

Mono-, di- and tri-dentate binding modes of a substituted isocytosine derivative in complexes of palladium and zinc

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The crystal and molecular structures of three metal complexes of the pyrimidine derivative, 1-(2-hydroxyethyl)-(2-aminoethyl-*N*²)-5-methylisocytosine reveal that, as a ligand, this heterocyclic base exhibited a diverse range of co-ordination modes. With zinc(II), monodentate co-ordination *via* the carbonyl oxygen of the pyrimidine base was observed. In the case of palladium(II), both a didentate mode, *via* endo- and exo-cyclic nitrogen donors, and a tridentate mode, involving exocyclic nitrogens and the alcohol oxygen donors, was observed. In the latter case the pyrimidine exists in the rare iminooxo tautomeric form.

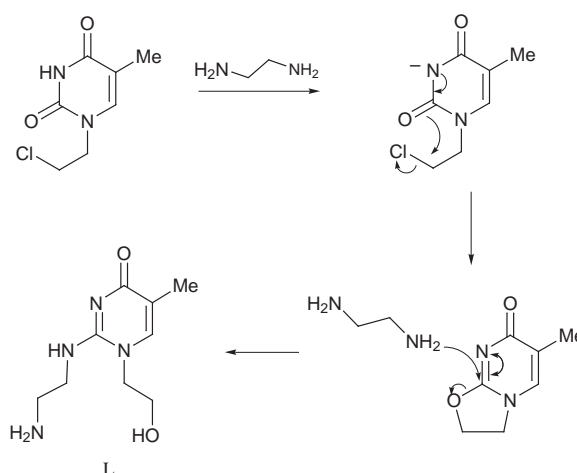
Studies on the interactions of metal ions with purine and pyrimidine bases are central to bioinorganic chemistry.^{1,2} While the predominant binding sites are now well established, an increasing number of reports indicate that metal binding may occur at relatively unreactive sites in both biological and model systems with significant consequences.^{1,3–10} For example, such binding has been shown to stabilize rare tautomeric forms,^{7,8} and this may be an important factor in the general toxic effect of metal ions, since base-pair mismatching can result.^{1,7,8}

We have recently begun to explore the co-ordination chemistry of modified nucleobase derivatives which feature tethered chelating groups.^{9,10} For the purines adenine and guanine, the effect of such a tether is profound with the result that nucleobase–metal binding occurs at typically unreactive sites, such as N³ or C⁸.^{9,10} Having extended these ideas to pyrimidines, we report here on the reaction of 1-(2-chloroethyl)thymine with ethylenediamine, which results in a rearrangement to form a substituted isocytosine derivative. Some aspects of the co-ordination chemistry of this substituted pyrimidine have been explored and we present the crystal and molecular structures of complexes containing zinc(II) and palladium(II).

Results and Discussion

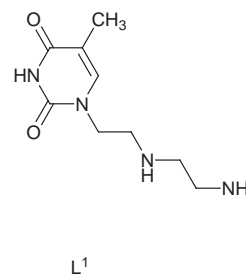
Synthesis

Reaction of 1-(2-chloroethyl)thymine¹¹ with excess ethylenediamine yields 1-(2-hydroxyethyl)-(2-aminoethyl-*N*²)-5-methylisocytosine, L, as a hydrochloride salt. A proposed mechanistic scheme for the reaction is shown in Scheme 1. On the basis of NMR experiments alone an unequivocal assignment of structure L rather than 1-{2-[(2-aminoethyl)amino]ethyl}thymine, L¹, is difficult. The expected sets of four triplets of the two ethyl chains are apparent, as is the C⁵–CH₃ group. The through-space interaction between the C⁶ proton and the N¹-bonded methylene group, seen in the ROESY spectrum, confirm alkylation at N¹, but none of these allows discrimination between L and L¹. The absence of a broad resonance at δ ≈ 11.0, typically seen for the imide proton at N³, and the reduction in intensity of the carbonyl stretching vibrations in the infrared spectra compared to 1-(2-chloroethyl)thymine are however suggestive of some



Scheme 1 Proposed mechanism for the formation of L from 1-(2-chloroethyl)thymine

modification of the pyrimidine moiety. Conclusive proof for the structure of L was obtained from X-ray crystallography (see below).



Co-ordination chemistry of L. *Zinc(II).* Reaction of [LH]⁺Cl⁻ with ZnCl₂ in water (1 : 1 molar ratio) followed by concentration and the addition of ethanol produced, on standing, colourless crystals of 1, [ZnCl₃(LH)], suitable for X-ray analysis.

