Directed Metallation of Adenine-N^3 *via* Nucleobase–Ligand Conjugation

Clayton Price, Mark R. J. Elsegood, William Clegg and Andrew Houlton*†

Department of Chemistry, Bedson Building, University of Newcastle upon Tyne, Newcastle upon Tyne, UK NE1 7RU

The crystal and molecular structure of a copper complex prepared by reaction of metal salt with the nucleobase–ligand conjugate, ethylenediamine-*N*,9-propyladenine, reveals the unprecedented coordination of adenine-N^3.

Purine and pyrimidine nucleoside bases play fundamental roles in biology and are used extensively as therapeutic agents.[1,2] That metal ions interact with these bases is very well established, and this chemistry is now known to be the basis of antitumour drug action and is also exploited in the heavy-metal staining of RNA/DNA.[4–6] Many studies on the interaction of transition metals with nucleoside bases have focused on modelling the binding to the DNA-polymer by using N^9-substituted purines and N^1-substituted pyrimidines in an effort to determine the preferred metal binding sites. These have been established as N^7 of purines and the oxygen and N^3 sites on pyrimidines, although examples of metallation at other donor sites are known.[6]

A notable exception to this is the N^3 site of adenine, which has been observed to coordinate only for unsubstituted adenine, and then only in concert with N^9 to form polynuclear complexes.[6] With these examples excluded, metallation, at N^3 has not been observed.

We are interested in synthesizing metal-containing nucleoside analogues where the metal–base interactions are modified. The ability to redirect the site of metallation, for instance, may ensure that the capability of the nucleobases to take part in biological molecular recognition events, *e.g.* enzyme–substrate binding, is not severely impaired. Compounds of this type would then be of interest for their potential as therapeutic agents and also as small nucleolytic agents for use in molecular biology. As such N$^3_{ade}$ represents an interesting target site for metallation as it is located in the minor groove of the DNA duplex, and would not be expected to be involved in protein–DNA binding interactions. Our initial approach towards the preparation of such compounds has been through directed metallation using nucleobase–ligand conjugation. Here we report the synthesis and crystal and molecular structure of a mononuclear copper–adenine complex, **1**, based on an adenine–ethylenediamine conjugate which contains N^9-blocked adenine binding through N^3 for the first time.

To an aqueous solution of copper(II) nitrate hemipentahydrate an excess of ethylenediamine-*N*,9-propyladenine hydrochloride was added in water–Me_2SO.‡ On addition of the ligand the colour of the solution darkened. On slow evaporation blue crystals of **1** were obtained and the single-crystal X-ray structure was determined.§

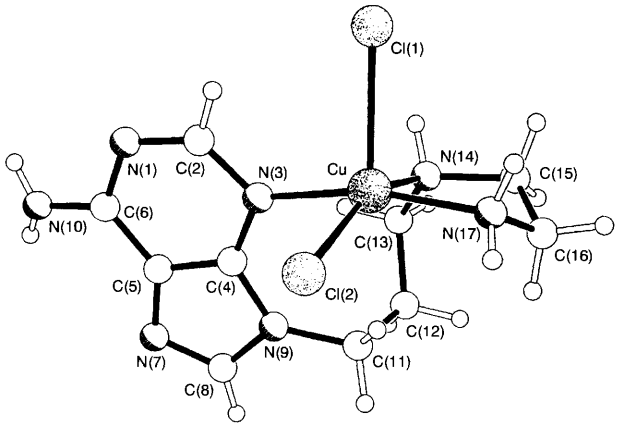
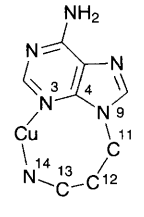


Fig. 1 Molecular structure of **1** showing the distorted square-pyramidal coordination geometry and the eight-membered chelate ring formed by chelation of copper by N(3) and N(14). Only the chloride ion Cl(2) is shown at the disordered site for clarity.

