl)amine.

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1. Introduction

The field of nucleic acid–metal ion interactions is very broad with increasing multidisciplinary contributions, going beyond the points of view of traditional areas of science such as biology, biochemistry, genetics, medicinal chemistry and others. The diversity of research contributions has been affected by a large variety of studies concerning the chemical and biological aspects of the interactions between metal ions and nucleic acids or their constituents. Over the past decades, the consolidation of the bioinorganic, bio-organometallic and bioorganic chemistries as multidisciplinary fields has been carried out parallel to the increasing interest in developing potent synthetic nucleobases, nucleosides and nucleotides with suitable antiviral and/or anticancer properties. Undoubtedly, after less relevant attempts, the well-recognised success of Barnett Rosenberg with the discovery of Cisplatin as the first potent inorganic anticancer drug opened new and interesting axes of research which pointed to various attractive frontiers, thus initiating the so-called 'Platinum era'. This and other broad trends in the metallo-nucleic acid field invite substantial doses of rational understanding on the basis of the overall discussion of the results reported by most systematic studies.

Regarding metal ion binding patterns to nucleobases, an excellent review by Lippert [1], appeared a few years ago in this journal, summarising the multiplicity of behaviours known for most relevant purines (adenine, guanine and other 6-oxopurines) and pyrimidines. Lippert's paper presents a series of general rules with which to survey the different metal–nucleobase coordination modes with different metal ions. The aim of the present review is to look at the structures of ternary and related copper(II) complexes with a purine nucleobase and other(s) ligand(s) as a valuable source of information on molecular recognition patterns controlling the formation of these mixed-ligand complexes. We then focus our attention not only on metal–nucleobase binding modes but also on the intra-molecular interligand which cooperates with the coordination bond in the stabilization of the resulting mixed-ligand complexes.

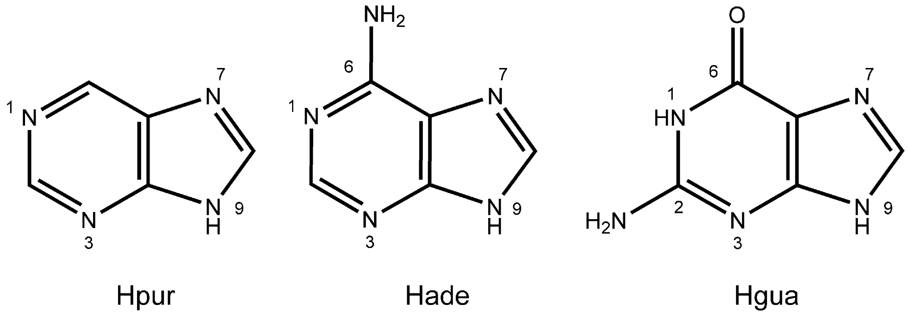
To better understand the roles of the 6-amino or 6-oxo groups in adenine or guanine and related nucleobases, respectively, we have also included the limited information available concerning purine copper(II) complexes. The coordination modes of purine, not summarised by Lippert, are also reported. Most structural data can be obtained from the Cambridge Structural Database (CSD). Thus, in addition to the reference literature, the CSD code (of six capital letters) for each compound is also indicated. Relevant features are the protonation degree of the nucleobases as well as the possibilities of proton tautomers. Thus, for clarity, the N atoms supporting the protons are identified when necessary in the abbreviation of the nucleobase or derivative. For example, H(*N*3)ade corresponds to the adenine tautomer which has the dissociable proton on the less basic heterocyclic N3 atom, instead of on the most basic N9 one. The numbering adopted for the hetero-atoms agrees with the internationally accepted system, as follows for Hpur, Hade and Hgua (Scheme 1). All the figures have been prepared using the atomic coordinates deposited in the CSD.

2. Purine complexes

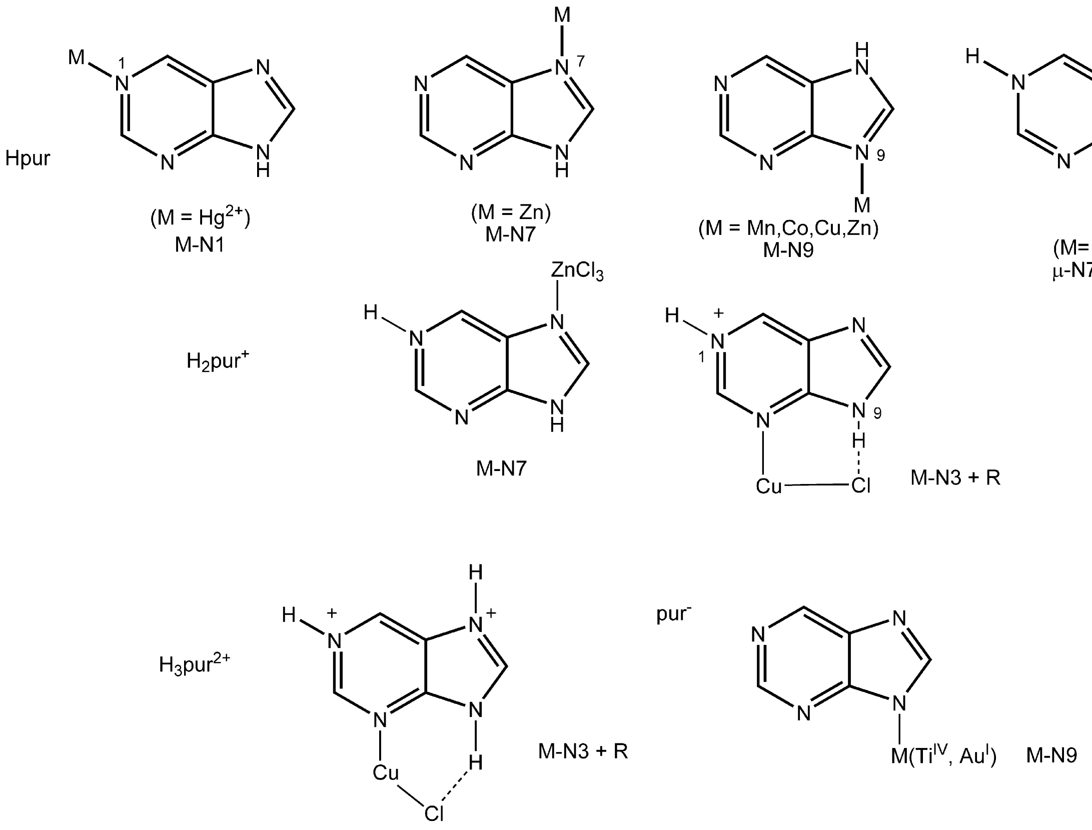
Excluding C-derivatives, the number of structures in CSD concerning purine (Hpur) is surprisingly low. Some of them refer to the free base (PURINE, PURINE01) [2] and some to organic derivatives. The crystal structure of Hpur locates the tautomerizable H atom on the N7 atom (H(*N*7)pur, Scheme 2), which should be the most basic one. However, the adduct bis(purine) urea (PURURE) [3] seems to contain the H(*N*9)pur tautomer and the crystal structure of $[Sn(CH_3)_2 Cl_2(H_2O)_2]\cdot 4Hpur$ perhaps have a mixture of both. It should be noted that the H(*N*7)pur tautomer will be unable to reinforce the metal binding on N1, N3 or N9 with an interligand interaction N7–H···A (hereafter A = H-acceptor atom of a counter-ligand).

The purinium(1+) ion is present in a metal-free derivative (WIVFIQ) [4] along with a macrocycle and perchlorate anion (this later as the counter-ion). Interestingly the H_2pur^+ ion has the ionisable protons on N1 and N9 atoms. We can assume that the proton binding on N1 in the tautomer H(*N*7)pur molecule decreases the basicity of N7 enough to promote the transfer of its H atom to N9. This feature could enable the cationic H_2pur^+ ion to carry out metal binding on N3 and reinforce the coordination bond using the N9–H group to build an N9–H···A interligand interaction.

Regarding the metal–purine binding modes, supported by structural data (Scheme 2), we also take into account the protonation degree of the N_4-heterocyclic ligand. Neutral Hpur is known to be bonded as the tautomer H(*N*9)pur, to Hg(II) at the N1 atom (YAKREI) [5] and to Zn(II) at the N7 site (BIFWUI) [6], (ZAYDAE) [7] or as the tautomer H(N7)pur,



Scheme 1.



Scheme 2.

using its N9 donor atom, for $M^{II}(\mu_2\text{-ox})$ moieties in various coordination polymers (M = Mn (SEGCIR) [8], Co (LAFSAN, LAFSAN01) [9], Cu (LAFRUG) [9] or Zn (LAFSER) [9]). In addition, the bridging mode μ-*N*7,*N*9–H(*N*1)pur is also known in $\{[Cu(\mu_2\text{-}H(N1)pur)(H_2O)_4]SO_4\cdot 2H_2O\}_n$ (BIKJIO) [10]. In any of these compounds the Cu–N(Hpur) bond can be reinforced through an interligand H-bonding interaction. In clear contrast, the cationic forms $H_2(N1,N9)pur^+$ and $H_3(N1,N7,N9)pur^{2+}$ give the polymers $\{Cu_2Cl_2(\mu_2\text{-}Cl)_3(H_2pur)\}_n$ (CLPRCV) [11] and $\{Cu_2Cl_2(\mu_2\text{-}Cl)_4(H_3pur)\}_n$ (GOJGOB) [12] where the Cu(II) ions exhibit $CuCl_5$ and $CuCl_4$ chromophores of type 4 + 1, the Cu–N3 bond is the longest (2.563 and 2.561 Å, respectively) and the protonation of the N9 atom of the purinium(1+ or 2+) cation enables the reinforcement of these coordination bonds by means of an interligand H-bonding interaction of the type N9–H···Cl with a non-bridging chloro ligand (3.217 Å and 133.65° or 3.217 Å and 138.04°, respectively) (Fig. 1). It is remarkable that the tautomer $H_2(N1,N9)pur^+$ is the same cation referred to above for the free metal salt (WIVFIQ) [4]. Additionally, we consider that 9-methylpurine (9Mpur) does not have possibilities for building intra-molecular H-bonding interactions displaying a donor role, as indeed is proved in the crystal structure of $\{[Cu(\mu\text{-}N1,N7\text{–}9Mpur)(H_2O)_4]SO_4\cdot H_2O\}_n$ (AMPCUS) [13]. In this polymeric compound, the 9Mpur acts as a bridging lig-