Owing to the acidic nature of the reaction media (pH 0.8) the pH-dependence of the species present in solution was investigated. From electrospray MS, an aqueous solution of the complex at pH 7.1 contained peaks at *m/z* 213 (*M*⁺, LH) and 171

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Table 1 Selected bond lengths (Å) and angles (°) for compounds 1–3

	1	2	3*
N(1)–C(2)	1.362(5)	1.360(6)	1.361(11)
C(2)–N(2)	1.343(5)	1.332(7)	1.323(10)
C(2)–N(3)	1.332(5)	1.351(6)	1.364(11)
N(3)–C(4)	1.349(5)	1.391(6)	1.387(10)
C(4)–O(4)	1.273(5)	1.237(6)	1.242(10)
C(4)–C(5)	1.437(5)	1.446(7)	1.432(13)
C(5)–C(6)	1.343(6)	1.343(7)	1.358(12)
C(6)–N(1)	1.399(5)	1.370(7)	1.376(10)
M–O(4)	2.014(3)		
M–N(2)			2.040(7)
M–N(3)		2.044(4)	
M–N(12)		2.039(4)	1.987(7)
M–Cl(1)	2.2835(12)	2.2970(12)	2.303(2)
M–Cl(2)	2.3125(12)	2.3185(12)	
M–Cl(3)	2.2677(14)		
M–O(1)			2.045(6)
C(2)–N(3)–C(4)	119.6(4)	121.6(4)	126.1(7)

* Average values of independent molecules A and B of compound 3.

(M^- , $[ZnCl_3]^-$), while at pH 0.8 the positive-ion spectrum also contained peaks at 279 [M^+ , $Zn(LH)$], and a higher molecular weight ion at 491 [M^+ , $Zn(LH)_2$]. Proton NMR spectra of aqueous solutions of the isolated product were measured over a similar pH range (0.8–7.1). The spectra show only one set of signals for the ligand, indicating that if multiple complexes are present they are in fast exchange. Furthermore, no significant changes in the spectral features were observed over the pH range.

Palladium(II). From 1H NMR spectroscopic and ES-MS studies it is evident that the reaction of Pd^{2+} with LH^+ does not yield a single species in solution. Indeed, two different products were isolated from the reactions with LH^+ (see below).

Monitoring the reaction of K_2PdCl_4 and LH^+ with 1H NMR spectroscopy revealed that the reaction yields a complex mixture of species over time. Monitoring the signals from the C(5)–Me group, initially one major (C) and two minor species (D and E) were formed. After 15 min all the ligand had reacted and a new major species (A) was detected in addition to the previous signals. Over a period of 2 h the concentration of A reduced and a new minor species B was detected along with an increase in D and E. Over the next 18 h no additional species were detected, though the relative concentrations of B, D and E gradually increased as A decreased. Electrospray MS of the reaction media indicated the presence of ions at m/z 355 [M^+ , $PdCl(L)$], 317 [M^+ , $Pd(L)$]. The negative ionization for this reaction mixture was very poor and peaks corresponding to $[PdCl_4]^{2-}$ or $[Pd_2Cl_6]^{2-}$ were not easily discerned.

From a preparative scale reaction, following work-up, these conditions yielded unreacted K_2PdCl_4 , $[PdCl_2L]$ **2**, and a third material, $[PdClL]_2[Pd_2Cl_6]$ **3** (all three species were identified by their unit cell parameters). Compound **2** was also isolated as the major product from the reaction with $PdCl_2(MeCN)_2$. Electrospray MS data of the reaction media containing $PdCl_2(MeCN)_2$ and LH^+ revealed the presence of the following complex ions: m/z 443 $\{M^-, [PdCl_3(L)H_2O]^+\}$, 440 [M^+ , $PdCl(LH)(MeCN)_2 + 2H$], 425 $\{M^-, [PdCl_3(L)]\}$, 396 [M^+ , $PdCl(LH)MeCN$], 355 [M^+ , $PdCl(L)$], 317 [M^+ , $Pd(L) - H$]. These data reveal that a mixture of products is formed in solution, of which two (compounds **2** and **3**) were isolated and studied by single-crystal X-ray structure analyses.

Crystal and molecular structures of 1, 2 and 3

Table 1 presents selected structural parameters for compounds 1–3. In compound **1**, $[ZnCl_3LH]$, the zinc ion adopts a distorted tetrahedral geometry with a $\{3Cl, 1O\}$ donor set involving the

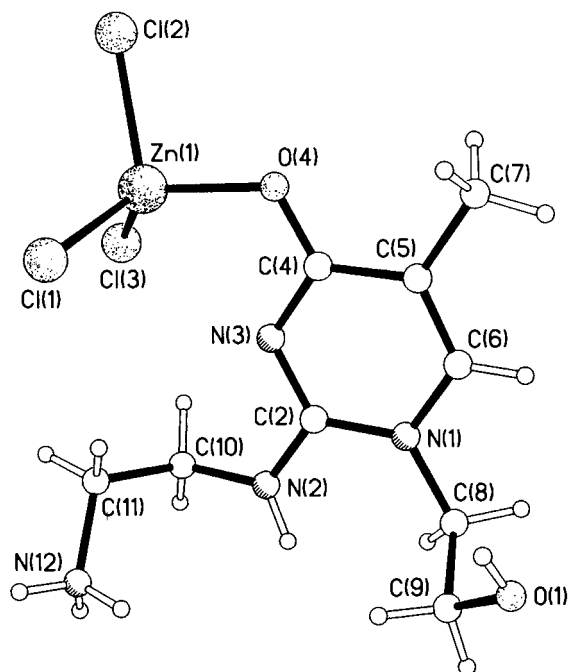


Fig. 1 Molecular structure of compound **1** showing the co-ordination geometry around zinc and the ligation by the carbonyl oxygen O(4)

