# Crystal Structures of an Antiallergic 8-Azapurine (*v*-Triazolo[4,5-*d*]pyrimidine) and its Metal Complex, 3-Methyl-8-azaxanthine Monohydrate and *trans*-Diamminebis(3-methyl-8-azaxanthinato)copper(II) Dihydrate

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*X*-Ray crystal structure analyses of 3-methyl-8-azaxanthine and its diamminecopper(II) complex show that the free base exists as the N(8) tautomer and the metal complex involves a *trans* square-planar copper atom co-ordinated by two deprotonated bases through the N(8) site and by two ammine ligands, suggesting that N(8) in the triazole system has considerable basicity.

The electronic structure of 8-azapurines is important[1] for their biological functions as anticancer[2] or antiallergic[3] agents. One way to study electronic structure is to observe proton or metal ion interactions with these bases, leading to a growing body of crystal structures of 8-azapurines[4] and their metal complexes.[5] However, in contrast to the well characterized protonation or metallation behaviour of natural purines, marked anomalies have been observed[5d] for 8-azapurines. Thus further structural information is required to explain these anomalies or to formulate a rule. There has been only one report[4f] on 8-azaxanthines and no example of their metal complexes. 8-Azaxanthines, including N(3)-substituted 8-azaxanthines, have more effective antiallergic properties than their parent xanthines. We report here the crystal structure of 3-methyl-8-azaxanthine and its diamminecopper(II) complex, showing protonation at the N(8) site in the free base and metal bonding to the same site, thus suggesting that the N(8) nitrogen had considerable basicity in the triazole ring of the 8-azaxanthine system. This is the first reported *X*-ray study of a metal–8-azapurine complex in which the metal ion is attached to N(8). A correlation effect concerning the protonation (and probably metallation) sites for 8-azapurines is briefly mentioned.

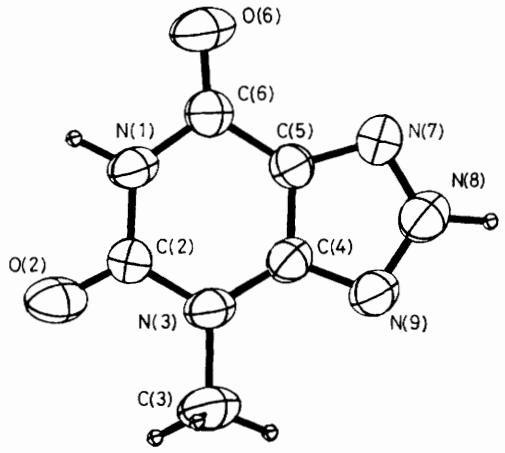


**Figure 1.** Molecular structure of 3-methyl-8-azaxanthine (**1**), showing the triazole protonation at N(8).

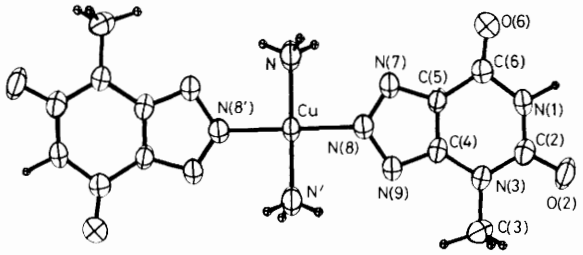


**Figure 2.** Molecular structure of *trans*-diamminebis(3-methyl-8-azaxanthinato)copper(II) (**2**), showing the metallation at N(8).

3-Methyl-8-azaxanthine (**1**) and its diamminecopper complex (**2**) were prepared according to the literature.[6] The molecular structure of the free base (**1**) is shown in Figure 1.† Unfortunately, in spite of a careful study of the difference Fourier map, the triazole proton could not be located. However, the geometry of the triazole moiety suggested that the hydrogen is attached to N(8), as indicated by the larger internal angle at N(8) [117.1(1)°] and the smaller and similar internal angles at N(7) and N(9) [102.6(1) and 102.1(1)°]. These values are comparable to those of other N(8)-protonated 8-azapurines.[4a–f,5c] Chemically, the tautomer having the N(8) site protonated is more stable than the other contributing tautomers for 8-azaxanthine, on the basis of bond energy considerations.[4f] Moreover, N(8) protonation is compatible with the hydrogen bonding scheme; N(8) forms a hydrogen bond with a water molecule [N(8)· · ·O(W) 2.675(3) Å], which in turn participates in hydrogen bonds with two neighbouring bases through O(6) and N(9) [2.789(3) and 2.911(3) Å]. There are two inter-base hydrogen bonds across a centre of symmetry [N(1)· · ·O(2) 2.825(3) Å], but no base–base stacking interactions.