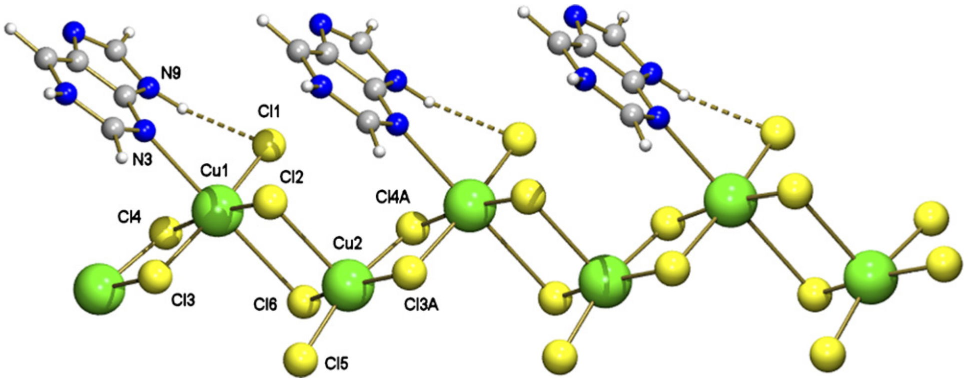


Fig. 1. Fragment of the polymeric chain of $\{Cu_2Cl_2(\mu_2\text{-}Cl)_3(H_2pur)\}_n$ (CLPRCV) [11] showing the N9—H···Cl interaction reinforcing the Cu—N3 coordination bond. Bond lengths (Å): Cu1—Cl1, 2.257; Cu1—Cl2, 2.266; Cu1—Cl4, 2.291; Cu1—Cl3, 2.355; Cu1—N3, 2.563; Cu2—Cl6, 2.250; Cu2—Cl5, 2.270; Cu2—Cl4A, 2.289; Cu2—Cl3A, 2.321; Cu2—Cl2, 2.754. Symmetry code A = *x*, *y* + 1, *z*.

and, in a role also known in two cyclic three- (CECJIE) [14] or tetra-nuclear (CECJEA) [14] Pt(II)-(μ_2-9Mpur) derivatives.

3. Adenine complexes

Adenine (Hade) is a purine nucleobase that is quite soluble in water and as a consequence has been extensively studied both in solution and in the solid state. Free Hade and a variety of N-derivatives produce more than 600 items in the CSD database. These include the crystal structure of Hade·3H_2O (FUSVAQ) [15], some adducts with organic molecules or with H_2O_2 (JOZZED) [16] and an important series of adeniniun(1+) or adeniniun(2+) ions with organic or inorganic counter-anions. This information agrees (with very few and disputable disagreements) that the neutral molecule corresponds to the H(*N*9)ade tautomer, whereas its cationic forms may be written as H_2(*N*1,*N*9)ade$^+$ and H_2(*N*1,*N*7,*N*9)ade^{2+} ions. On this basis, there is a general agreement that the decreasing basicity order of the N atoms in free Hade is $N9 > N1 > N7 > N3 \gg N6$ (exocyclic). In this respect, it has been observed that metal coordination by N6 requires the deprotonation of the exocyclic amino group, such as $-NH^-$ (or $-NR^-$) [1]. Moreover, five N atoms of adenine are borderline Pearson bases.

In spite of its lower basicity, the presence of primary or secondary 6-amino groups in the adenine molecule offers interesting possibilities for being involved as an H-donor in H-bonding interligand interactions. In principle, H(*N*9)ade can bind a metal ion (M) to N7 and use an –N6–H bond as an H-donor to build an intra-molecular interligand interaction (providing that another ligand supplies an appropriate H-acceptor). It is interesting that such a possibility could also apply to *N*1-, *N*3- or *N*9-methyl adenines and related N-heterocyclic adenine derivatives (but not to *N*7-substituted adenines or *N*6,*N*6-bisubstituted adenines). In fact, supposedly, Hade (or ade$^-$) can also bind a metal on N1 and use a –N6–H bond to reinforce this coordination with a suitable H-bonding interaction, but it seems that this has never been supported by a crystal structure determination. Indeed, only four structures with M–N1(9Made) bond are available (with M = Pt (LEBSAM) [17], (WERYUN) [18], (WERZEY) [18] or Ag (WERYOH) [18]) and this coordination has not been reinforced by an H-bonding intra-molecular interligand interaction. A plausible reason for this could be the steric hindrance of the 6-amino group with respect to the N1 atom. On the other hand, for free Hade we cannot neglect the possibility of the formation of a metal–N9(Hade) coordination bond, with the concomitant proton migration from N9 to another N-heterocyclic atom of this nucleobase. If this occurs on the less basic N-heterocyclic N3 atom, the resulting N3–H bond should form a suitable H-bonding interaction, thus reinforcing the N9–metal ion coordination bond. If the H(N9) atom migrates to N7, the N9–metal bond could be reinforced by an H-bonding interaction using the N3 atom as H-acceptor.

Regarding adenine–copper(II) derivatives, we obtained around 50 structures with Hade or related derivatives. From a systematic point of view, we would consider the Cu(II) compounds that have this free nucleobase in them to be cationic (H_2ade$^+$), neutral (Hade) or anionic (ade$^-$) forms, followed by additional information about their *N*-substituted derivatives.

3.1. Adeninium(1+) complexes

An interesting compound without a Cu–*N*(adenine) bond, but with suggestive insights into inter-molecular interactions, is found in the structure of a salt produced by the reaction of the acid chelate [Cu(H_2EDTA)(H_2O)] and Hade, with the formula {(H_2(*N*1,*N*9)ade) [Cu(HEDTA)(H_2O)]·2H_2O}$_2$ (EGOWIG) [19]. The H_2ade$^+$ cation and [Cu(HEDTA)(H_2O)]$^-$ recognise each other by two rather linear H-bonding interactions, N1$^+$–H···O(coordinated) (2.638 Å, 172.79°) and N6–H···O(non-coordinated) [2.804 Å, 174.78°] with two O atoms from the same HEDTA-carboxylate group. Furthermore, in the crystal, pairs of salt ions recognise each other by means of an intense π,π-stacking interaction between their adeninium(1+) cations (Fig. 2). In the molecular complexes [Cu(H_2(*N*1,*N*7-ade)$_2X_2$] (X = Cl (CADENC) [20], Br (BRADCU) [21]) the formation of the Cu–N9 bond takes place with the protonation of N1 and N7, but not on N3. Thus this coordination bond cannot be reinforced with any N3–H···X interaction. However the tautomer H_2(*N*1,*N*7-ade)$^+$ has proven to be able to act as a μ_2-*N*3,*N*9-bridging ligand in the trinuclear compound [Cu_3(μ_2-H_2ade)(μ_2-Cl)$_4$Cl$_4$]·4H_2O (ADEHCU10) [22] also without intra-molecular interligand H-bonding interactions. Note that the tautomer H_2(*N*1,*N*7-ade)$^+$ differs from that mostly found in a large variety of salts (including examples such as ADENZN [23] with coordinated and non-coordinated H_2(*N*1,*N*9-ade)$^+$ ions).

3.2. Neutral adenine complexes

The N-rich and N–H-rich Hade ligand, with broad coordination and H-donor possibilities (including those due to tautomerism), is a highly versatile ligand, which displays a noticeable variety of monodentate and bridging bidentate metal-coordination modes [1]. In such a context, copper(II) complexes are not an exception.

The formation of a single Cu–N9 coordination bond through the most basic N–Hade donor is known in two derivatives of the tautomer H(*N*7)ade. In the mononuclear complex [Cu(glygly)(Hade)(H_2O)] [24] the Cu–N9 bond is reinforced by an intra-molecular (glygly, N–H···)N3 interaction (2.924 Å, 138.5°) (Fig. 3). This is an interesting compound from a molecular recognition point of view because the glygly^{2-} ligand can, *a priori,* act as an H-acceptor via the negatively charged carboxylate group or as an H-donor via the neutral amino group. The structure of this molecule reveals that the H-donor role is preferred in spite of the use of the less basic N3 atom of Hade as acceptor. In the polymeric compound {[Cu(μ-ox)(Hade)(H_2O)]·[Cu(μ-ox)(Hade)(μ-H_2O)]}·~10/3H_2O (SEGCUD) [8] both slightly different complex units have the Cu–N9 bond reinforced by similar (equatorial-aqua)O–H···N3(Hade) interactions (1.696 Å, 139.96° and 2.635 Å, 134.36°). In this case, the ox ligand can only play an H-acceptor role, which is inappropriate versus

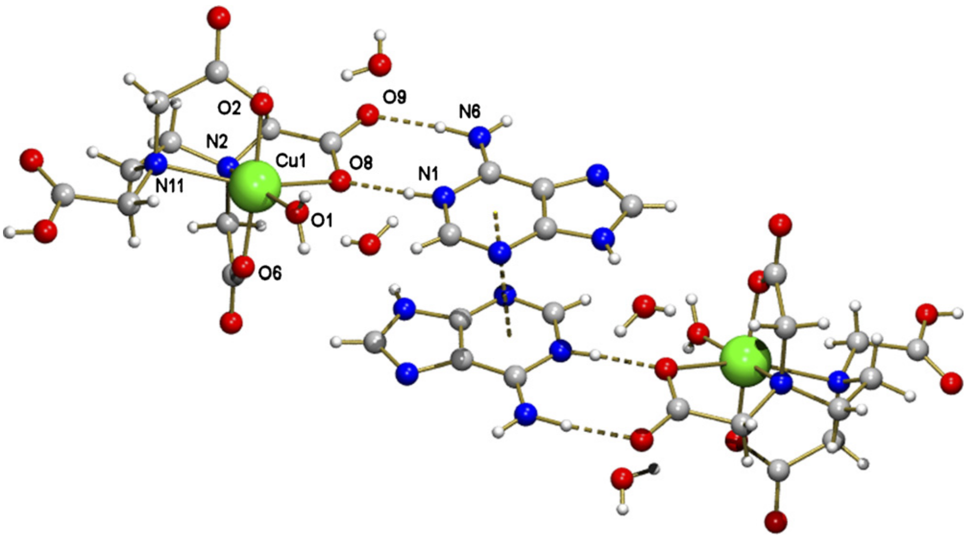


Fig. 2. H-bonding interactions and π,π-stacking interaction involved in the recognition pathway of two ion pairs in the crystal of $\{((H_2N1,N9)ade)[Cu(HEDTA)(H_2O)]\cdot 2H_2O\}_2$ (EGOWIG) [19]. Note that in spite of the aqua ligand in the anion $[Cu(HEDTA)(H_2O)]^-$, the $H_2(N1,N9)ade^+$ cation is not coordinated to the Cu(II) ion. Bond lengths (Å): Cu1—O6, 1.941; Cu1—O2, 1.953; Cu1—O1, 1.954; Cu1—N2, 2.067; Cu1—N11, 2.373; Cu1—O8, 2.404.

the *N*3(H(*N*7)ade) acceptor possibilities. Then, the interligand H-bonding interaction that reinforces the Cu–N9 coordination bond is built profiting from the H-donor possibilities of an equatorial aqua ligand.