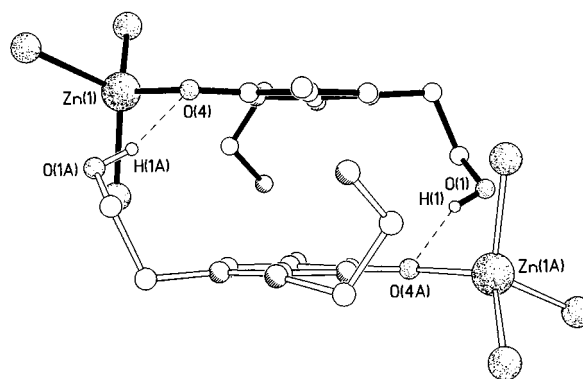


Fig. 2 Hydrogen-bonded dimers of compound **1** related through inversion centres generating an $R_2^2(18)$ motif

carbonyl oxygen O(4) of the pyrimidine (see Fig. 1). Bond lengths to the metal ion are Zn(1)–Cl(1) 2.2835(12), Zn(1)–Cl(2) 2.3125(12), Zn(1)–Cl(3) 2.2677(14) [$Zn(1)–Cl_{ave} = 2.288$ Å] and Zn(1)–O(4) 2.014(3) Å. The zinc-bound O(4) is also involved in intermolecular hydrogen-bonding interactions with the alcohol proton O(1)H [O(4)···O(1A) 2.90 Å] generating an $R_2^2(18)$ motif with dimers formed through an inversion centre (Fig. 2). Within a dimer the two aromatic rings are slipped with respect to one another; the vertical distance between the ring planes is 3.458 Å. Further hydrogen bonding exists, involving both the N(12)H $_3^+$ and the N(2)H group protons with metal-bound chloride ions [N(2)···Cl(1) 3.200, N(2)···Cl(2) 3.209, N(2)···Cl(3) 3.166 Å]. The two pendant ethyl chains of the molecules, although interacting with neither the metal nor with one another, lie on the same face of the aromatic ring. The geometry of N(2) is essentially trigonal [C(2)–N(2)–C(10) 122.0(4)°] indicating delocalization of the lone pair into the aromatic ring [H(20) was clearly located in the planar bisecting position in the difference map, then included in a constrained position for refinement].

A few structural reports have been made on alkylaminopyrimidines, though to the best of our knowledge none of their metal complexes.¹² The carbonyl bond lengths in 2-(5-bromo-3-methyl-2-pyridyl)butylaminopyrimidin-4-one,¹³ 1-methylcytosine¹⁴ and isocytosine¹⁵ are 1.249, 1.234 and 1.248 Å, respect-

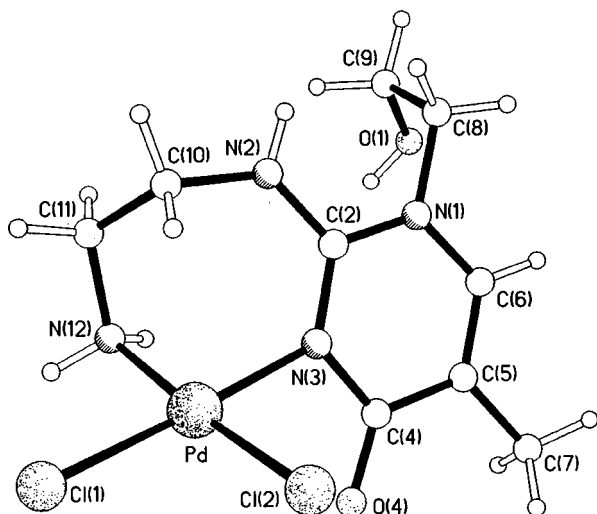


Fig. 3 Molecular structure of compound 2 showing the distorted square planar co-ordination geometry and the seven-membered chelate ring formed by N(12) and N(3) binding to palladium

ively. By comparison the equivalent C(4)=O(4) in **1** is longer at 1.273 Å, as may be expected due to metal co-ordination and is also longer than that seen in Zn(L²)₂(H₂O)₂ (HL² = 6-carboxyuracil) (1.244 Å) despite the fact that the metal is chelated through O⁴ and the oxygen of the C⁶-bound acid group.¹⁶

If comparison with nucleobases is to be made it is most appropriate for cytosine, as here both a carbonyl and amino function are present, although these are in the 2- and 4-positions, respectively. Crystallographically characterized Zn^{II} complexes of cytosine reveal that N³ is a general binding site,^{17,18} though in the trinuclear [Zn₃(OH)₂(1-MeCyt)₈][NO₃]₄ either of N³ or O² acts as donor atom.¹⁹ The Zn–O² bond lengths range from 2.010–2.046 Å. The C=O bond lengths are longer, at ≈1.24 Å, compared with the 1.234 Å of 1-methylcytosine,¹⁵ though again this is less than observed in **1**.

