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Synthesis of neutral gold(III) pyrimidine-complexes and theoretical studies on the proton affinity of the coordinated ligands

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ABSTRACT

The neutral gold(III) complexes $AuCl_3$(pm) (pm = pyrimidine, 2-methylpyrimidine, 4-methylpyrimidine, 5-methylpyrimidine, 4,6-dimethylpyrimidine, 2-aminopyrimidine) have been synthesised and characterised. The proton affinity (PA) values of the free and coordinated N-heterocycles have been theoretically estimated on the basis of DFT calculations. The coordination to the $AuCl_3$ metal fragment causes a strong lowering of the basicity of the residual protonation sites, with PA variations around −25 kcal mol^{-1}. The lowering of PA caused by the bonding to the gold centre results related to the presence of space-demanding groups near the coordinating nitrogen atom and to the π-back donation of electron density from the metal to the protonated ligand.

1. Introduction

Several square-planar gold(III) complexes stabilized by N-donor heterocycles are potentially interesting species in biological systems and have been found to be anti-cancer and anti-parasitic drugs [1]. Moreover, the chemical features of gold(III) complexes stabilized by six-membered N-donor heterocycles are of current interest in homogeneous catalysis. For example, Hashmi and co workers reported in the last few years the use of pyridine-based Au(III) complexes as efficient catalysts in organic syntheses [2]. Square–planar d^8 gold complexes with monodentate N-donor heterocycles in their coordination sphere have been extensively studied also from kinetic and theoretical points of view, in order to give insight into the Au–N bond [3]. The chemistry of gold(III) complexes of nitrogen ligands has been recently reviewed by M.A. Cinellu [4].

The pyrimidine ring is present in nucleic acids, several vitamins and antibiotics and provides potential binding sites for Brønsted and Lewis acids. In this paper the synthesis and characterisation of several gold(III) complexes having general formula $AuCl_3$(pm) {pm = one of a number N-donor pyrimidines, namely: pyrimidine, 2-methylpyrimidine, 4-methylpyrimidine, 5-methylpyrimidine, 4,6-dimethylpyrimidine, 2-aminopyrimidine} is reported. The proton affinity (PA) values of the free and coordinated N-heterocycles have been compared by means of DFT calculations, in order to estimate the effects of the $AuCl_3$ fragment on the basicity of these polydentate ligands.

2. Experimental

2.1. Materials and instruments

$K[AuCl_4]\cdot 2H_2O$ was prepared following a standard procedure from pure gold foils (99.9999%) purchased from CHIMET, Italy. The pyrimidines (Aldrich) were used without further purifications. Acetone, deuterated acetone and dimethylformamide (dmf) were pure-grade Aldrich products. ^1H NMR spectra were obtained with Bruker Avance 300 and Bruker AC 200 spectrometers and are referred to internal tetramethylsilane. The organic ligands were numerated following common conventions. The conductivity of 10^{-3} mol dm^{-3} solutions in dmf and acetone at 25 °C was measured with a Radiometer CDM 83 instrument. Elemental analyses (C, H, N, Cl) were performed by the Microanalytical Laboratory of the Faculty of Pharmaceutical Science, University of Padua.

2.2. Preparation of the complexes

All the complexes were prepared following the same synthetic strategy. In a typical procedure to a solution of 0.414 g (1.0 mmol) of $K[AuCl_4]\cdot 2H_2O$ in water (30 ml) was added drop by drop, under stirring, a equimolar amount (1.0 mmol) of the proper pyrimidine pm (pm = pyrimidine, 2-methylpyrimidine, 4-methylpyrimidine, 5-methylpyrimidine, 4,6-dimethylpyrimidine, 2-aminopyrimidine) dissolved in methanol (1 ml). The bright yellow precipitate, formed almost immediately, was filtered off, washed twice with water and dried under vacuum. Yields were in all cases nearly quantitative (>95%). Analytical and ^1H NMR data are collected in Tables S1 and S2 (Supplementary data) respectively.