Cu–N7(*N*-alkyl-IDA) coordination is known in ternary complexes derived from *N*-alkyl-iminodiacetates (MIDA, EIDA) of the formula $[Cu(N\text{-alkyl-IDA})(Hade)(H_2O)]\cdot H_2O$ (UHEDIU, UHECUF, respectively) [25]. In these compounds, the Cu–N7 coordination bond is reinforced by an intra-molecular interligand interaction N6–H···O(IDA-like) bond, and this recognition mode between the Cu(*N*-alkyl-IDA) chelate and the H(*N*9)ade tautomer is believed to be the most suitable to enable the π,π-stacking interaction between pairs of nucleobases (Fig. 4). Interestingly, molecular and crystal structures of three compounds of the general type $[Cu(N\text{-benzyl-IDA})(Hade)(H_2O)]\cdot H_2O$ (Fig. 5) (UHEDAM, UHEDOA) [25], (EGUXUZ) [26] are known where the Cu–N3 coordination bond is reinforced by an intra-molecular interligand interaction N9–H···O(*N*-benzyl-IDA-like) bond, and this recognition mode between the Cu(*N*-benzyl-IDA-like) chelate and the H(*N*9)ade tautomer is believed to be the most suitable to enable the formation of π,π-stacking multi-stacked chains where the benzyl moiety of one molecule interacts with the Hade ligand of the next one. Note that in these latter compounds the 'expression' of the benzyl aromaticity from the chelating ligand introduces changes in the Cu–*N*(Hade) coordination and in the π,π-stacking pattern with respect to the analogous compounds derived from *N*-alkyl-IDA^{2-} chelating ligands. Furthermore, in a tetranuclear ternary Cu(II) compound having *N*-phenetyl-IDA^{2-} and ligands (UHEDEQ) [25] the H(*N*9)ade tautomer displays a bridging μ-N3,N7 mode and the Cu–N3 and Cu–N7 bonds are reinforced by the appropriate intra-molecular H-bonding interactions [N9–H···O and N6–H···O]. In this compound the π,π-stacking interactions are missing. Curiously the three Cu(*N*-substituted-IDA) chelates recognise the most stable tautomer of Hade, but displaying three different modes depending on the fact that the non-coordinating arm of the IDA derivative be alkyl, benzyl or phenetyl. Moreover, it was structurally proved that the reaction between the Cu(*N*-benzyl-IDA) chelate with the complementary base pair adenine:thymine

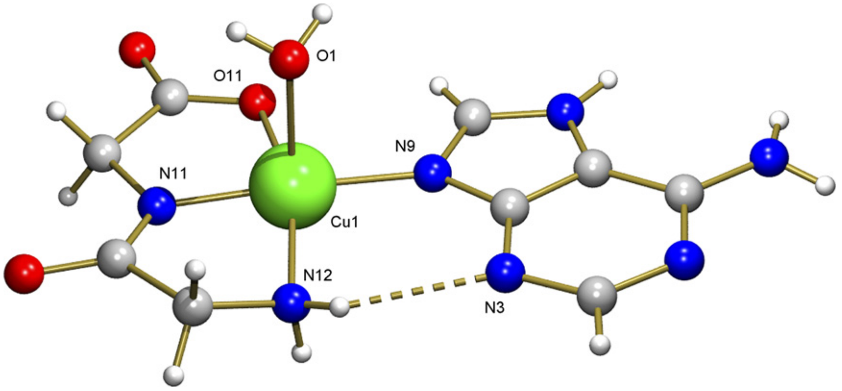


Fig. 3. Intra-molecular interligand interaction (glygly, N—H···)N3 interaction reinforcing the Cu—*N*9(Hade) coordination bond in the recognition pathway of $[Cu(glygly)(Hade)(H_2O)]$ [24]. Bond lengths (Å): Cu1—N11, 1.903; Cu1—N9, 1.972; Cu1—O11, 2.025; Cu1—N12, 2.030; Cu1—O1, 2.309.

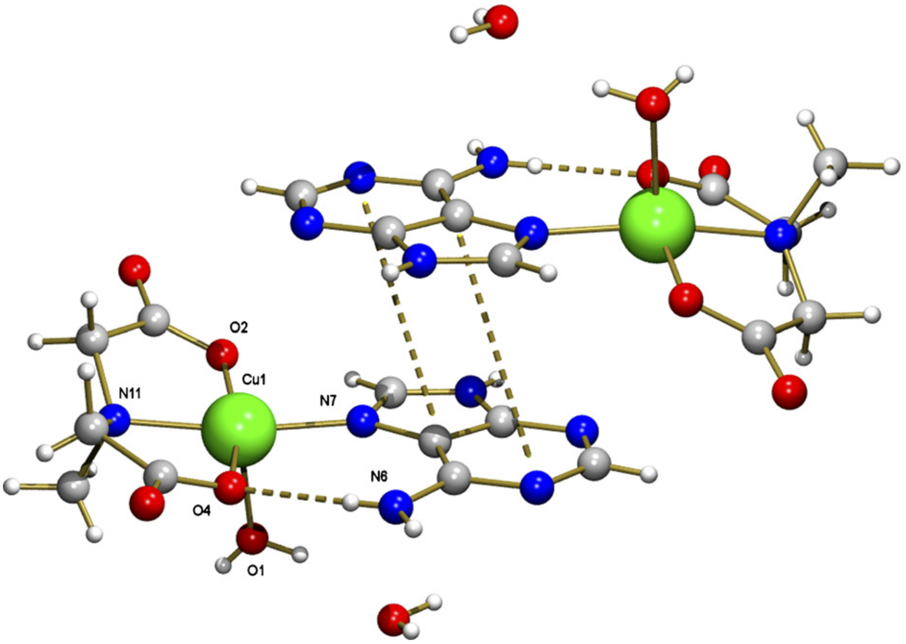


Fig. 4. In *N*-alkyl-IDA derivatives, as $[Cu(MIDA)(Hade)(H_2O)]\cdot H_2O$ (UHEDIU) [25], the molecular recognition chelate-Hade represents the coordination bond Cu—N7 and the H-bonding interaction N6—H···O(coordinated atom). The Hade ligands from pairs of complex molecules are involved in a rather strong π,π-stacking interaction. Bond lengths (Å): Cu1—O4, 1.930; Cu1—O2, 1.945; Cu1—N7, 2.017; Cu—N11, 2.030; Cu1—O1, 2.299.

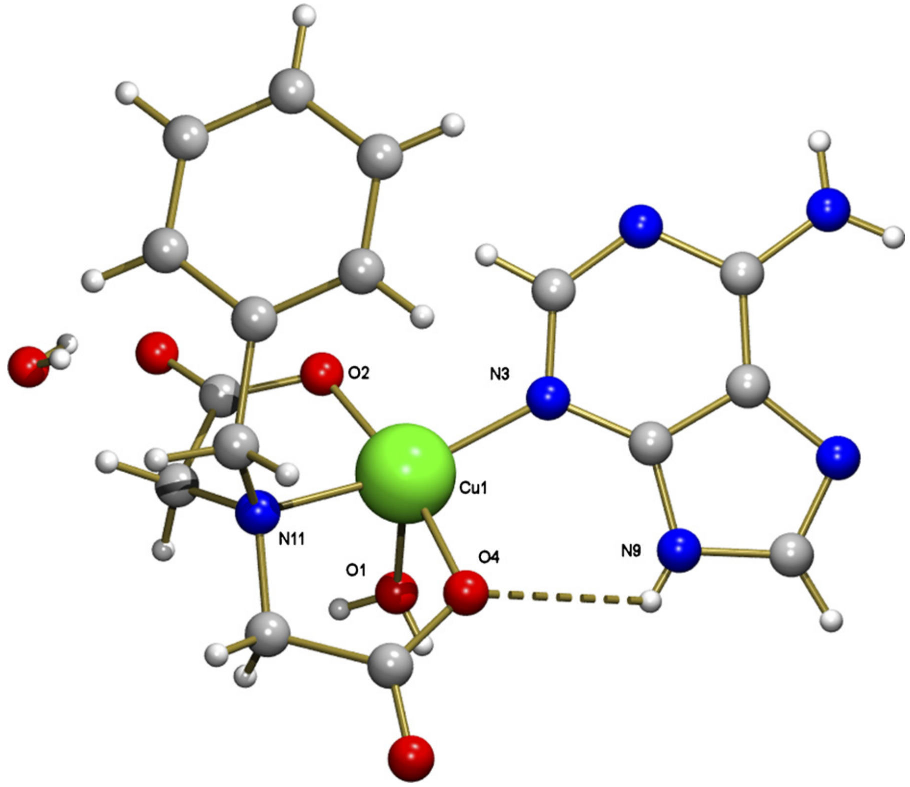


Fig. 5. In three compounds of the type $[Cu(N\text{-benzyl-IDA})(Hade)(H_2O)]\cdot H_2O$, as is shown for the NBzIDA (UHEDAM) [25], the molecular recognition chelate-Hade represents the coordination bond Cu—N3 and the H-bonding interaction N9—H···O(coordinated atom). This seems to be the most suitable pathway to build multi-π,π-stacked chains between each Hade ligand and the aromatic ring of the NBzIDA ligand of the next adjacent complex unit. Bond lengths (Å): Cu1—O2, 1.936; Cu1—O4, 1.943; Cu1—N3, 1.981; Cu1—N11, 2.012; Cu1—O1, 2.303.