Fig. 3 shows the molecular structure of [PdCl₂L] **2**. The palladium adopts a distorted square planar co-ordination geometry comprising a {2Cl, 2N} donor set, which involves the formation of a seven-membered chelate ring resulting from the endocyclic N(3) and exocyclic N(12) donor atoms binding to the metal. The bond lengths to palladium are Pd–N(3) 2.044(4), Pd–N(12) 2.039(4), Pd–Cl(1) 2.2970(12) and Pd–Cl(2) 2.3185(12) Å. The Pd–N bond length is typical for N³-palladated pyrimidines.²⁰ The angle between the co-ordination plane and the pyrimidine ring is 115°. The mode of ligation in **2** is analogous to that seen in [Zn(H₂O)₂L³] (HL³ = 2-hydrazino-4-hydroxy-6-methylpyrimidine) where the pyrimidine also acts to chelate the metal *via* N³ and the terminal NH₂ group of the hydrazino function, here forming a five-membered ring.²¹

Extensive intermolecular hydrogen bonding is observed within the crystal structure of **2**. Among these are the interactions between carbonyl oxygen O(4) with an N(2)H proton of the adjacent molecule [N(2)⋯O(4) 2.901 Å] and several involving the co-ordinated chloride ions [*e.g.* Cl(2)⋯O(1) 3.255, Cl(2)⋯N(12) 3.440 Å]. Fig. 4 shows the infinite chains generated through the first two such interactions.

Compound **3**, isolated as a minor component of the reaction of [LH]⁺Cl[−] with K₂PdCl₄, comprises [PdClL]₂[Pd₂Cl₆] and contains two crystallographically independent, though chemically equivalent, [PdClL]⁺ cations. The distorted square planar metal ion in the cation comprises a {1Cl, 2N, 1O} donor set (Fig. 5). The ligand L adopts a tridentate binding mode utilising N(2), N(12) and the alcohol oxygen O(1) as donors. Bond lengths to Pd, averaged over the two independent molecules A and B are Pd–Cl 2.303(2), Pd–N(2) 2.040(7), Pd–O(1) 2.045(6), Pd–N(12) 1.987(7) Å. The angles between the co-ordination

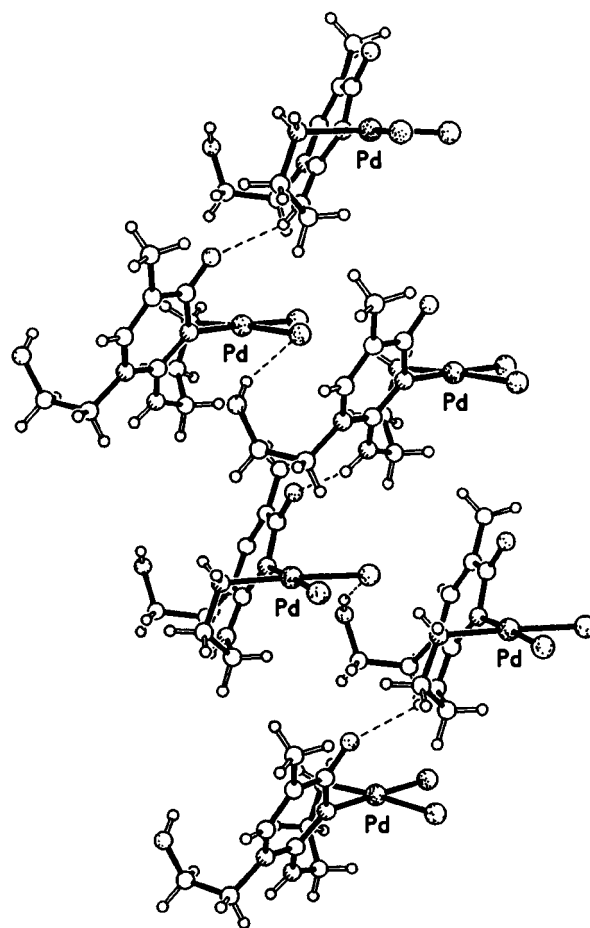


Fig. 4 Hydrogen-bonding interactions in the crystal structure of **2**. Intermolecular interactions involving C(4)=O⋯H₂N(2) and OH⋯Cl–Pd generating a chain motif

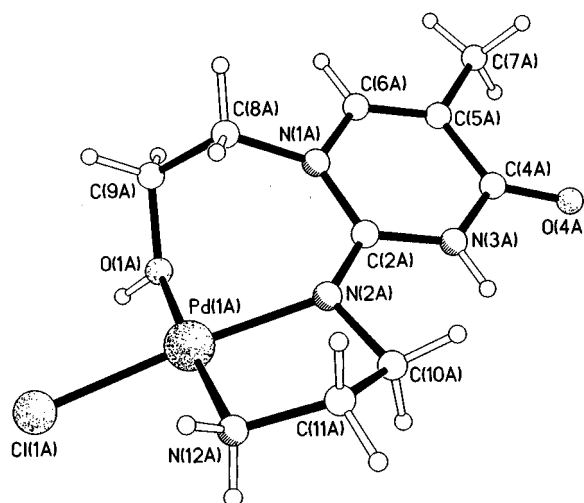


Fig. 5 Molecular structure of one of the cations in **3** highlighting the tridentate binding mode involving five- and seven-membered chelate rings

planes and the pyrimidine ring are 36 and 39° for molecules A and B respectively. The [Pd₂Cl₆]^{2−} anions have typical Pd–Cl distances.¹²