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2.3. DFT calculations

The ground-state computational geometry optimisations of the $AuCl_3$(pm) complexes were carried out using the DFT B3LYP and M06 functionals [5,6] without symmetry constrains, in combination with the LACVP** ECP-based basis set [7]. The LANL2DZ pseudopotential used in this basis set was applied in the past by our research group on gold(III) complexes with N-donor ligands and the comparison between experimental and calculated geometries was really good [8]. The geometry optimisations of the free ligands and of their conjugate acids $[pmH]^+$ were carried out with the B3LYP hybrid DFT functional [5] using Pople's split-valence double-ζ polarised 6-31G** basis set [9]. The "restricted" formalism was applied in all calculations and no solvation model was added. All the resulting stationary points were characterised as true minima (*i.e.*, no imaginary frequencies). From the IR simulations, carried out with the harmonic oscillator approximation, the zero-point vibrational energy (ZPVE) values were computed. The thermal contributions to enthalpy were calculated on the basis of statistical mechanical standard formulas (rigid-rotor approximation). The proton affinities (PA) of the free and coordinated ligands were computed on the basis of Eq. (1) as the total energy difference between the heterocycle pm (E_{pm}) and its protonated counterpart $[pmH]^+$ ($E_{(pmH)+}$). These energy values were corrected for zero-point vibrational energies (ZPVE) and the thermal contributions to enthalpy at 298 K ($\Delta H^{0\rightarrow 298}$). Finally, the pressure-volume work term $-RT$, where R is the gas constant, which is equal to -0.6 kcal mol^{-1} at 298 K, was added to Eq. (1) [10].

$$PA = E_{pm} + ZPVE_{pm} + \Delta H^{0\rightarrow 298}_{pm} - E_{[pmH]+} - ZPVE_{[pmH]+} - \Delta H^{0\rightarrow 298}_{pmH+} - RT \quad (1)$$

All calculations were carried out using a Intel Core-I7-based x86-64 workstation. The software used was SPARTAN '08 [11].

3. Results and discussion

3.1. Synthesis and characterisation of the gold(III) pyrimidine complexes

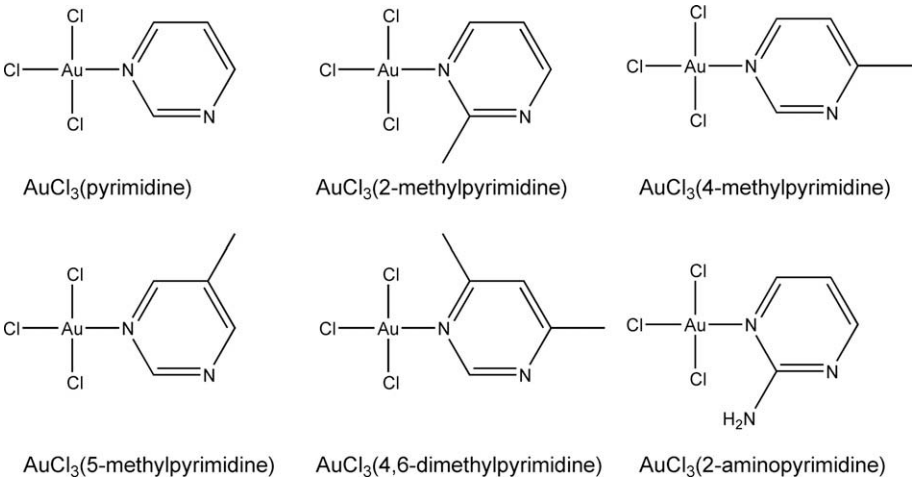
The reaction of $K[AuCl_4]\cdot 2H_2O$ with one of the pyrimidines (pm) considered in this work in water at room temperature caused the immediate formation of the corresponding neutral $AuCl_3$(pm) complexes in nearby quantitative yields. These species resulted to be non-conductive in acetone or dmf solutions. Elemental analyses and ^{1}H NMR data agreed with the proposed formulations. All the NMR spectra clearly showed the presence of a single isomer (see Table S2), but for the ligands 4-methylpyrimidine and 2-aminopyrimidine there is the possibility of different coordination modes of the heterocycles to the metal fragment. 4-methylpyrimidine can coordinate the gold centre through the N-atom in *ortho* or in *para*-position with respect to the methyl group, while the Au–N bond in the 2-aminopyrimidine derivative can occur through two chemically equivalent sp^2 nitrogen atoms or through the amino group. The energies of all the potential isomers have been therefore computed using the DFT and M06 functionals. The ZPVE was also computed from the IR analysis on the B3LYP-optimised species. All data are reported in Table 1. Energy calculations showed that in the $AuCl_3$(4-methylpyrimidine) complex the coordination of the metal centre through the N-atom in *para*-position with respect to the methyl group is slightly preferred. The 2-aminopyrimidine coordinates the gold(III) ion through a sp^2 nitrogen atom of the ring. The complexes considered in this work are sketched in Scheme 1 for clarity.