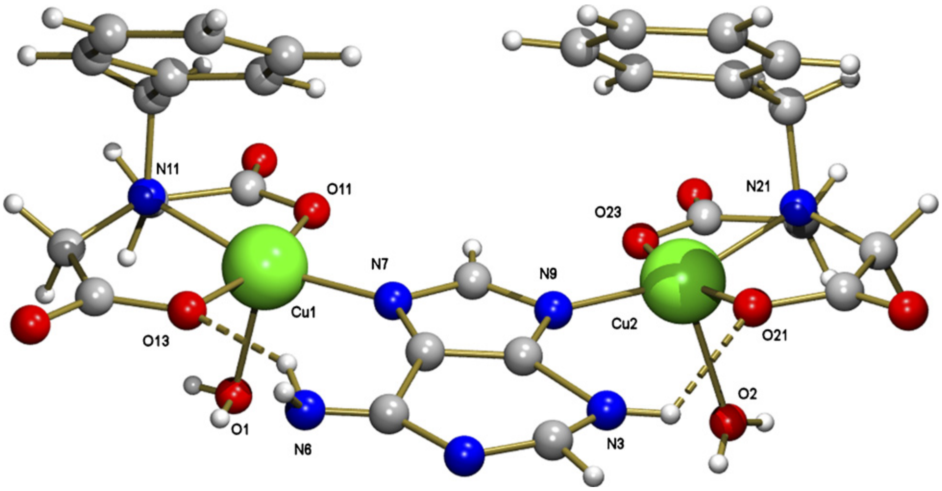


Fig. 6. Twofold Cu—N(Hade) coordination bonds and N—H···O(coordinated) interactions are involved in the molecular recognition pattern of the compound $[(H_2O)(NBzIDA)\ Cu(\mu_2\text{-}N7,N9\text{-}H(N3)ade)Cu(NBzIDA)(H_2O)]\cdot 3H_2O$ (MUNXUO) [27] obtained with the adenine–thymine base pair (instead of Hade alone). Bond lengths (Å): Cu1—O13, 1.954; Cu1—O11, 1.976; Cu1—N7, 2.005;Cu1—N11, 2.024; Cu1—O1, 2.250; Cu2—O23, 1.937; Cu2—O21, 1.958; Cu2—N9, 1.988; Cu2—N21, 2.019; Cu2—O2, 2.242.

has a unique behaviour, giving the dinuclear compound $[(H_2O)(NBzIDA)Cu(\mu_2\text{-}N7,N9\text{–}H(N3)ade)\ Cu(NBzIDA)(H_2O)]\cdot 3H_2O$ (MUNXUO) [27] where the Cu–N7 and Cu–N9 bonds are reinforced by the intra-molecular H-bonding interactions N6–H···O and N3–H···O, respectively (Fig. 6). No π,π-stacking interactions are operative in this compound and until now other *N*-(*p*-substituted-benzyl)IDA–Cu(II) complexes have been shown to be unable to discriminate their reaction against the free Hade base or its complementary base pair.

For a few years the molecular recognition between the Cu(IDA) chelate and Hade has remained unknown, in spite of the different attempts to find an answer to this case. Very recently we were successful in solving the molecular and crystal structure of the compound $[Cu(IDA)(Hade)(H_2O)]$ [28]. The compound has a 4 + 1 Cu(II) coordination, with the aqua as apical ligand. The chelate-nucleobase molecular recognition is a surprise, because of the formation of the Cu–N3 bond (with the less basic Hade donor) which is reinforced by the N9–H···O(coordinated, IDA) interaction (Fig. 7). Note that the formula of this compound differs from the general formula $[Cu(N\text{-}R\text{-}IDA)(Hade)(H_2O)]\cdot H_2O$ with R = alkyl (methyl, ethyl) or benzyl (including some *p*-substituted-benzyl groups). Moreover, it seems clear that reasons for the formation of the Cu–N3(H(*N*9)ade) bond and the concomitant N9–H···O interaction in $[Cu(IDA)(Hade)(H_2O)]$ are essentially different from those found for the compounds $[Cu(N\text{-}benzyl\text{-}IDA)(Hade)(H_2O)]\cdot H_2O$ (UHEDAM, UHEDOA) [25], (EGUXUZ) [26] where this recognition pattern is accomplished by building the π,π-multi-stacked chains mentioned above. Indeed, the π,π-stacking interactions are completely missing from the crystal of $[Cu(IDA)(Hade)(H_2O)]$ where each H(*N*9)ade ligand involves its $-N(6)H_2$ exocyclic group in N6–H···N3 and N6–H···N7 interactions with two adja-

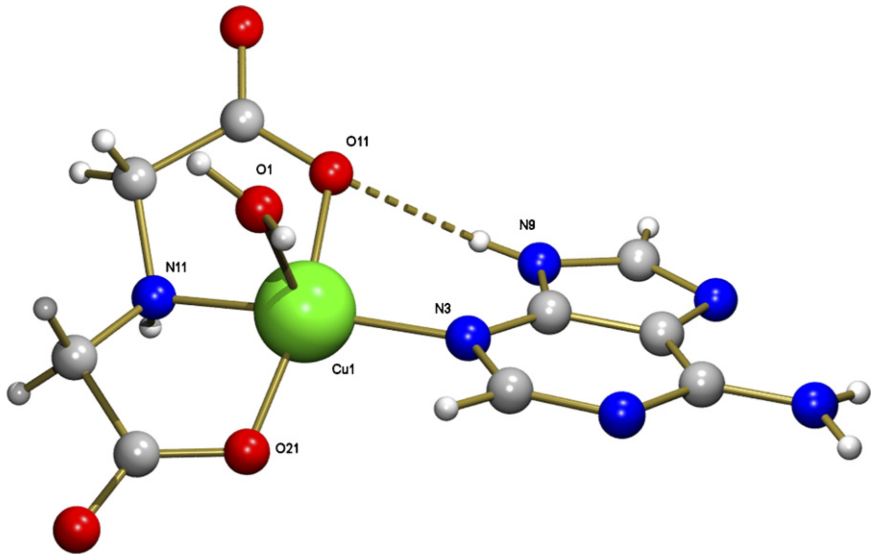


Fig. 7. Structure of the complex molecule $[Cu(IDA)(Hade)(H_2O)]$ showing the formation of the Cu—N3 coordination bond and the N9—H···O(coordinated) intra-molecular interaction [28]. Bond lengths (Å): Cu1—O11, 1.948; Cu1—O21, 1.953; Cu1—N11, 1.972; Cu1—N3, 1.987; Cu1—O1, 2.348.

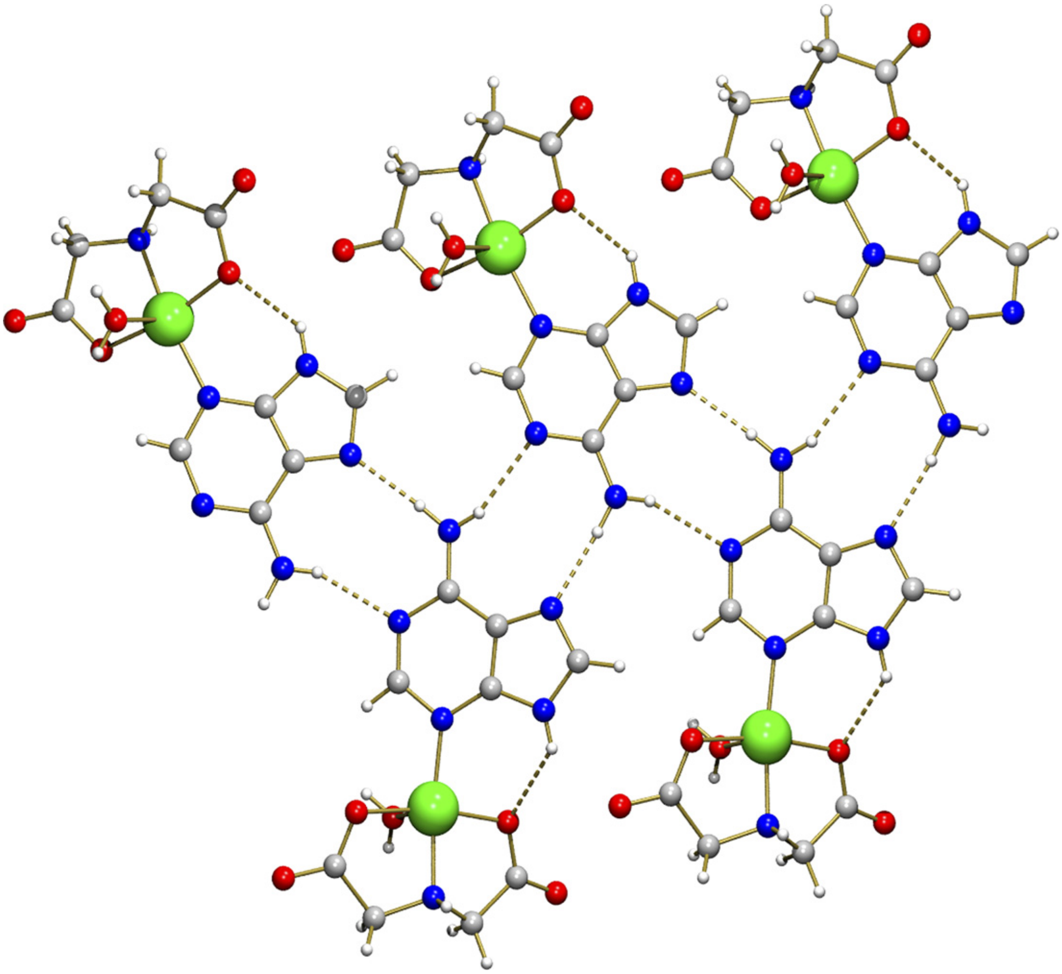


Fig. 8. Pairs of N6H· · ·N1 interactions between Hade ligands involved in the ribbon formation of [Cu(IDA)(Hade)(H_2O)] molecules [28].

cent nucleobases, thus forming ribbons of complex molecules (Fig. 8).

Another bridging mode has been reported for the polymer [Cu(gly)(μ_2-*N*1,*N*9–H(*N*7)ade)(NO_3)(H_2O)]$_n$ (CARCEE) [29] where the Cu–N9 bond is reinforced by one intra-chain O(aqua, apical)–H· · ·N3 interaction (2.777 Å, 154.62°) whereas the Cu–N1 bond is reinforced by one intra-chain N6–H· · ·O(aqua, apical) interaction (2.899 Å, 150.00°) (Fig. 9).