Intermolecular hydrogen-bonding interactions in the crystal lattice involving the pyrimidine ring are distinct for the two independent molecules. For molecule A, N(3)H interacts with occluded water [N(3A)⋯O(100) 2.929 Å], while for molecule B, a chain motif is formed through interactions between N(3B)⋯Cl(1B) and O(4)⋯O(1)H [N(3)⋯Cl(1) 3.399, O(4)⋯O(1) 2.573 Å].

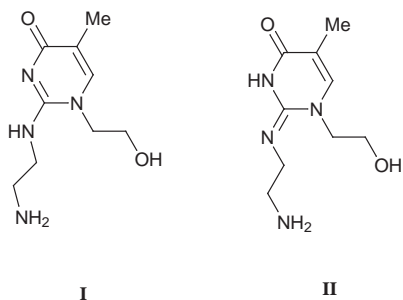


Fig. 6 Aminooxo (I) and iminooxo (II) tautomeric forms of L

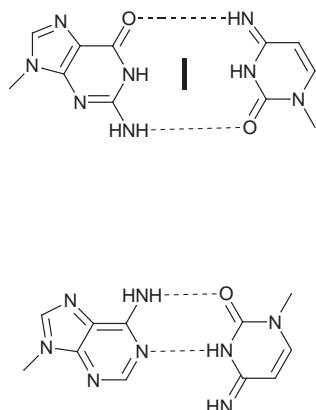


Fig. 7 Incompatible hydrogen-bonding interactions for the G-C pair (top) containing the iminooxo tautomer, and mismatched base pair between A-C (bottom)

A search of the Cambridge Structural Database¹² reveals that complexes of 1-alkylcytosine generally prefer N³ as the binding site.²⁰ However, other modes of co-ordination involving N⁴ are known.²² Bond lengths for the exocyclic amino group of cytosine binding to Pd^{II} as an anionic donor group lie in the range 1.973–2.014 Å and compare with a Pd–N(2) distance of 2.040(7) Å in **3**.²²

A significant difference in **3** compared to **1** and **2** is that the pyrimidine ring exists in a different tautomeric form. Two principal resonance structures, **I** and **II**, may be written for the pyrimidine (Fig. 6). Evidence suggestive of the iminooxo tautomer in **3** was obtained by consideration of the bond lengths within the pyrimidine ring (refer to Table 1). The C(2)–N(3) bond in **3** is longer [1.364(11) Å] than that observed in **1** and **2** [1.332(5) and 1.351(6) Å, respectively]. The greater bond length in **3** is indicative of single bond character, and conversely in both **1** and **2** greater double bond character is apparent. It should be noted that due to the effect of N(3) metallation the bond length is greater in **2** than in **1**. The C(2)–N(2) bond length in **3** [1.323(10) Å] is shorter than that observed in **1** [1.343(5) Å] and **2** [1.332(7) Å]. Again these bond length data are consistent with the pyrimidine existing as the iminooxo tautomer in **3** and the aminooxo tautomer in both **1** and **2**. Further support for the existence of L as the iminooxo tautomer in **3** is gained from the bond angle data of the three complexes. The large value of the angle at N(3) [126.1(7)°] in **3** agrees with a proton being bonded to this nitrogen. Generally the angle is significantly smaller in cases where the N(3) site carries no proton, as in isocytosine (119.7°) for example. In **1** the angle is 119.6(4)°, again as expected for form **I**. Finally, an analysis of difference electron density maps gave a clear indication as to the location of indicative protons in the three structures: N(2) in **1** with no peak near N(3), a single proton on N(2) in **2** and a single proton on N(3) for both molecules in the structure of **3**.

Lippert and co-workers have reported on various metal-stabilized rare tautomers of the nucleobases adenine⁷ and cyto-

sine.⁸ These latter examples are highly comparable to the case of **3**, particularly the complexes *trans,trans,trans*-[Pt(NH₃)₂(OH)₂(1-MeCyt-N⁴)₂]²⁺ and *trans*-[Pt(NH₃)₂(1-MeCyt-N⁴)₂]²⁺ (1-MeCyt = 1-methylcytosine).⁸ The authors have discussed the biological implications of these metal-stabilized tautomers with respect to DNA base-pair mismatching, and it is of interest to consider such effects here. Stabilization of the iminooxo form should preclude base-pairing with guanine but allow for mismatching with adenine or thymine for example (Fig. 7). The data presented here further indicate that Pd^{II} binding at the exocyclic nitrogen donors can stabilize the iminooxo form.⁸

Conclusion

The substituted pyrimidine, 1-(2-hydroxyethyl)-(2-aminoethyl-N²)-5-methylisocytosine, has been shown to bind metal ions as a mono-, di- and tri-dentate ligand, the last two examples being observed for Pd^{II}. In addition to exhibiting different modes of co-ordination, the pyrimidine moiety in the two Pd^{II} complexes exists in different tautomeric forms, with the iminooxo form associated with the tridentate binding mode involving co-ordination to the N(2) amino group. This result further indicates that metal-ion binding at the exocyclic nitrogen atoms of nucleobases may induce nucleobase tautomerism and is thus implicated as a mechanism for metal-based mutagenicity.

