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Gold(I) Derivatives of Heterocycles*

FLAVIO BONATI, ALFREDO BURINI, BIANCA ROSA PIETRONI and ELISABETTA GIORGINI
Dipartimento di Scienze Chimiche dell'Università, 62032 Camerino, Italy

Abstract

In gold(I) derivatives of several nitrogen-containing heterocycles it was found that: (1) the metal is two-coordinated even when the formula may suggest otherwise; (2) when tautomers are possible, one or more Au–N bonds, or even Au–C bonds, are more readily formed then Au–O bonds; (3) the presence of a (ligand) AuN group increases the tendency towards H-bond formation on another nitrogen of the heterocycle.

Introduction

Amongst the several metals which are of interest to chemotherapy, gold has been studied for a long time [1]. However, its relevance to the treatment of cancer has been small up to now, but, following a preliminary publication [2], it is possible that some success might be obtained in the near future. The history of the pharmaceutical application of gold seems to support such a view. After the birth of modern experimental medicine, the use of 'aurum potabile' disappeared, until around 1920 when another soluble derivative of this noble metal found its way into the pharmacopoeia as a cure for tuberculosis (TB), then a raging disease. The introduction of antibiotics and their success in curing TB extinguished any interest towards chrysotherapy, until the late thirties when it was found that gold derivatives can be used in the treatment of rheumatoid arthritis: the result was good, and the compounds are still being used, but it had been reached through a false assumption. Indeed in those years rheumatoid arthritis was believed to be strictly related to TB, a belief disproved by subsequent investigations. No satisfactory explanation is presently available on the mechanism of action of the various gold-containing drugs (*cf.* ref. 3), and research is being carried out in several places in order to try and understand it or, at least, to reduce the side effects connected with the introduction in the human body of a derivative of a heavy metal (e.g. ref. 4).

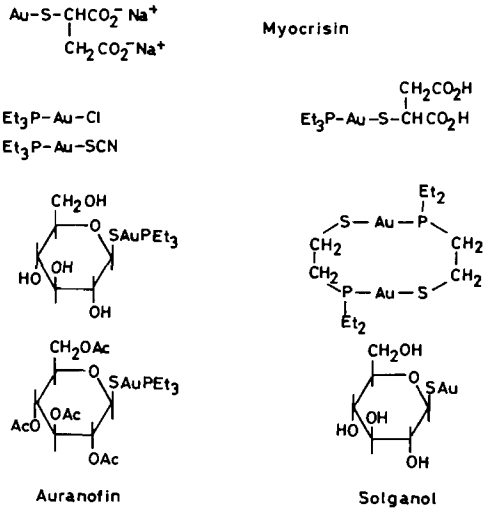

Fig. 1. Commonly used gold(I) drugs.

The compounds currently employed or likely to be employed are shown in Fig. 1. The molecules indicated there have one common characteristic: they are all derivatives of gold(I). Although the other common oxidation state of gold, namely gold(III), has the same square-planar coordination as platinum(II), as such it does not seem to be equally well suited for pharmaceutical uses owing to several reasons, two of which may be the following: (i) although the strength of gold(III) as an oxidizing agent is influenced by the type of ligands surrounding it, generally the metal in the higher oxidation state is easily reduced, especially *in vivo*; (ii) gold(III) is not as kinetically robust as platinum(II), so that the chemical bonds of gold(III) with other molecules, for example with DNA, are more easily broken than those of platinum(II).