Fig. 1 shows the molecular structure of **1**. The copper is five-coordinate in a distorted square-pyramidal geometry. The metal is bound by three nitrogen donor atoms, one of which is adenine N(3). Such binding is *unprecedented* for an N^9-substituted adenine derivative and **1** represents the *first* mononuclear complex involving N$^3_{ade}$–metal binding. The remaining N-donor atoms are from the ethylenediamine group. The Cu–N distances are Cu–N(3) 2.018(2), Cu–N(14) 2.070(2) and Cu–N(17) 1.996(2) Å, (Cu–N_{av} = 2.028 Å). The fourth basal coordination site is disordered between chloride and nitrate (ratio 38 : 62). However, either of the distances to the disordered anion is shorter than the apical Cu–Cl(1) distance, which at 2.560(8) Å compares with 2.408(6) Å for Cu–Cl(2) and 1.985(3) Å for Cu–O(3). The copper ion lies 0.35 Å out of the plane formed by N(3)N(14)N(17)Cl(2) [−0.08 Å out of the plane formed by N(3)N(14)N(17)O(3)]. As a result of the metallation the bond lengths N(3)–C(2) and N(1)–C(2) are increased and decreased, respectively, [N(3)–C(2) 1.341(3) Å in **1** *cf.* 1.304(5) Å in 9-MeAde and N(1)–C(2) 1.328(3) Å in **1** *cf.* 1.355(5) Å in 9-MeAde].[8] The remaining intraring distances are not significantly affected. The tridentate binding mode of the adenine–ethylenediamine conjugate generates an eight-membered chelate ring formed by N(14) and N(3). The chelate ring adopts a boat-type conformation as shown schematically below. The fold angles between planes formed by CuN(3)N(14), N(14)N(3)C(13)C(4), C(13)C(4)C(12)N(9) and C(12)N(9)C(11) are also indicated in Fig. 2.

Previous structural studies of adenine complexes have revealed a diverse range of structural types and binding modes.[5,6,9–19] For instance, adenine can act as either a neutral or an anionic unidentate ligand *via* N^9. Representative examples of this coordination mode are the octahedral[9] $[Cu(HAde)_2Br_2]Br_2$ (adenine protonated at N^1) and the mixed ligand complexes [Cu(dien)$(Ade)_2$] (dien = diethylenetriamine) and [Cu(tren)(Ade)]Cl [tren = tris(2-aminoethyl)amine].[10,11] Only in higher nuclearity complexes has binding by N^3 been observed, and this is always in conjunction with N^9. Dinuclear species are those based on copper,[12,13] $[Cu_2(Ade)_4Cl_2]Cl_2$ and $[Cu_2(HAde)_4(H_2O)_2][ClO_4]_4$, and non-copper examples have also been reported in the cases of Pd and Ag.[14,15] In these complexes adenine acts as a bridging ligand, coordinating *via* N^9 and N^3, and this same coordination mode is seen in a trinuclear species isolated at low pH.[16]



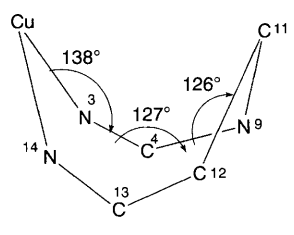


Fig. 2

When the N^9 site is blocked, by the glycosidic bond in adenosine or through alkylation as in 9-methyladenine (9-MeAde), coordination has previously been observed exclusively *via* N^7 for copper, and N^7 and N^1 for other metals.[6] Structural examples of Cu–N^7 binding[17,18] are seen in $[Cu(9\text{-}MeAde)_2(H_2O)_4]Cl_2$ and $[Cu(9\text{-}MeAde)(H_2O)_5]SO_4$ and also in mixed-ligand systems containing 9-MeAde.[19]

The coordination of N^3 in **1** clearly reflects the effect of the ethylenediamine group in directing the site of metallation and confirms that the preferred nucleobase binding modes can be modified through multidentate ligand conjugation. It is as a result of this that the complex may participate in both Watson–Crick and Hoogsteen base-pair interactions, the latter of which is inhibited by undirected metallation which occurs at N^7.[1,6]

Hoogsteen-type interactions are indeed exhibited in **1**, with the formation of hydrogen-bonded chains, generated through translation along the crystallographic *a*-axis (Fig. 3). Hydrogen bonds are formed between N(7) and N(17)H and N(10)H and between Cl(1) on adjacent molecules in the chain [N(7)···N(17) 3.104, N(10)···Cl(1) 3.251 Å]. These chains are crosslinked *via* hydrogen bonds between N(10)H and Cl(1) [N(10)···Cl(1) 3.324 Å] which form sheets with chloride/nitrate anions alternating above and below the plane.