There are a series of compounds with binuclear units of the type [Cu_2(μ_2-*N*3,*N*9–H(*N*7)ade)$_4$(H_2O)$_2$]A_2 where A is a counter-anion such as perchlorate (ADAQCU) [30] or chloride (CADCUC) [31]. Within the dinuclear cation of this compound, the N3· · ·N9 distance is close to 2.41–2.42 Å, whereas the intermetallic distance Cu· · ·Cu is 2.95 or 3.01 Å depending on the counter-anion. There are no H-bonding interactions within the binuclear cations, but these compounds are remarkably interesting because of their expanding possibilities (*vide infra*, see below).

3.3. Adeninate(1−) complexes

The adeninate(1−) anion represents the loss of the tautomerizable proton from the free neutral Hade. Presumably, it is suitable for metal binding at N7 and reinforces this coordination as H-donor from the exocyclic amino group, but is also able to coordinate to N9 (or N3) and acts as an H-acceptor at N3 (or N9). These roles are compatible. In addition, the adeninate(1−) anion have proved to be able to act as bridging ligands for three metal centres, using N3, N7 and N9 as donor atoms (but not by another set of three N-heterocyclic atoms as seems to have been proved for Cu(II) ions).

Many years ago, Sletten reported the structures of two compounds of formula Cu(ade)$_2$·$n$$H_2O$ [with $n = 3.5$ or 4 in QQQAAR [32] or AMPUCU10 [32], respectively; atomic coordinates not available] with the anion ade$^-$ displaying a *N*6,*N*7-bidentate chelating role. No other Cu(II) derivative has been reported with a Cu–N6 coordination bond. Indeed, Lippert has noted that an anionic form (by deprotonation) is required in the *N*6-exocyclic amino group of the adenine to be able to produce metal binding [1]. Thus, hereafter, ade$^-$ represents the adeninate(1−) ion which retains the integrity of its exocyclic amino group, –N(6)H_2.

The *N*9(ade) binding of Cu(II) ions seems favoured in ternary complexes having another ligand with suitable H-donor properties. Thus, in the bis-adeninate complex molecule [Cu(dien)(ade)$_2$]·H_2O (ADDNCU) [33] at least one ade$^-$

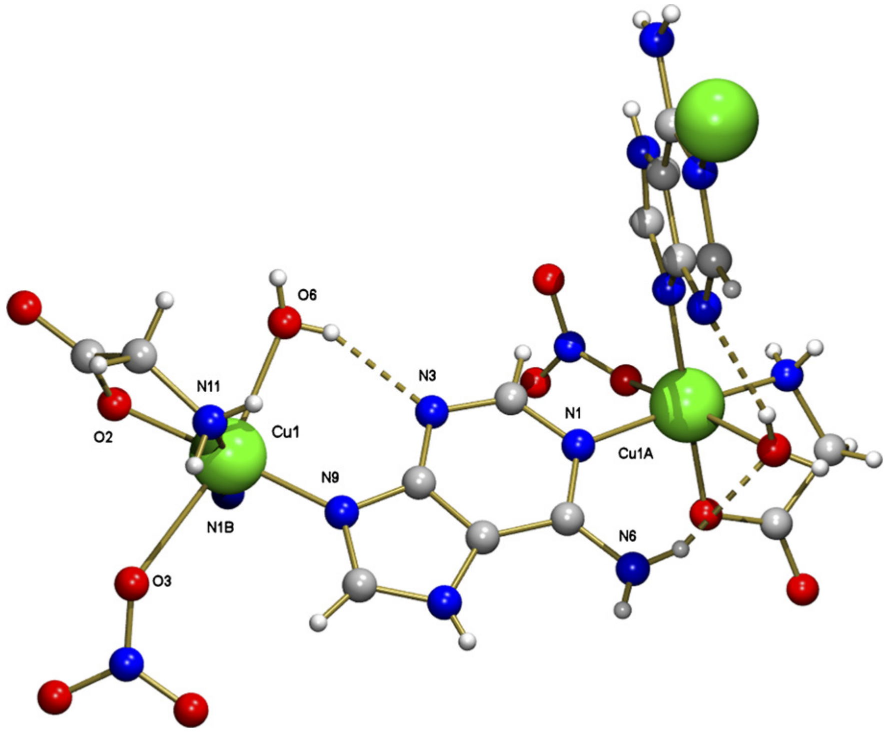


Fig. 9. Two Cu—N coordination bonds are reinforced by one N—H···O(aqua) or one O—H(aqua)···N interactions in the polymeric compound $[Cu(gly)(\mu_2\text{-}N1,N9\text{-}H(N7)ade)(NO_3)(H_2O)]_n$ (CARCEE) [29]. Bond lengths (Å): Cu1—O2, 1.986; Cu1—N11, 1.995; Cu1—N9, 2.020; Cu1—N1B, 2.025; Cu1—O6, 2.348; Cu1—O3, 2.610. Symmetry code A = −x + 2, y + 1/2, −z + 3/2, B = −x + 2, y−1/2, −z + 3/2.

ligand is oriented favouring a terminal-dien(N–H···*N*3(ade) interaction. Using the tripodal-tetradentate amine tren, the structures of two salts, $[Cu(tren)(ade)]ClO_4$ (MIQVOX) [34] and $[Cu(tren)(ade)]Cl\cdot 2H_2O$ (YURWOX) [35], have been reported where the Cu–N9 bond is reinforced with a (tren)N–H···N3 H-bonding interaction (2.925 Å, 130.86° and 3.141 Å and 135.82°, respectively).

The adeninate anion displays a μ_2-*N*3,*N*9-binucleating role in the compound $[Cu_2(\mu_2\text{-ade})_4(H_2O)_2]\cdot 7H_2O$ (VAZTEW) [36] where each Cu(II) exhibits a 4 + 1 coordination in a chromophore of the type $CuN_4 + O$ (Fig. 10). Interestingly, in addition to the apical aqua ligand, every one of the Cu centres are built with a set of two N3 and two N9 donors of the four ade^- ligands in such a manner that in the basal square of coordination, both kinds of N donors lie in *trans* each other. In this binuclear molecule there are no intra-molecular H-bonding interactions. The rather rigid $[Cu_2(\mu_2\text{-ade})_4(H_2O)_2]$ core, with N3···N9 and Cu···Cu separations of 2.416 and 2.938 Å, is similar to those referenced for neutral H(*N*7)ade (ADAQCU) [30], (CADCUC) [31], but the anionic nature of ade^- ligands seems to favour the possibility that they can act as bridging-tridentate ligands. This is, for example, the case with the 3D polymer $\{[Cu_2(\mu_3\text{-ade})_4(H_2O)_2][Cu(ox)(H_2O)]_2\cdot\sim 14H_2O\}_n$ (XACZEH) [37]. The $Cu(ox)(H_2O)$ moieties complete their 4 + 1 coordination with two N7 donor atoms belonging to ade^- from adjacent binuclear motifs $[Cu_2(\mu_2\text{-ade})_4(H_2O)_2]$. One of these ade^- is involved in one interligand interaction N6–H···O(aqua) (2.855 Å, 145.25°). In this way all $Cu(ox)(H_2O)$ moieties are involved in two Cu–N7 bonds and one N6–H···O(aqua) interaction, stabilizing the 3D array in such a manner that it can lose the non-coordinated water without breakdown. From a complementary design strategy, it has also been reported that the controlled expansion of the core $[Cu_2(\mu_2\text{-ade})_4(H_2O)_2]$ with a fourfold addition of the Cu(II)-oxydiacetate chelate makes it possible to build a windmill hexanuclear molecule with the formula $\{(H_2O)_2Cu_2(\mu_3\text{-ade})_4[Cu(oda)(H_2O)]_4\}\cdot 6H_2O$ (PECNUH) [36]. In this case every $Cu(oda)(H_2O)$ fragment is linked to one ade^- ligand of the core thus forming a Cu–N7 bond (1.945 or 1.955 Å) which is reinforced by an intra-molecular (ade)N6–H···O(oda) interligand interaction (2.876 Å, 153.08° or 2.791 Å, 168.31°, respectively) (Fig. 11). Both the 3D polymer and the hexanuclear molecule maintain N3···N9 and Cu···Cu separations of ∼2.41 and ∼2.94 Å, revealing the remarkable conformational rigidity of the binuclear motif.

In a series of hydrothermal syntheses with mixtures of $[Cu^{II}(IDA)(H_2O)_2]$ and Hade, suitable single crystals of two closely related mixed-valence copper complexes were obtained [28] (Fig. 12). These interesting compounds, $\{[Cu^{II}(IDA)(H_2O)]_2[Cu^{I}_2(\mu_3\text{-ade})_2(H_2O)_2]\}\cdot 2H_2O$ and $\{[Cu^{II}(\mu_2\text{-IDA})]_2[Cu^{I}_2(\mu_3\text{-ade})_2]\}_n$ have μ_3-*N*3,*N*7,*N*9-adeninate ligand forming Cu^{I}–N3, Cu^{I}–N9 and Cu^{II}(IDA)–N7 coordination bonds. This latter bond is reinforced by the appropriate N6–H···O(IDA) interligand interaction. In the molecular compound IDA acts a tridentate ligand, with the expectable *mer*-NO_2 conformation, whereas in the polymer analogue this chelating role is accomplished by a twofold μ_2-anti, syn role, which increases the role of IDA to pen-

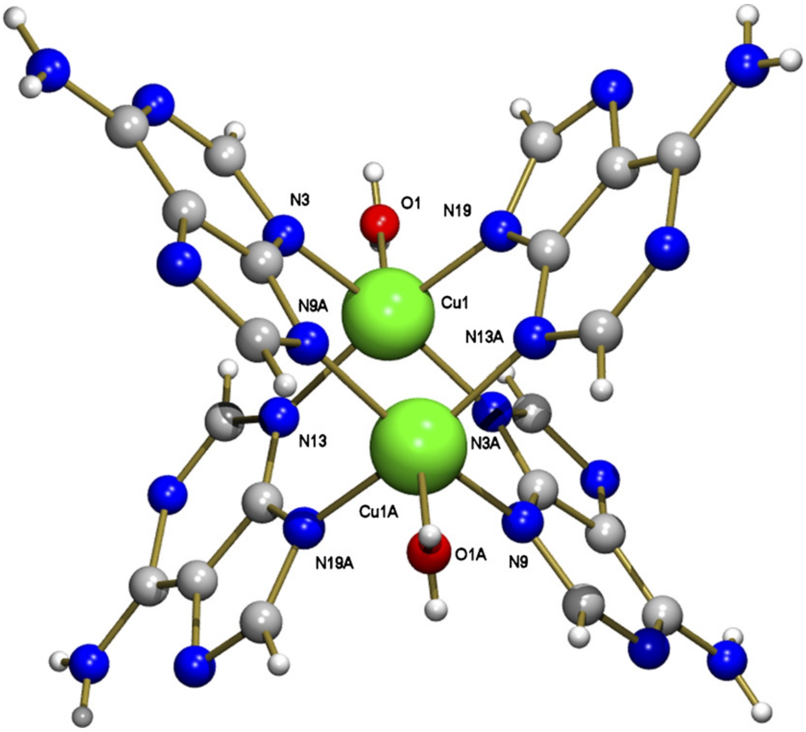


Fig. 10. Structure of the binuclear complex molecule in the crystal of $[Cu_2(\mu_2\text{-}N3,N9\text{-ade})_4(H_2O)_2]\cdot 7H_2O$ (VAZTEW) [36]. Bond lengths (Å): Cu1—N19, 2.002; Cu1—N9, 2.012; Cu1—N3, 2.023; Cu1—N13, 2.025; Cu1—O1, 2.181. Symmetry code A = $-x+1$, $-y+1$, $-z$.