In any case, since gold(I) affords chemotherapeutic agents, and since, in addition, some literature reports suggest that compounds of this element are worth trying at least against certain forms of cancer, we here report some results obtained while investigating this low oxidation state of the element. Our interest has centered on its derivatives with nitrogen-containing heterocycles, some of which (for example, pyrazolone) have been on sale at chemists' shops since the turn of the century. Besides, the simple

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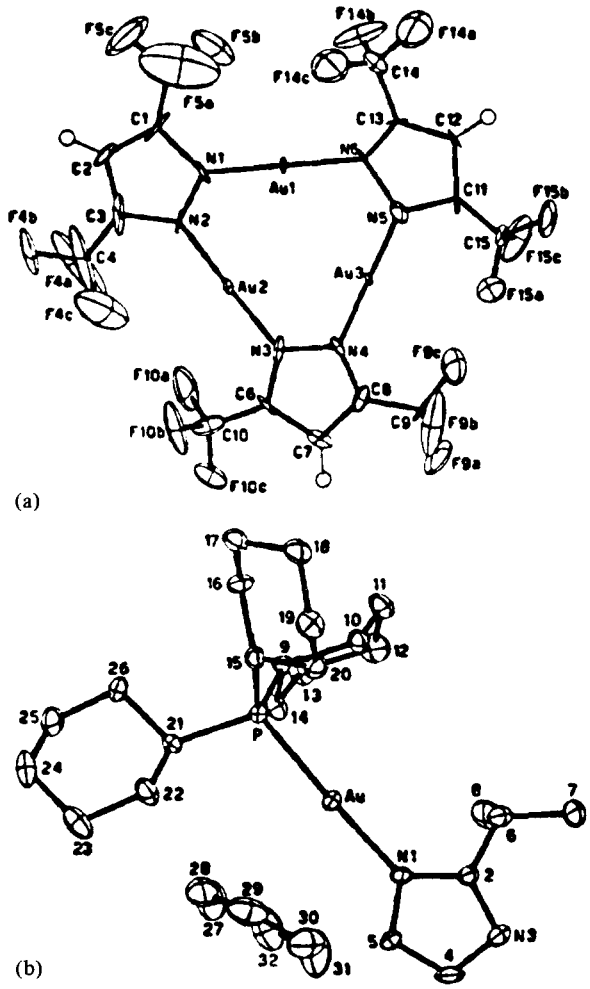

Fig. 2. (a) [Au(μ-pyrazolato-*N*,*N*′)]$_3$; (b) [1-(tricyclohexylphosphinegold)-2-(isopropyl)imidazole]·benzene.

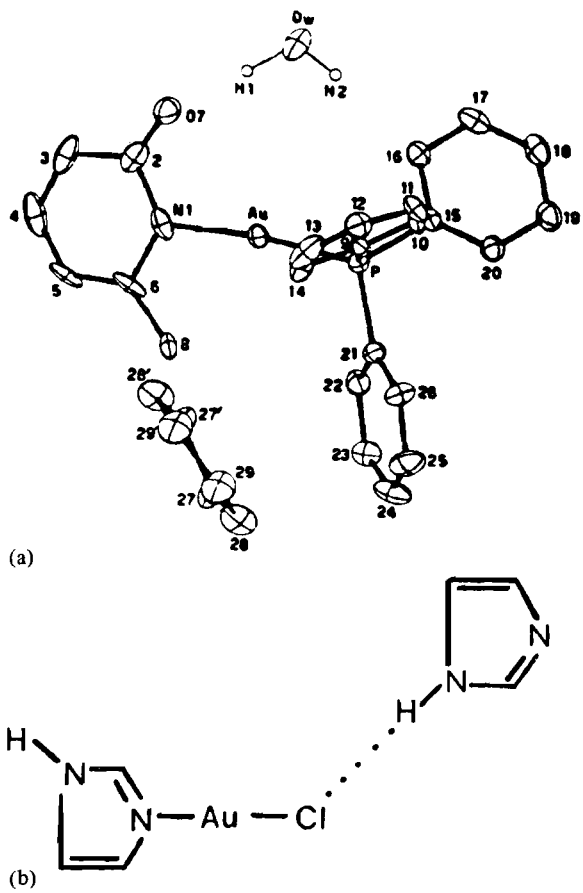

Fig. 3. (a) [1-(triphenylphosphinegold)-6-methyl-2-pyridone]·benzene·water; (b) [(imidazole)$_n$AuCl].

heterocycles such as imidazole are suitable models for the interaction between gold(I) and those biomolecules of which they are constituents.