The potential of metal complexes to act as therapeutic agents is well established and copper complexes are known to exhibit antitumour activity.[2] The results presented here demonstrate that nucleobase–ligand conjugation is capable of invoking atypical metallation reactions and represent a novel addition to the nucleobase–metal complexes isolated to date. In **1**, the site of metallation retains the nucleobase's ability to take part in molecular recognition events, as illustrated by the Hoogsteen-type hydrogen-bonding interactions which are precluded in N^7-metallated derivatives. As a result, this general approach may provide a rich source of biologically active compounds with the potential for inhibition of DNA synthesis. Studies on the interaction of these and similar compounds with nucleic acids and whole cell systems are in progress.

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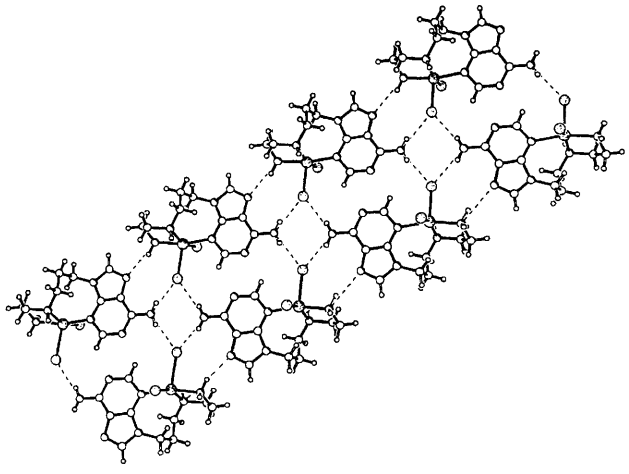

Fig. 3 Hydrogen bonded chains formed by Hoogsteen-type interactions between adjacent molecules involving N_{ade}···NH and NH_{ade}···Cl interactions. These chains are themselves crosslinked to generate sheets *via* NH_{ade}···Cl interactions.

Footnotes

† email: andrew.houlton@newcastle.ac.uk

‡ Ethylenediamine-*N*,9-propyladenine hydrochloride was prepared from reaction of 9-(3-chloropropyl)adenine[7] with ethylenediamine in 54% yield. Analysis: calc. for $C_{10}H_{18}ClN_7$: C, 44.20; H, 6.68; N, 36.08. Found: C, 43.60; H, 6.31; N, 34.70%.

§ *Crystal data* for **1**: $C_{10}H_{17}Cl_{1.38}CuN_{7.62}O_{1.86}$, blue crystal of dimensions 0.44 × 0.14 × 0.10 mm, M = 386.19, monoclinic, space group $P2_1/c$, a = 9.7759(10), b = 10.0962(10), c = 15.037(2) Å, β = 96.660(2)°, U = 1474.1(3) Å^3, Z = 4, $F(000)$ = 791, D_c = 1.740 g cm^{-3}, μ(Mo-Kα) = 1.751 mm^{-1}. 7660 reflections (2930 unique with R_{int} = 0.0269) were collected on a Siemens SMART CCD area detector diffractometer with narrow frames (0.3°) and three-dimensional profile fitting using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were collected at 160 K and were corrected for absorption semiempirically by psi-scans. Cell parameters were refined by locally written software from the positions of 5529 reflections in the range $1.36 \leqslant \theta \leqslant 26.36°$ with $I > 10\sigma(I)$. The structure was solved by direct methods and refined by full-matrix least squares on F^2 values. All non-H atoms were refined anisotropically, H-atoms were constrained except for H(10A) and H(10B) where the coordinates were freely refined to give a final $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ of 0.0764, conventional R = 0.0327 [for F values of 2676 reflections with $F^2 > 4\sigma(F^2)$]. One coordination site at Cu was occupied partially by chloride [38.2(5)%], and partially by nitrate [61.8(5)%]. Programs: Siemens SHELXTL, SMART and SAINT software for data collection and reduction, and local programs.

Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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