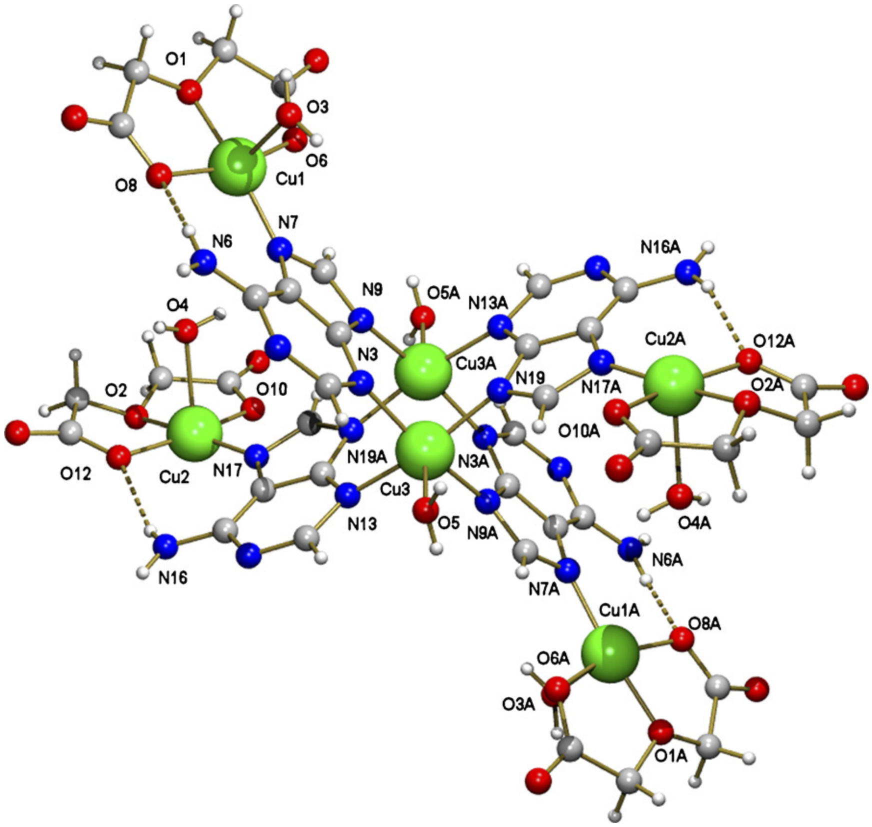


Fig. 11. Hexanuclear complex molecule in the crystal of $\{(H_2O)_2Cu_2(\mu_3\text{-ade})_4\ [Cu(oda)(H_2O)]_4\}\cdot 6H_2O$ (PECNUH) [36] built by the recognition (Cu—N7 bond + N6—H···O interaction) between $[Cu_2(\mu_2\text{-}N3,N9\text{-ade})_4(H_2O)_2]$ and $[Cu(oda)(H_2O)]$ complexes. Bond lengths (Å): Cu1—O8, 1.933; Cu1—O6, 1.951; Cu1—N7, 1.955; Cu1—O1, 1.958; Cu1—O3, 2.228; Cu2—O12, 1.935; Cu2—N17, 1.945; Cu2—O2, 1.959; Cu2—O10, 1.959; Cu2—O4, 2.301; Cu3—N19, 1.991; Cu3—N9A, 2.001; Cu3—N3, 2.018; Cu3—N13, 2.028; Cu3—O5, 2.178. Symmetry code A = $-x+1$, $-y$, $-z+1$.

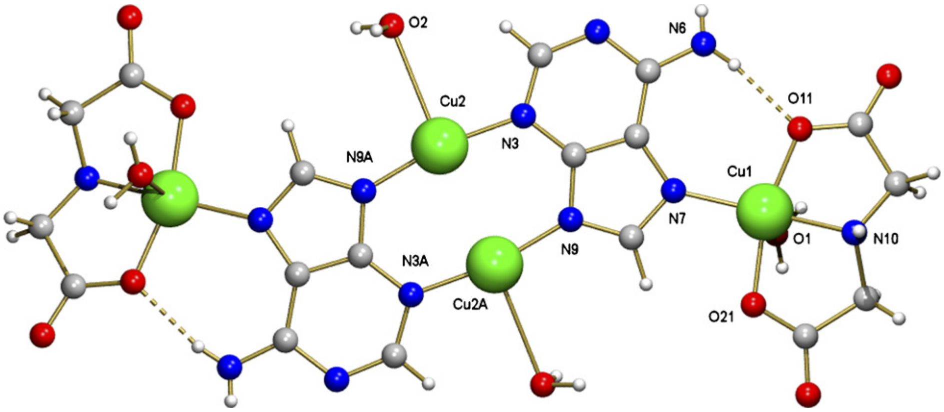


Fig. 12. Structure of the mixed-valence complex molecule in the crystal of $\{[Cu^{II}(IDA)(H_2O)]_2[Cu^I_2(\mu_3\text{-ade})_2(H_2O)_2]\}\cdot 2H_2O$ [28]. Bond lengths (Å): Cu1—O11, 1.939; Cu1—N10, 1.990; Cu1—O21, 1.991; Cu1—N7, 1.991; Cu1—O1, 2.417; Cu2—N9A, 1.878; Cu2—N3, 1.889; Cu2—O2, 2.748. Symmetry code A = $-x$, $-y$, $-z$.

tadentate. Both compounds can be looked as the result of the recognition between the Cu^{II}(IDA) chelate with binuclear fragments $Cu^I_2(\mu_2\text{-}N3,N9\text{-ade})_2(H_2O)_2$. From this point of view, we can appreciate that these mixed-valence compounds exhibit remarkable similarities to the hexanuclear molecule $\{(H_2O)_2Cu_2(\mu_3\text{-ade})_4\ [Cu(oda)(H_2O)]_4\}\cdot 6H_2O$ (PECNUH) [36] discussed above.

3.4. N9-methyladenine complexes

The use of *N*(heterocyclic)-substituted adenines represents the lack of the tautomerizable H atom, normally on N9. In this sense, as a suggestive example, the use of 9Made prevents the implication of the most basic N9 donor atom of Hade and will favour the coordination of N7 atom and the exocyclic amino group to build N6–H···A interligand interaction (Fig. 13). This consideration applies to four crystal structures reported to Cu–9Made, of formulas $[Cu(9Made)(H_2O)_4(SO_4)]\cdot H_2O$ (AMADCS) [38] $[Cu(9Made)_2(H_2O)_4]Cl_2\cdot H_2O$ (AMADCU) [39], $[Cu(glygly)(9Made)(H_2O)]\cdot 4H_2O$ (GLMACU) [40] and $[Cu(N\text{-sal},N'\text{-M-en})(9Made)(H_2O)]NO_3\cdot 2H_2O$ (SMEADC) [41]. In the first of these compounds the Cu–N7 bond is reinforced by one intra-molecular interligand interaction N6–H···O(apical, sulphate) (2.856 Å, 158.48°), whereas in the chloride analogue AMADCU each 9Made builds one symmetric 'bifurcated' N6–H···O(aqua) interaction (2.944 Å, 136.74°) with two aqua ligands. This unusual interligand interaction leads to the four equivalent Cu–O(aqua) bonds of 2.161 Å (Fig. 14). The ternary complex derived from glygly has the Cu–N7 coordination bond reinforced by the N6–H···O(aqua, apical) (2.820 Å, 160.83°), in clear contrast to that referenced for [Cu(glygly)(Hade)(H₂O)] (see before, *vide supra*). This comparison also revealed that the 9-methylation of the Hade also significantly alters the molecular recognition between the

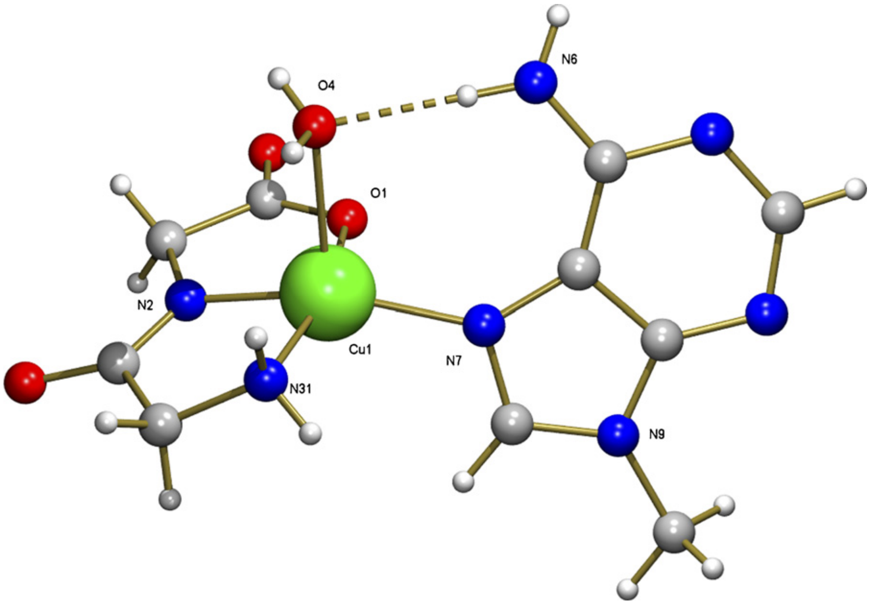


Fig. 13. In $[Cu(glygly)(9Made)(H_2O)]\cdot 4H_2O$ (GLMACU) [40], the Cu—N7(9Made) coordination bond is reinforced by the N6—H···O(aqua) interaction, without participation of the dipeptide(2−) ligand (for comparison, see Fig. 3). Bond lengths (Å): Cu1—N2, 1.917; Cu1—O1, 1.963; Cu1—N7, 2.021; Cu1—N31, 2.023; Cu1—O4, 2.347.