Experimental

The NMR data were measured on a JEOL Lambda 500 instrument with either D₂O or (CD₃)₂SO as solvent.

Syntheses

1-(2-Hydroxyethyl)-(2-aminoethyl-N²)-5-methylisocytosine hydrochloride [LH]⁺Cl⁻. 1-(2-Chloroethyl)thymine¹¹ (1.00 g, 5.79 mmol) was stirred with an excess of ethylenediamine (5 ml, 75 mmol) at room temperature under an atmosphere of nitrogen for 24 h. Excess ethylenediamine was removed under reduced pressure, the resultant yellow viscous liquid was taken up in ethanol (10 ml). The mixture was warmed gently, after a short time a white solid precipitated. The resultant crude product was recrystallized from ethanol (25 ml). The white solid (0.89 g, 62%) was collected by filtration, washed with cold ethanol and air dried. ¹H NMR [(CD₃)₂SO]: δ 1.73 (s, 3 H, pyrimidine CH₃), 2.99 (t, 2 H, CH₂NH₃⁺), 3.50 (t, 2 H, NHCH₂CH₂), 3.62 (t, 2 H, CH₂OH), 3.79 (t, 2 H, CH₂CH₂OH), 7.13 (s, br, 1 H, pyrimidine NH), 7.27 (s, 1 H, C⁶H); ¹³C NMR [(CD₃)₂SO]: δ 13.18 (pyrimidine CH₃), 38.55 (NHCH₂CH₂), 38.68 (CH₂NH₃), 51.89 (CH₂CH₂OH), 58.74 (CH₂OH), 140.55 (C⁶), 112.61, 153.29, 170.36 (C², C⁵, C⁴) (Found: C, 40.69; H, 6.26; N, 20.68. Calc. for C₉H₁₉ClN₄O₃: C, 40.53; H, 7.18; N, 21.01%). Infrared; ν (cm⁻¹) 3352, 3280 (N–H) and 1660 (C=O).

[ZnCl₂(LH)] 1. To a solution of zinc chloride (0.14 g, 1.00 mmol) in H₂O (15 ml) was added with stirring an aqueous solution (15 ml) of 1-(2-hydroxyethyl)-(2-aminoethyl-N²)-5-methylisocytosine hydrochloride (0.25 g, 1.00 mmol), the mixture was allowed to stir overnight. The colourless solution was concentrated to a minimum volume on a rotary evaporator, ethanol (60 ml) was added and the mixture was allowed to stand undisturbed overnight. Complex **1** crystallized as colourless crystals which were found to be suitable for a single-crystal X-ray structure analysis (Found: C, 27.35; H, 4.45; N, 14.14. Calc. for C₉H₁₇Cl₃N₄O₂Zn: C, 28.23; H, 3.95; N, 14.63%). Infrared; ν (cm⁻¹) 3471, 3293 (N–H) and 1654 (C=O).

[PdCl₂L] 2. To a refluxing solution of PdCl₂ (0.18 g, 1.0 mmol) in acetonitrile (25 ml) was added dropwise an aqueous (25 ml) solution of 1-(2-hydroxyethyl)-(2-aminoethyl-N²)-5-methylisocytosine hydrochloride (0.25 g, 1.0 mmol). The mixture was allowed to remain at reflux for 24 h. The cooled solu-