3.2. Proton affinity studies

The pK_a values for the conjugate acids of the pyrimidine, 4-methylpyrimidine, 4,6-dimethylpyrimidine, and 2-aminopyrimidine ligands are reported in the literature [12]. The pK_a values for

Table 1
Computed energy data (B3LYP and M06 DFT functionals) for the complexes $AuCl_3$(4-methylpyrimidine) and $AuCl_3$(2-aminopyrimidine).

Complex	Isomer	E_{B3LYP} (a.u)	E_{M06} (a.u)	ZPVE (kcal mol^{-1})
$AuCl_3$(4-methylpyrimidine)	N_1–Au	−1819.7668	−1819.4300	78.1
$AuCl_3$(4-methylpyrimidine)	N_3–Au	−1819.7655	−1819.4278	78.1
$AuCl_3$(2-aminopyrimidine)	N_1–Au	−1836.8209	−1835.4894	71.3
$AuCl_3$(2-aminopyrimidine)	N_{sp3}–Au	−1835.8045	−1835.4716	71.7



Scheme 1. Sketches of the gold(III)–pyrimidine-complexes considered in this work.

the acids $[pmH]^+$ derived from pyrimidine and methyl-substituted pyrimidines are in the range 1.23–2.7, while the 2-aminopyrimidine conjugate acid has a pK_a value of 3.45. The proton affinity (PA) values for the free ligands have been calculated in this work on the basis of DFT B3LYP/6-31G** calculations. A correlation between experimental and B3LYP/6-31G** computed proton affinities for sixteen N-heterocycles [13] shows that the PA variations from a nitrogen ligand to another one are correctly predicted on this level of theory, even if the calculated absolute values are about the 3% higher than real. Table 2 reports the PA values computed on the basis of Eq. (1). For the N-bases having different possible protonation sites, *i.e.* 4-methylpyrimidine and 2-aminopyrimidine, all the possible conjugate acids have been considered.

Table 2
DFT B3LYP calculated proton affinity values for the free pyrimidine ligands.

Ligand	Protonation site	PA (kcal mol^{-1})
Pyrimidine	N_1–H	215.1
2-Methylpyrimidine	N_1–H	221.7
4-Methylpyrimidine	N_1–H	221.0
4-Methylpyrimidine	N_3–H	220.3
5-Methylpyrimidine	N_1–H	219.1
4,6-Dimethylpyrimidine	N_1–H	225.7
2-Aminopyrimidine	N_1–H	223.8
2-Aminopyrimidine	N_{sp3}–H	206.6

Table 3
DFT B3LYP calculated proton affinity values for the $AuCl_3$-coordinated pyrimidine ligands and PA variation (ΔPA) of the protonation sites after coordination.

Complex	Protonation site	PA (kcal mol^{-1})	ΔPA (kcal mol^{-1})
$AuCl_3$(pyrimidine)	N_3–H	191.1	−24.0
$AuCl_3$(2-methylpyrimidine)	N_3–H	194.2	−27.5
$AuCl_3$(4-methylpyrimidine)	N_3–H	196.8	−24.2
$AuCl_3$(5-methylpyrimidine)	N_3–H	195.2	−23.9
$AuCl_3$(4,6-dimethylpyrimidine)	N_3–H	198.6	−27.1
$AuCl_3$(2-aminopyrimidine)	N_3–H	197.7	−26.1
$AuCl_3$(2-aminopyrimidine)	N_{sp3}–H	189.0	−17.6

Table 4
Selected B3LYP calculated geometry parameters (bond lengths *r* and dihedral angles ω) for the $AuCl_3$(pm) complexes and their conjugate acids.