Results and Discussion

Our interest in this field has been only chemical, as previously with Pt(II). We have been trying to understand, as far as possible for a chemist, the mode of interaction of gold(I) with several various nitrogen-containing heterocycles. Although the molecules we have been studying might be chemotherapeutic agents, we have been able to carry out only chemical investigations, and here we report our conclusions, in the hope that they will be of some use to somebody else.

The first point we are reasonably sure of is that in the interaction between gold and most nitrogen-containing heterocycles only two-coordinated products are formed, even if the formula of the resulting, isolated compound may suggest otherwise, and even if a higher coordination number, such as three or four, is not rare in the coordination chemistry of gold(I). This result may be reached in several ways, e.g. through oligomerization or polymerization, through hydrogen bonding, or through clathration, as can be seen in the four examples illustrated in Figs. 2 and 3.

In the first compound shown, [Au(pyrazolato-*N*,*N*′)]$_3$ [5], two-coordination is reached through a bidentate and bridging pyrazolato group; it should be noted that in this molecule the trimeric arrangement and two-coordination around gold are stable in the crystal, in solution, and even in the vapor phase. In the second compound shown in Fig. 2, 1-(Cy_3PAu)-2-isopropylimidazole [6], clathration of one molecule of benzene in the crystal is ascertained through the X-ray crystal structure: clathration is a rather common occurrence with gold derivatives having bulky ligands, and natural products are generally bulky ligands. Although clathration takes place only in the solid state, it is good evidence of the complicated steric requirements of gold derivatives. Besides, not only solvents such as ben-

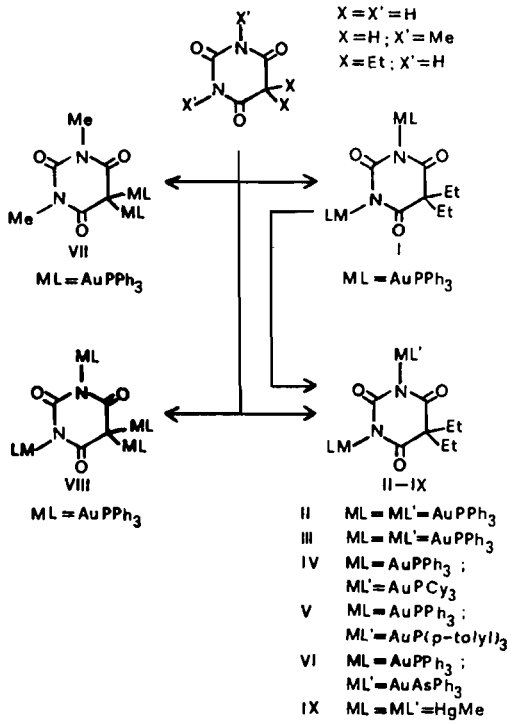

Fig. 4. Metal compounds of barbituric acid and of some of its derivatives.

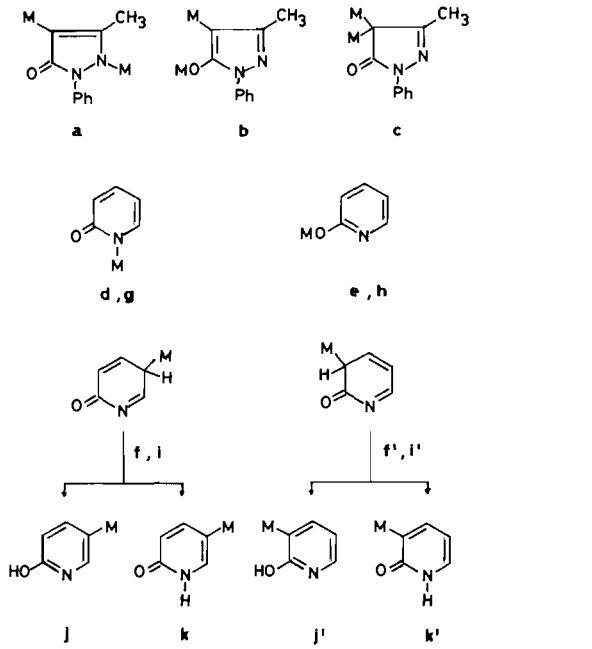

Fig. 5. Tautomers and their metal derivatives. M indicates either hydrogen (a–f) or tri-alkylphosphinegold(I) (a, b, c and g–k').