Table 2 Summary of crystal data and structure determination for compounds 1–3

Compound	1	2	3
Formula	C ₉ H ₁₇ Cl ₃ N ₄ O ₂ Zn	C ₉ H ₁₆ Cl ₂ N ₄ O ₂ Pd	C ₉ H ₁₆ Cl ₄ N ₄ O ₂ Pd ₂ ·0.5H ₂ O
<i>M</i>	384.99	389.56	575.87
<i>T</i> /K	160	160	160
Crystal size/mm	0.70 × 0.20 × 0.16	0.44 × 0.29 × 0.09	0.26 × 0.10 × 0.01
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> <i>c</i>	<i>P</i> $\bar{1}$
<i>a</i> /Å	7.539(3)	12.6211(14)	8.4069(10)
<i>b</i> /Å	14.800(4)	17.1181(19)	9.8060(12)
<i>c</i> /Å	13.169(4)	6.2311(7)	21.805(3)
α /°			90.973(3)
β /°	93.74(4)	90.939(3)	90.010(3)
γ /°			105.406(3)
<i>U</i> /Å ³	1466.2(8)	1346.0(3)	1732.7(4)
<i>Z</i>	4	4	4
<i>D</i> _f /g cm ⁻³	1.744	1.922	2.208
μ /mm ⁻¹	2.224	1.775	2.702
<i>F</i> (000)	784	776	1116
Reflections for cell refinement	28	4002	8135
θ Range/°	10.16–12.52	2.00–28.44	1.87–28.26
2 θ Range for data collection/°	5.5–50.0	4.0–50.0	4.3–56.8
Maximum indices: <i>h</i> , <i>k</i> , <i>l</i>	–8 to 8, –17 to 17, –15 to 15	–14 to 15, –20 to 11, –7 to 7	–10 to 11, –12 to 12, –28 to 26
Reflections measured	6998	3513	11 943
Unique reflections	2574	2215	7538
Reflections with $F^2 > 2\sigma(F^2)$	2256	2152	5476
Transmission	0.530 to 0.649	0.694 to 0.862	0.498 to 0.927
<i>R</i> _{int}	0.0393	0.0248	0.0407
Weighting parameters ^a <i>a</i> , <i>b</i>	0.0703, 3.8892	0.0384, 1.3244	0.0978, 0
Extinction coefficient <i>x</i> ^b	—	0.0012(3)	—
<i>R</i> [$F^2 > 2\sigma(F^2)$] ^c	0.0430	0.0274	0.0619
<i>wR</i> 2 [all data] ^d	0.1259	0.0697	0.1700
Number of refined parameters	175	166	396
Goodness of fit ^e	1.070	1.071	1.006
Maximum, minimum electron density/ e Å ⁻³	1.146, –0.735	0.662, –0.784	2.141, –3.001

^a $w^{-1} = \sigma(F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2F_c^2)/3$. ^b $F_c = F_o(1 + 0.001x F_o^2 \lambda^3 / \sin^2 2\theta)^{-1}$. ^c $R = \sum ||F_o| - |F_c|| / \sum |F_o|$. ^d $wR2 = [\sum w(F_o^2 - F_c^2)^2] / \sum w(F_o^2)^2$. ^e $S = [\sum w(F_o^2 - F_c^2)^2 / (\text{no. of unique reflections} - \text{no. of variables})]^{1/2}$.

tion was concentrated under reduced pressure, the addition of ethanol precipitated the crude product which was collected by filtration, washed with ethanol and vacuum dried (0.21 g, 54%). Crystallization from water–ethanol (1:1) produced orange platelets suitable for X-ray analysis. ¹H NMR (D₂O): δ 1.78 (s, 1 H, pyrimidine CH₃), 3.14 (t, 2 H, CH₂NH₃), 3.62 (t, 2 H, NHCH₂CH₂), 3.77 (t, 2 H, CH₂OH), 3.87 (t, 2 H, CH₂CH₂OH), 7.37 (s, 1 H, C⁶H); ¹³C NMR (D₂O): δ 10.90 (pyrimidine CH₃), 40.00 (CH₂NH₃), 41.00 (NHCH₂CH₂), 50.00 (CH₂CH₂OH), 59.09 (CH₂OH), 145.45 (C⁶) (Found: C, 27.25; H, 3.91; N, 13.84. Calc. for C₉H₁₆Cl₂N₄O₂Pd: C, 27.75; H, 4.14; N, 14.38%).

[PdCl]₂[Pd₂Cl₆] 3. To K₂PdCl₄ (0.26 g, 0.80 mmol) in aqueous solution (30 ml) was added with stirring a solution of 1-(2-hydroxyethyl)-(2-aminoethyl-*N*²)-5-methylisocytosine hydrochloride (0.20 g, 0.80 mmol) in water (20 ml). The mixture was allowed to stir at room temperature for 18 h. The solvent was removed *in vacuo*. The resultant brown-red solid was dissolved in a small volume of water, ethanol (20 ml) was added and the mixture was left to stand undisturbed overnight. This resulted in the formation of a variety of crystalline material, which was mechanically separated and analysed by single-crystal X-ray structure analyses (crystals of unreacted K₂PdCl₄ and compounds **2** and **3** were formed and identified by their unit cell parameters).

Crystallography

Details of crystal data, structure solution and refinement for compounds **1–3** are given in Table 2. For **1** data were collected on a Stöe-Siemens four-circle diffractometer using graphite-monochromated Mo-*K* α radiation ($\lambda = 0.710 73$ Å). Cell

parameters were refined from 2 θ values measured at $\pm\omega$ to minimize systematic errors. Intensities were measured with ω – θ scans and on-line profile fitting.²³ Data were corrected semiempirically for absorption using ψ scans.

For **2** and **3** all diffraction measurements were made on a Bruker AXS SMART CCD area-detector diffractometer using graphite-monochromated Mo-*K* α radiation. Cell parameters were refined from observed setting angles of all strong reflections in the complete data set. Intensities were integrated from several series of exposures, each taken over 0.3° ω rotation, covering more than a hemisphere of reciprocal space. Data were corrected semiempirically for absorption based on equivalent and repeated reflections. There was no significant intensity decay during the experiments.