The molecular structure of the metal complex (**2**) is shown in Figure 2.† The copper atom, which lies on a crystallographic centre of symmetry, is co-ordinated to two *trans*-arranged ammine ligands [Cu · · · N 1.996(7) Å] and to two 3-methyl-8-azaxanthinato ligands through N(8) [Cu · · · N(8) 2.024(7) Å]. By symmetry, the geometry around the metal centre is strictly planar with N(8)–Cu–N angles of 89.5(4) and 90.5(4)°. The aza-base is nearly co-planar with the square plane with a dihedral angle of 23.3°, indicating no steric constraints between the ligands. This is the first *X*-ray structure of a metal complex of 8-azapurine in which the N(8) site is involved in metal co-ordination, although a closely related structure is available, *i.e.*, [$Cu^{II}Cl_4$(5-amino-4-carboxamidiniotriazole)$_2$],[5a] a metal complex of a hydrolysis product of 8-aza-adenine which is believed to be produced by assistance of metal co-ordination at N(8). The internal angle at N(8) [113.8(5)°] is slightly but significantly affected by metallation but the effect is not so prominent as that resulting from protonation; the average value of the internal angle at N(8) in seven N(8)-deprotonated 8-azapurines is 109.2°, while that in seven N(8)-protonated 8-azapurines is 117.3°. This metallation effect is rather uncommon, as compared with minor effects observed[7] in metal–purine complexes. There are extensive base–base stacking interactions (3.53 and 3.40 Å average spacings), but no inter-base hydrogen bonds. The ammine group has no close contacts other than metal co-ordination.

The most interesting structural feature is that protonation in the free base and metallation occur at the same N(8) site; metal co-ordination at N(8) is somewhat unexpected because of the possibility of forming an intramolecular hydrogen bond between the exocyclic carbonyl O(6) of the base and an ammine ligand, which favours metal bonding to N(7), as is the case for [$Cd^{II}(H_2O)_4$(8-azahypoxanthinato)].[5b] Thus this observation strongly suggests considerable basicity of the N(8) nitrogen.

It has been well documented[5c] by Hodgson and co-workers that substitution of nitrogen for C(8) in the purine ring lowers the basicity of N(7) and increases the basicity of N(3), reversing the basicity order for the purine system. In fact, protonation does not occur at N(7) in all the known 8-azapurine structures, and instead protonation frequently occurs at N(3) in the cationic 8-azapurines; the N(7)–metal bonded Cd–8-azahypoxanthinato complex[5b] is an exception. We note here an additional prominent correlation effect concerning the protonation (and probably metallation) site for the triazole nitrogen atoms; *i.e.* when N(3) is substituted by a group such as a proton, an alkyl group, or a metal ion, protonation (or metallation) mostly occurs at N(8), whereas, when N(3) is not substituted, it predominantly occurs at N(9). The former examples include cationic, 2,6-diamino-8-azapurine,[4a] 8-aza-adenine,[4b] 8-azaguanine,[4c,d] 3-methyl-8-azaguanine,[4e] N(3)-$Zn^{II}$ bonded 8-aza-adenine,[5c] neutral 8-azaxanthine[4f] and the present 3-methyl-8-azaxanthine [and its $Cu^{II}$ complex in which the anionic ligand is metallated at N(8)]; the only exception is the N(3)-$Hg^{II}$ bonded neutral 8-aza-adenine[5d] in which N(9) protonation is favoured by

† *Crystal data:* $C_5H_5N_5O_2\cdot H_2O$, (**1**), monoclinic, space group $P2_1/c$, $a$ = 7.976(1), $b$ = 5.898(1), $c$ = 16.335(2) Å, $\beta$ = 97.54(1)°, $U$ = 761.8(2) Å$^3$, $Z$ = 4, $R$ = 0.047 for 1047 reflections [$F_o \geq 4\sigma(F_o)$; $2\theta \leq 50°$]. *trans*-[$Cu(NH_3)_2(C_5H_4N_5O_2)_2]\cdot 2H_2O$, (**2**), triclinic, space group $P\bar{1}$, $a$ = 8.811(2), $b$ = 7.985(2), $c$ = 6.934(1) Å, $\alpha$ = 99.62(1), $\beta$ = 83.32(1), $\gamma$ = 115.01(1)°, $U$ = 435.3(1) Å$^3$, $Z$ = 1, $R$ = 0.046 for 1706 reflections [$F_o \geq 4\sigma(F_o)$; $2\theta \leq 55°$]. Intensity data were collected on a Rigaku diffractometer with graphite-monochromated Mo-$K_\alpha$ radiation. Structures were solved by direct methods for (**1**) and Patterson methods for (**2**). Full-matrix least-squares refinement; anisotropic thermal parameters for all non-H atoms. All H atoms of (**1**) and (**2**) were located from a difference Fourier map except for two H atoms of a water molecule and N(8)-H for (**1**) and N(1)-H for (**2**), for which the atomic positions were calculated from the known stereochemistry. The H atom positions were not refined but included in the structure factor calculations in the final cycles of the refinement with the isotropic thermal parameters of the atoms to which they are bonded. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.

interligand hydrogen bond formation with a bound chloride ion. Examples of N(3) unsubstituted compounds include the neutral 8-azaguanine[4g] and two 8-azahypoxanthine derivatives[4h] [and N(9)-$Hg^{II}$ bonded anionic 8-azahypoxanthine[5d]]; exceptions are the neutral 8-azahypoxanthine[4i] and its derivative[4h] in which N(8) is protonated. Clearly, more crystallographic studies are necessary to examine further this prediction, and in particular to elucidate which factors are responsible for N(9) or N(8) protonation in N(3)-unsubstituted 8-azapurines.

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