zene, but many other molecules, including ligands, may be clathrated. This can be seen in one of the compounds shown in Fig. 3: it is the crystal of 1-(triphenylphosphinegold) - 2 - pyridone•benzene•H_2O [7]. Here the gold atom is not three-coordinated, as it might appear, since the molecule of water does not behave as a ligand because it is not in the neighborhood of the metal, but it is hydrogen bonded to the oxygen of the aurated pyridone. A similar situation was indicated by Mössbauer spectra in the case of several $(azole)_nAuCl$ compounds where $n > 2$: hydrogen bonding between chlorine and N–H is likely [8].

The second point we are reasonably sure of is that with nitrogen-containing heterocycles one or more Au–N, or even Au–C, or both type of bonds, are more readily formed than an Au–O bond at room or body temperature [9]. For example (Fig. 4), with barbituric acid and some of its derivatives either *N*-, *N,N'*- or *C,C*-auration or a combination of these is observed; in the last instance up to four gold atoms have been introduced into the molecule, thus giving a per-metallated heterocycle [10]. The gold–nitrogen, or the gold–carbon bond, is easily formed and readily broken, but not by water, air or carbon dioxide. When both a primary and a secondary amino group are present in the same molecule, as in several purines, the gold–nitrogen bond or bonds replace the single hydrogen(s) of the secondary N–H group (or groups), rather than NH_2 hydrogens. Its formation seems to be decidedly favored in comparison with that of an Au–O bond: indeed in several biomolecules, such as barbituric acid, or in their models such as 2-pyridone, several tautomers are possible having O–H, N–H, or C–H bonds, and all have been detected in the case of the pyrazolone shown in Fig. 5 (M = H). 2-Pyridone undergoes metallation, but the gold derivative isolated up to now has always been that deriving from the N–H tautomer (Fig. 5: formula g); the same happens with several natural products (Fig. 6). The resulting Au–N bond here and in many other species is easily broken by any acid reagent (HY), the anion of which is polarizable. As shown in Fig. 7 the reagent HY may be a thiol (e.g. cysteine) or, amongst compounds of chemical interest, terminal acetylenes or hydrogen iodide; when the reagent HY is an organic acid, such as acetic acid, no reaction is observed. In line with this pattern of reactivity, when the HY reagent may give two tautomers, as in the case of 2-thiopyridone, the gold derivative contains an Au–S bond [11].

The third point which we would like to point out is this: substitution of the hydrogen of an N–H group by a (ligand) Au group increases the tendency towards hydrogen bond formation. The required hydrogen may be present in the same heterocycle, or may come from water; it interacts with any other electronegative atom available on the heterocycle. Two examples of hydrogen bonding are illustrated in Fig. 3; another one is shown in Fig. 8. This com-