For all three structures all non-H atoms were refined anisotropically. Hydrogen atoms were located in difference maps and then included using a riding model with isotropic *U* values set to be 150% of those of the carrier atoms for methyl and hydroxyl hydrogens and 120% for all others, except for H(1A) and H(1B) in **3** for which the coordinates were refined freely. Programs used were SHELXTL²⁴ for structure solution, graphics and tables, and SHELXL 97²⁵ for structure refinement.

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References

- 1 *Metal Ions in Biological Systems*, eds. A. Sigel and H. Sigel, Marcel Dekker, New York, Basel, Hong Kong, 1996, vol. 32, pp. 1–814; *ibid.*, 1996, vol. 33, pp. 1–678.
- 2 B. Lippert, *Prog. Inorg. Chem.*, 1989, **37**, 1; B. Lippert, *Coord. Chem. Rev.*, 1997, **156**, 275.
- 3 S. S. Massoud and H. Sigel, *Eur. J. Biochem.*, 1989, **179**, 451.
- 4 J. W. Suggs, M. J. Dube and N. Nichols, *J. Chem. Soc., Chem. Commun.*, 1993, 307.
- 5 C. A. Blindauer, A. H. Emwas, A. Holy, H. Dvorakova, E. Sletten and H. Sigel, *Chem. Eur. J.*, 1997, **3**, 1526.
- 6 C. Mesier, B. Song, E. Freisinger, M. Peilert, H. Sigel and B. Lippert, *Chem. Eur. J.*, 1997, **3**, 388.
- 7 F. Zamora, M. Kunsman, M. Sabat and B. Lippert, *Inorg. Chem.*, 1997, **36**, 1583.
- 8 F. Pichierri, D. Holthenrich, E. Zangrando, B. Lippert and L. Randaccio, *J. Biol. Inorg. Chem.*, 1996, **1**, 439.
- 9 C. Price, M. R. J. Elsegood, W. Clegg and A. Houlton, *J. Chem. Soc., Chem. Commun.*, 1995, 2285.
- 10 C. Price, M. R. J. Elsegood, W. Clegg, N. H. Rees and A. Houlton, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1762; unpublished work.
- 11 O. F. Schall and G. W. Gokel, *J. Am. Chem. Soc.*, 1994, **116**, 6089.
- 12 F. H. Allen and O. Kennard, *Chem. Design Automation News*, 1993, **8**, 31.
- 13 C. Bannister, K. Burns, K. Prout, D. J. Watkin, D. G. Cooper, G. J. Durant, C. R. Ganellin, R. J. Ife and G. S. Sach, *Acta Crystallogr., Sect. B*, 1994, **50**, 221.
- 14 M. Rossi and T. J. Kistenmacher, *Acta Crystallogr., Sect. B*, 1977, **33**, 3962.
- 15 B. D. Sharma and J. F. McConnell, *Acta Crystallogr.*, 1965, **19**, 797.
- 16 J. H.-U. M. N. Moreno-Carretero, M. A. Romero-Molina, J. M. Salas-Peregrin, M. P. Sanchez-Sanchez, G. A. de Cienfuegos-Lopez and R. Faure, *J. Inorg. Biochem.*, 1993, **51**, 613.
- 17 A. L. Beauchamp, *Inorg. Chim. Acta*, 1984, **91**, 33.
- 18 S. K. Miller, L. G. Marzilli, S. Dörre, P. Kollat, R.-D. Stilger and J. J. Stezowski, *Inorg. Chem.*, 1986, **25**, 4272.
- 19 E. C. Fusch and B. Lippert, *J. Am. Chem. Soc.*, 1994, **116**, 7204.
- 20 E. Sinn, C. M. Flynn and R. B. Martin, *Inorg. Chem.*, 1977, **16**, 2403; M. Krumm, I. Mutikainen and B. Lippert, *Inorg. Chem.*, 1991, **30**, 884; M. Wienken, E. Zangrando, L. Randaccio, S. Menzer and B. Lippert, *J. Chem. Soc., Dalton Trans.*, 1993, 3349; J. E. Kickham, S. J. Loeb and S. L. Murphy, *J. Am. Chem. Soc.*, 1993, **115**, 7031; J. E. Kickham and S. J. Loeb, *Inorg. Chem.*, 1994, **33**, 4351.
- 21 H. Sakaguchi, H. Anzai, K. Furuhashi, H. Ogura and Y. Iitaka, *Chem. Pharm. Bull.*, 1977, **25**, 2267.
- 22 M. Krumm, E. Zangrando, L. Randaccio, S. Menzer and B. Lippert, *Inorg. Chem.*, 1993, **32**, 700; M. Krumm, B. Lippert, L. Randaccio and E. Zangrando, *J. Am. Chem. Soc.*, 1991, **113**, 5129.
- 23 W. Clegg, *Acta Crystallogr., Sect. A*, 1981, **37**, 22.
- 24 G. M. Sheldrick, *SHELXTL user manual*, Bruker AXS, Madison, WI, 1994.
- 25 G. M. Sheldrick, SHELXL 97, program for crystal structure refinement, University of Göttingen, 1997.

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