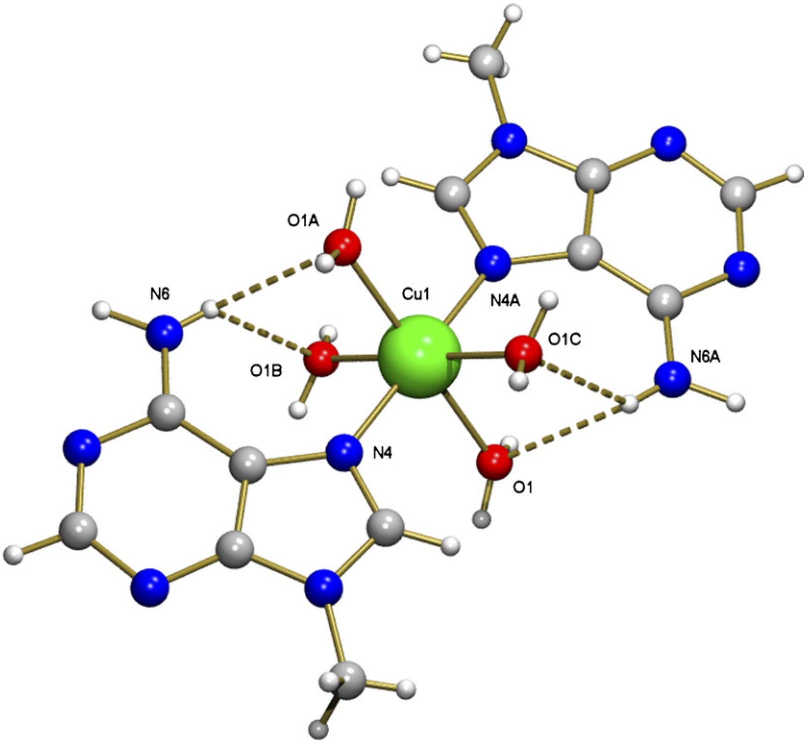


Fig. 14. Structure of the complex cation in the crystal of [Cu(9Made)$_2$(H$_2$O)$_4$]Cl$_2$·H$_2$O (AMADCU) [39], showing that each Cu—N7 bond is reinforced by a 'bifurcated' H-bonding interaction with two *cis*-aqua ligands. Bond lengths (Å): Cu1—N7 = Cu1—N7A, 2.008; Cu1—O1 = Cu1—O1A = Cu1—O1B = Cu1—O1C, 2.161. Symmetry code A = −*x*, *y*, −*z*, B = −*x*, −*y*, −*z*, C = *x*, −*y*, *z*.

Cu(glygly) chelate and the purine-like nucleobase (Hade or 9Made). Finally, the *N*-sal,*N*′-M-en derivative represents an additional example where the Cu–N7 bond is reinforced by the 'expectable' N6–H···O(salicylate) interligand interaction (2.870 Å, 160.83°).

4. Guanine complexes and related compounds

The guanine, H(N9)gua, is a very important purine-like nucleobase and around 450 items were found in the CSD database in a search using its structure. This broad search includes inorganic salts of the protonated cations H$_2$(*N*7,*N*9)gua$^+$ (see DUKKOJ [42], ELEYID [43], among others) and H$_3$(*N*3,*N*7,*N*9)gua^{2+} (see GODYUT [44], HUMNEI [45], HUSBEC [46]), but not this slightly insoluble free base. In his review, Lippert [1] provides a good outline of the various and remarkable reasons for which guanine moiety is believed to be the major metal binding site in nucleic acids as well as in most guanine containing ligands. Both heterocyclic and exocyclic N atoms of guanine are considered as borderline Pearson bases, whereas its O6 atom is a hard donor. In this respect, binding alkali metal ions to O6-gua to maintain the guanine quartet structure in telomeres and other known O6-(hard)metal binding features seems to be easily understood by the general Pearson criterion (hard acids prefer hard bases, and so on).

For the purposes of this review, the presence of the exocyclic amino group –N(2)H$_2$ as a potential H-donor or that of the O6 atom as a suitable H-acceptor will be considered as sources of intra-molecular interligand H-bonding interactions. In this respect, Lippert [1] has noted that the H-acceptor role of the exocyclic *O*6-gua atom can cooperate in appropriate *N*7-metalated ternary complexes, most noteworthy being those with *N*9-substituted guanine derivatives as a ligand. The active preference (region-selectivity) of *cis*-Pt^{II}(NH$_3$)$_2$ fragments by intra-strand sequences of two or more adjacent G nucleotides can be explained by the possibility of reinforcing the Pt–N7 coordination bond by an intra-molecular interligand H-bonding interaction of the Pt(aqua)···O6 type, but also a large variety of structural evidence is found in the CSD database for related Pt(II) model compounds where Pt–(amine N–H)···O6 intra-molecular interligand interactions cooperate with the Pt–N7 coordination bonds in the molecular recognition pattern between this nucleobase and the remaining Pt complex moiety. Indeed, this is crystallographically supported for a variety of cases in which an N-9 blocking group also favours *N*7(guanine)-metal binding. These kinds of observations also apply to a variety of related complexes with other *O*6-purines (such as hypoxanthine, xanthine, theophylline). However, in some cases where this cooperation between a coordination bond and an H-bonding interaction would be expected, it is not supported in practice by the X-ray crystallographic results. On the other hand, in free guanine, the N9 atom will be considered as an attractive metal binding donor if its H atom is removed or tautomerized to N7 or N3. In this respect, the crystal structure of the H$_2$(*N*3,*N*7)gua$^+$ ion in the binuclear complex {CuCl$_2$(H$_2$gua)(μ-Cl)}$_2$ (GUANCU10) [47] reveals that each Cu–N9 bond is reinforced by a bifurcated H-bonding interaction: N3–H···Cl (3.352 Å, 123.06°) + N3–H···μ-Cl (3.355 Å,

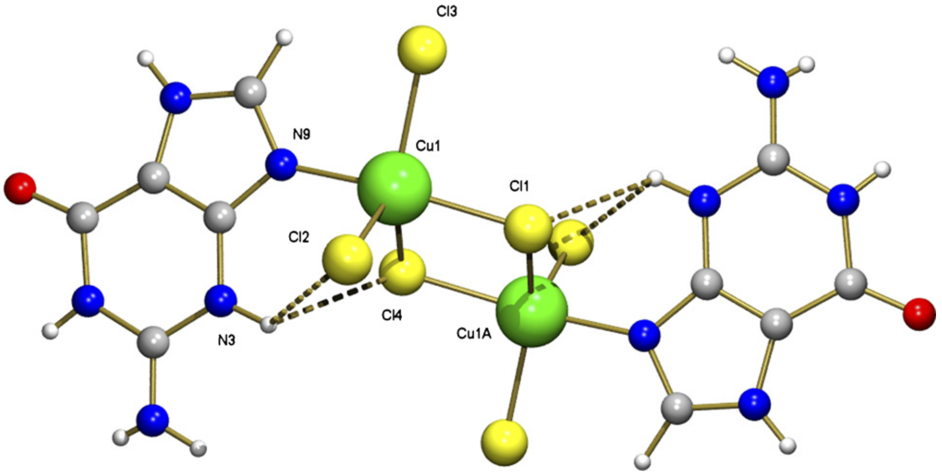


Fig. 15. A 'bifurcated' H-bonding interaction reinforces the Cu—N9 coordination bond in the crystal structure of binuclear complex $\{CuCl_2(H_2gua)(\mu\text{-}Cl)\}_2$ (GUANCU10) [47] derived of the $H_2(N3,N7)gua^+$ ion. Bond lengths (Å): Cu1—N9, 1.977; Cu—Cl1, 2.288; Cu1—Cl3, 2.329; Cu1—Cl2, 2.366; Cu1—Cl4, 2.447. Symmetry code A = $-x+1/2$, $-y+1/2$, $-z+1$.

105.30°) (Fig. 15). In this case, the protonation of the guanine and the formation of the Cu–N9 bond represent the stabilization of the $H_2(N3,N7)gua^+$ ion tautomer, which in turn enables the contribution of the $N3^+$–H bond to build the H-bonding interaction above discussed.

The 9-methylguanine (9Mgua) molecule is the simplest *N*9-substituted Hgua derivative. It is unable to perform metal binding at N9 and thus favouring metallation on N7. In the salt $[Cu(9Mgua)_2(H_2O)_3]SO_4\cdot 3H_2O$ (MGUCUS) [48] the Cu(II) atom exhibits a 4 + 1 type coordination, but the formation of the Cu–N7 bonds is not accompanied by any intra-molecular interligand H-bonding interaction of the type O(aqua)···O6(9Mgua). This kind of H-bonding interaction is also missing in the interesting bi-metallic Pt^{II}/Cu^{II}-compound having 1-methylcytosinato, 9-ethylguanine and apical aqua as ligands of the Cu(II) atom (REBCEG) [49]. In clear contrast, the octahedral centro-symmetric molecule $[Cu(9Mgua)_2(H_2O)_2(NO_3)_2]$ (NAMGCU) [50] shows each 9Mgua linked to the metal by N7 and reinforcing this coordination with an intra-molecular interaction O(aqua)–H···O6(9Mgua) (2.677 Å, 163.59°).