Complex	Neutral form		Conjugate acid	
	r_{Au-N} (Å)	$\omega_{Cl-Au-N-C}$ (°)	r_{Au-N} (Å)	$\omega_{Cl-Au-N-C}$ (°)
$AuCl_3$(pyrimidine)	2.124	41.8	2.266	9.4
$AuCl_3$(2-methylpyrimidine)	2.107	83.1	2.200	66.0
$AuCl_3$(4-methylpyrimidine)	2.120	41.3	2.253	9.6
$AuCl_3$(5-methylpyrimidine)	2.112	42.6	2.261	10.0
$AuCl_3$(4,6-dimethylpyrimidine)	2.104	81.3	2.191	59.5
$AuCl_3$(2-aminopyrimidine)	2.118	59.4	2.236	47.8

The protonation of 4-methylpyrimidine appears to occur preferentially on the N_1 nitrogen atom. In the 2-aminopyrimidine ligand the protonation of the ring nitrogen atoms results strongly favourable with respect to the NH_2 groups. The comparison of the data reported in Tables 1 and 2 show that the coordination to the gold centre occurs through the most basic N-atom of the pyrimidine ligands. The maximum PA difference among the considered pyrimidines is 8.7 kcal mol^{-1}, corresponding to a pK_a range of 2.22.

Table 3 reports the proton affinity values of the $AuCl_3$-coordinated pyrimidines and the PA variation (ΔPA) of the ligands protonation sites after coordination. The lowering of proton affinity of the non-coordinated N-atoms in the heterocycle rings caused by the bonding is around −25 kcal mol^{-1}. The PA of the NH_2 group of the 2-aminopyrimidine ligand results less affected by coordination, with a calculated ΔPA of −17.6 kcal mol^{-1}.

A more careful analysis of Table 3 data allows observing that for the ligands having space-demanding groups in *ortho*-position with respect to the coordinating N-atom, *i.e.* 2-methylpyrimidine, 4,6-dimethylpyrimidine and 2-aminopyrimidine, the lowering of PA of the ring N-atoms caused by coordination is about 3 kcal mol^{-1} higher than that of the other pyrimidines. In other words, the basicity of pyrimidine, 4-methylpyrimidine and 5-methylpyrimidine results less affected by coordination to $AuCl_3$ than that of 2-methylpyrimidine, 2-aminopyrimidine and 4,6-dimethylpyrimidine. An explanation for this difference between these two groups of ligands can be obtained from the geometry data of the neutral complexes and their conjugate acids, reported in Table 4. The Au–N bond lengths are increased after protonation and, more interestingly, the protonated ligands tend to rotate itself around the Au–N bond in order to become more coplanar to $AuCl_3$, as observable from the *cis*Cl–Au–N–C dihedral angles. In the conjugate acids of the $AuCl_3$(pyrimidine), $AuCl_3$(4-methylpyrimidine) and $AuCl_3$(5-methylpyrimidine) complexes these dihedral angles are in the range 9.4–10.0°. The same angle is comprised between 47.8° and 66.0° for the $AuCl_3$(2-methylpyrimidine), $AuCl_3$(2-aminopyrimidine) and $AuCl_3$(4,6-dimethylpyrimidine) conjugate acids, because of the bulk of the space-demanding groups near the Au–N bond.

The geometry difference between the two groups of complexes leads to different interactions between the protonated ligand and the gold complexes. An analysis of the molecular orbitals of two strictly related complexes, $[AuCl_3$(2-methylpyrimidine-H)$]^+$ and $[AuCl_3$(4-methylpyrimidine-H)$]^+$, shows that the most striking difference between the MOs of the two compounds occurs for the HOMO-12 orbitals, depicted in Fig. 1.