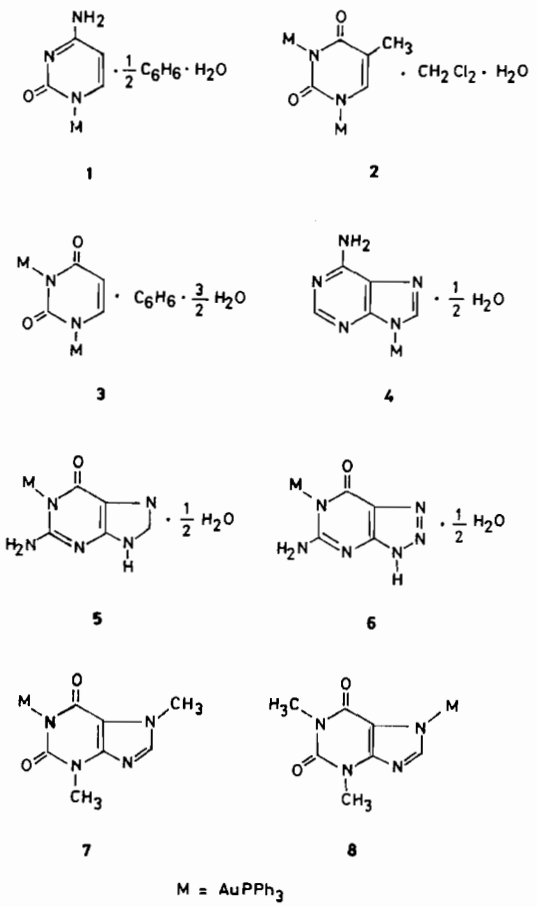

Fig. 6. Metal derivatives of several natural products.

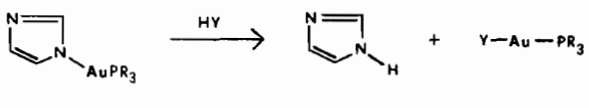

Fig. 7. Reaction of gold(I) derivatives of heterocyclic molecules.

pound was obtained upon crystallization of the product of the reaction between 1-[tris(cyclohexyl)-phosphinegold]benzimidazole with 1-methyl-2-mercaptoimidazole (HY); other solid compounds could also be obtained which analysed as 1-Me-2(Cy_3PAu)imidazole·nHY where $n = 0$ or 1, in addition to the one having $n = 2$ shown in Fig. 8. The tendency of this and of related compounds to maintain the HY molecule in the crystal shows that auration favors hydrogen bonding; in addition the N...H–N distances in the complex are shorter than in free benzimidazole, as required for a stronger bond. Indeed here N(3)...H(28) and N(26)...H(35) are 192(2) and 164(2) pm, respectively, against 200(4) pm in benzimidazole [12].

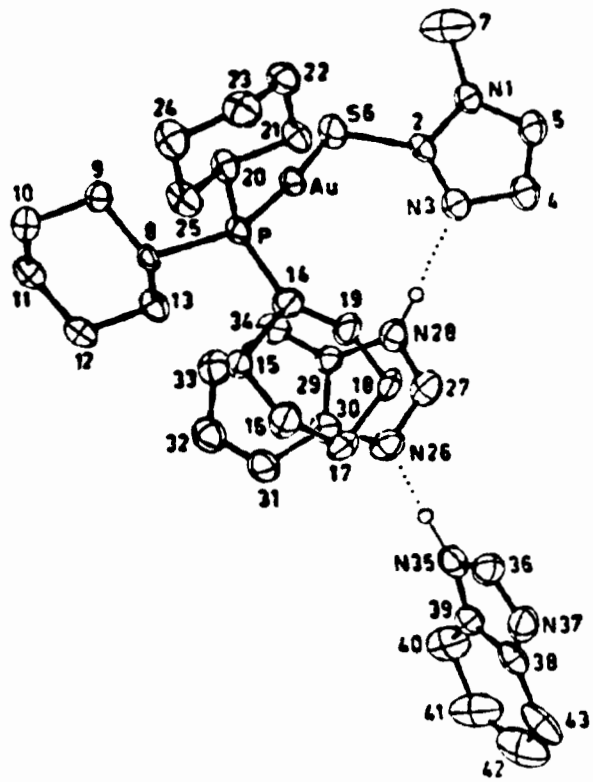

Fig. 8. [1-methyl-2-(tricyclohexylphosphinegoldthio)imidazole]·2-benzimidazole.

Conclusions

In conclusion, gold(I) derivatives of heterocycles can be obtained readily, provided that suitable experimental conditions are used (for example, phase transfer catalysis); they are stable to air, water and carbon dioxide, and are often soluble in organic solvents. Their chemical behavior can be interpreted and, in part, forecast, so that now they are available without too much trouble for use outside pure chemistry.

Acknowledgments

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