Other interesting cases are ternary compounds having the antiviral drug acyclovir as an open chain sugar nucleoside which binds the Cu(II) via its N7 donor atom. In the centro-symmetric complex of the salt $[Cu(acv)_2(H_2O)_2](NO_3)_2$ (HOSQUB) [51] the donor–acceptor H_2O···O6 distances (3.106 Å) and the angles O–H···O6 (59.83° and 98.06°) do not seem to be suitable when considering efficient intra-molecular interligand H-bonding interactions. A similar case is the compound $[Cu(acv)_2(H_2O)_3](NO_3)_2\cdot H_2O$ (RUMGAH) [52] where the O6 atoms fall at 3.185 and 3.223 Å from the O atom of the same aqua ligand, again with O–H···O6 angles (117.94° and 92.79°) which strongly suggest weak electrostatic interactions. In clear contrast, the octahedral complex molecule $[Cu(acv)_2(H_2O)_2Cl_2]$ (ZATJIN) [53] exhibits twofold the formation of a Cu–N7(acv) bond reinforced by an effective intra-molecular H-bonding interaction (donor–acceptor H_2O···O6 distances of 2.593 Å) involving the two pairs of acv-aqua ligands present in the complex. On the basis of these and other obervations, we have recently synthesized and structurally characterized two ternary copper(II) complexes with acv and IDA or glygly as ligands. We have considered that IDA can only use its carboxylate groups as H-acceptors whereas glygly offers a terminal carboxylate group (H-acceptor) and a terminal amino group (H-donor). The IDA derivative is a polymer, $\{[Cu(IDA)(acv)]\cdot 2CH_3OH\}_n$ [54], with type 4 + 1 Cu(II) coordination, which is built via a bridging IDA-carboxylate group, but without intra-molecular H-bonding interactions reinforcing the Cu–N7(acv) bond. In clear contrast, the compound $[Cu(glygly)(acv)]\cdot H_2O$ [54] exhibits a square-planar Cu(II) coordination and its Cu–N7(acv) bond is reinforced by an intra-molecular glygly(terminal)-NHa···O6(acv) interaction (2.961 Å, 140.5°) (Fig. 16).

Extending the insights discussed above to other 9-substituted guanines, we can include a few cases as some interesting compounds. For example, the structure of the guanosine (guo) derivative of formula $[Cu(dien)(guo)(NO_3)]NO_3$ (GIVRUY) [55] (Fig. 17) reveals that the 4 + 1 coordination is accomplished by the tridentate *mer*-dien, the N7–guo coordination bond and the *O*-nitrate as apical donor. The guanine moiety of the nucleoside falls nearly perpendicular to the basal Cu(II) coordination plane. That enables the reinforcement of the Cu–N7 bond with the intra-molecular interligand interaction dien-(terminal)NH···*O*6(guo) (3.089 Å, 150.10°). The other interatomic distance dien-(terminal)N···*O*6(guo) (4.534 Å) is large enough to consider a bifurcate H-bonding interaction in this compound. The structure of an interesting binuclear Cu(II)-guo derivative (YEQROC) [56] of formula $[Cu_2(\mu_2\text{-}L)(\mu_2\text{-}O6,N7\text{-}guo)](ClO_4)_3\cdot CH_3OH$ (L^- = *N*,*N*,*N′*,*N′*-tetrakis(2-pyridylmethyl)-2,6-diaminophenolate(1−) ligand) reveals that the nucleoside and the binuclear chelate $Cu_2(\mu\text{-}L)^{3+}$ are recognised through the formation of the Cu(a)–N7 (1.989 Å) and Cu(b)–O6 (1,995 Å) coordination bonds, with an unusual μ_2-*O*6,*N*7-guo bridging role, but without any intra-molecular H-bonding interligand interaction. A close similar – but not

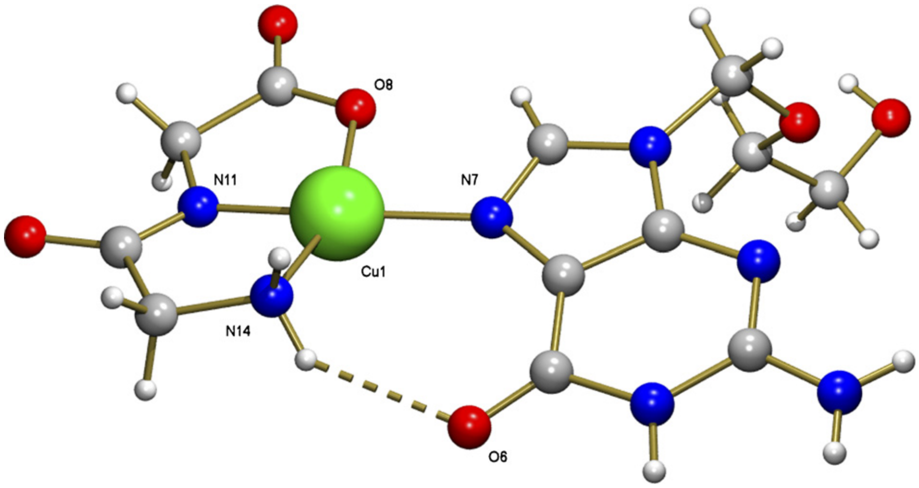


Fig. 16. The crystal structure of [Cu(glygly)(acv)]·H_2O [54] revealed that the Cu—N7(acv) bond is reinforced by the N—H(glygly)· · ·O6(acv) intra-molecular interaction, according to the appropriate H-acceptor role of the O6 atom in the guanine moiety of acv. Bond lengths (Å): Cu1—N11, 1.888; Cu1—O8, 1.957; Cu1—N7, 1.995; Cu1—N14, 2.010.

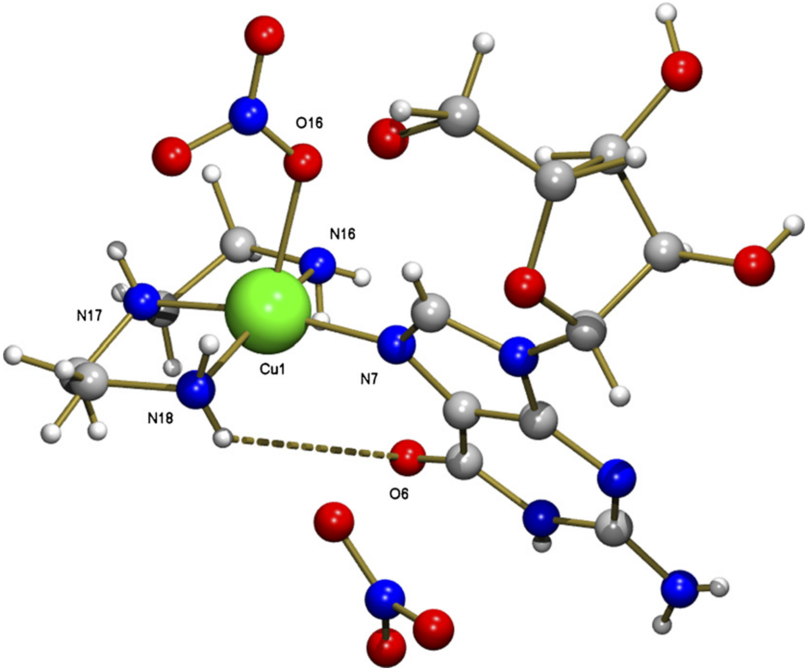


Fig. 17. The crystal structure of [Cu(dien)(guo)(NO_3)]NO_3 (GIVRUY) [55] where the Cu—N7(acv) bond is reinforced by the N—H(dien)· · ·O6(acv) intra-molecular interaction. Bond lengths (Å): Cu1—N7, 2.006; Cu1—N17, 2.008; Cu1—N16, 2.015; Cu1—N18, 2.037; Cu1—O16, 2.252.

iso-structural – Zn(II) compound is known (YEQRES) [56]. In addition, the μ_2-*O*6,*N*7-9Mgua is found in a bimetallic Pt,Na-derivative (XAHZOV) [57] where N7 binds the soft Pt(II) atom, while O6 binds the hard Na(I) atom. Also, the μ_2-*O*6,*N*7-9Egua role has also been established for binuclear derivatives of Zn (UGOXOD) [58] and other few metals.

5. Concluding remarks

This review has shown that the presence of an amino or oxo group in the C6 atom in adenine or guanine and its derivatives, respectively, significantly increases their possibilities for developing a suitable intra-molecular interligand interaction that reinforces the corresponding Cu–N(nucleobase) coordination bond. The relevance of this cooperative mode in developing efficient molecular recognition patterns is added to the possibilities that the free nucleobases and some of their cationic forms have to tautomerize protons between N-heterocyclic atoms.

Free purine enhances the possibilities of using the cooperation of a Cu–N bond plus an N–H· · ·A reinforced in its cationic H_2pur^+ and H_3pur^{2+} cations. Similar behaviour is observed for the adeninium(1+) cation. In contrast, the adenine base exhibits a large diversity of coordination modes (such as Cu–N9, Cu–N7, Cu–N3 and the bridging modes μ-*N*3,*N*7, μ-*N*7,*N*9 and μ-*N*1,*N*9) which are reinforced by appropriate intra-molecular H-bonding interligand interactions, acting either as H-donor or as H-acceptor. The H-acceptor role is rather infrequent, but it is interestingly used by the less basic N3 in the molecular recognition of the Cu(glygly) chelate and in a polymer derived of Cu(ox)(H_2O) motifs. The H-acceptor role is reasonably enhanced in adeninate(1−) Cu(II) complexes with chelating tri- or tripodal tetra-dentate amines. However, binuclear tetra-μ-*N*3,*N*9-adeninate motifs have proved to display the μ-*N*3,*N*7,*N*9 coordination mode forming the Cu–N7 bond with Cu(II) chelates which in addition are able to build an N6–H···O interligand interaction. Moreover, the *N*9-substitution in adenine clearly favours the formation of a Cu–N7 coordination bond with one N6–H···A intra-molecular interligand interaction.

Guanine and other 6O-purines and their derivatives exhibit an efficient O6 H-acceptor character and thus relevant examples show the molecular recognition pattern involving the formation of the metal–N7 coordination bond reinforced by a suitable O6···H–D (D = O, N) interaction.

Evidence has been found from appropriate comparison that few modifications in the nucleobases or their derivatives or in the other(s) ligand(s) influence the mixed-ligand metal complexes decisively. However, we are far from being able to extend our prediction to all known cases, even in the reduced field that this review focuses on. Perhaps this is because of the influence of crystal packing in the molecular structure of some revised compounds. But we think that in next few years a reasonable understanding of the mixed-ligand complexes, so important in biological systems, will arise, emphasizing their formation as a consequence of the molecular recognition between a binary complex and another ligand.

Adendum in proofs

Recently, two interesting papers have appeared during the refereeing process. One concerns with the compound [Cu(tren)(9Egua)](ClO_4)$_2$ (CCDC 622183) [59] and the other one deals with a mixed-ligand binuclear-Cu(II) complex having two bridging μ-*N*3,*N*9-ade ligands (CCDC 643202) [60]. In addition, a closely related and complementary review by A. Terrón et al. [61] has been published in this journal.

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