The low *cis*Cl–Au–N–C dihedral angle in $[AuCl_3$(4-methylpyrimidine-H)$]^+$ allows the overlap between a d_π orbital of Au(III) and the π-system of the aromatic ring. The same interaction is absent, instead, for the $[AuCl_3$(2-methylpyrimidine-H)$]^+$ species. The

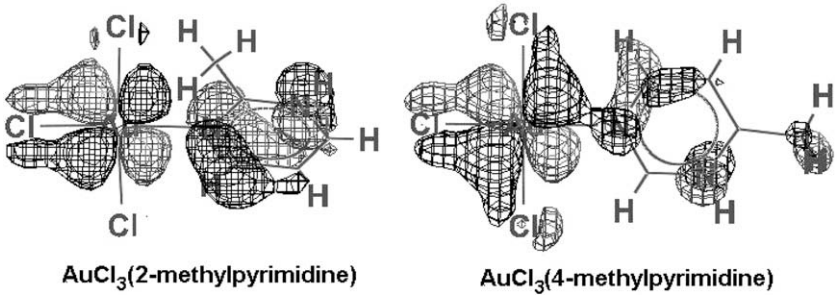
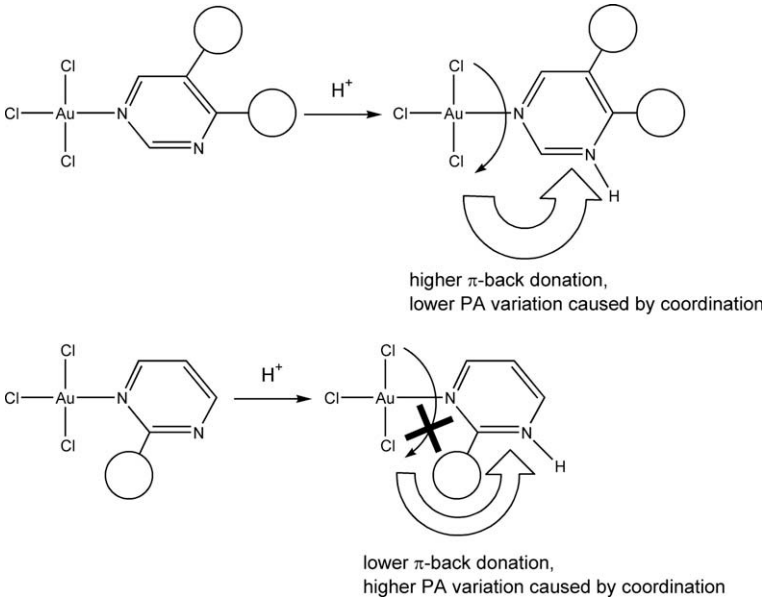


Fig. 1. HOMO-12 orbitals of $AuCl_3$(2-methylpyrimidine) and $AuCl_3$(4-methylpyrimidine).



Scheme 2. Effects of the position of the substituents on the π-back donation in the protonated complexes and on the PA variation of the pyrimidines after coordination.

HOMO-12 in $[AuCl_3(4\text{-methylpyrimidine-H})]^+$ appears to enforce the π-back donation of electron density from the metal centre to the protonated pyrimidine. This result can explain why the proton affinity of the pyrimidines not having space-demanding groups near the coordinating N-atom results less affected by coordination to $AuCl_3$.The π-back donation reduces the lowering of basicity caused by the coordination to the gold centre if the $AuCl_3$ fragment and the pyrimidine ring are about on the same plane in the protonated complexes. This interaction is not allowed if there are substituents on the pyrimidine ring near the coordinating nitrogen atom, therefore for these ligands the PA variation of the ring protonation sites after coordination is higher. These conclusions are summarised in Scheme 2.

4. Conclusions

In this work the synthesis of several gold(III) complexes of pyrimidines has been described. Theoretical studies on the proton affinity of free and coordinated pyrimidines have highlighted the role of space-demanding groups near the Au–N bond on the interaction between the gold fragment and the nitrogen ligands and the consequent effect on the basicity of the residual protonation sites.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.poly.2010.02.028.

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