

STRUCTURAL FEATURES OF ANTITUMOR GOLD(I)-PHOSPHINE DERIVATIVES ANALYZED WITH THEORETICAL METHODS

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Dedicated to Prof. Pedro J. Aymonino on the occasion of his 75th birthday

Abstract

A Density Functional Theory (DFT) analysis of the mixed phosphine complexes $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)X$ shows a clear trend in the metal geometry as the anion X is varied: the softer the anion, the more it is tetrahedral, or alternatively, the more ionic the complex, the more the complex geometry approaches trigonal planar. A strong (soft) donor as cyanide ($X = CN^-$) penetrates markedly the coordination sphere and establishes the most tetrahedral geometry. In the antitumor compound $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ ($X = Cl^-$), the weaker donor chloride is slightly displaced from the coordination sphere with consequent strengthening of Au-P bonds, thus stabilizing a more pyramidal geometry. If the anion is completely out of the coordination sphere, the cation $[Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)]^+$ shows further strengthening of Au-P bonds and a geometry very close to the trigonal planar "AuP₃" system. X-ray and DFT data for $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ show generally good agreement; however, in the crystal the Au-Cl bond appears lengthened with consequent strong Au-P bonds. This is probably due to packing effects; nevertheless, the X-ray structure agrees with the trend mentioned above as well.

Resumen

El análisis estructural teórico (Density Functional Theory, DFT) de los complejos de coordinación $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)X$ muestra diferentes propiedades al variar el anion X . Para aniones «blandos», por ejemplo $X = CN^-$, la geometría es tetraédrica y el anión está fuertemente unido al metal. En cambio para un anión fuera de la esfera de coordinación, el catión $[Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)]^+$ posee las uniones Au-P más fuertes y la geometría alrededor del metal es trigonal planar. Una configuración intermedia se verifica en el complejo antitumoral $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ ($X = Cl^-$), debido a que el Cl^- es menos «blando» que el CN^- . Los datos estructurales de difracción de rayos X y DFT del $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ muestran buen acuerdo, a pesar de un alargamiento de la unión Au-Cl y el reforzamiento de las uniones Au-P en el cristal. La estructura cristalográfica también sigue la tendencia descrita por los datos de DFT.

Introduction

When using soft ligands such as phosphines (PR_3) the gold(I) cation has a marked tendency to establish linear compounds, $(\text{PR}_3)_2\text{AuX}$, $\text{X}^- = \text{anion}$, in contrast with its homologue Ag(I) which prefers tetrahedral geometries, at least in the solid state, as in $\text{Ag}(\text{PR}_3)_3\text{X}$, $\{\text{Ag}[(\text{PR}_3)_2\text{X}]_2\}_2$, $[\text{Ag}(\text{PR}_3)\text{X}]_4$ and $[\text{Ag}(\text{PR}_3)_4]\text{X}$ [1-5]. In accordance, Ag(I) can be said to have the metal coordinatively saturated in a formal sp^3 state, whereas Au can be described as having an sp state in PR_3AuX . An example of these linear compounds is the orally administered anti-arthritic drug Auranofin[®] (1-thio- β -D-glucopyranosato-2,3,4,6-tetraacetato-S)(triethylphosphine)gold(I), $(\text{PET}_3)\text{AuL}$, whose anion L is a thio-glucose derivative.

In contrast with Ag^+ , the Au^+ cation is unstable but can be generated *in situ* from reduction by thiodiglycol of the Au(III) species $\text{Na}[\text{AuCl}_4]$ in aqueous solution [6]. Subsequent addition of PR_3 stabilizes PR_3AuX that can be easily isolated. The coordination number of Au(I) can be increased using this linear Au(I) species as starting material, and by reacting it in a different (organic) environment with addition of phosphine ligand. This technique has been used successfully to obtain a mixed phosphine gold complex [7]:



Therefore, a limiting coordination feature of Au(I) –its marked preference for linear geometry – can be used to obtain novel compounds where the metal is coordinated to *different* types of ligands. This is in contrast with Cu^+ and Ag^+ that saturate rapidly their coordination sphere with a unique ligand.

Our interest in metal compounds with antitumor activity prompted us to synthesize this type of compound because it is closely related to active tetrahedral Au(I) complexes $[\text{Au}(\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2)]\text{Cl}$, $n = 2, 3$ [8]. The antitumor activity of $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$ (Fig.1) was confirmed in the first 2 protocols of the *in vitro* screening of the National Cancer Institute [7] and displayed marked sensitivity for melanoma tumors. In this article we analyze the structural effects resulting from variation of the Cl^- ligand with theoretical methods.

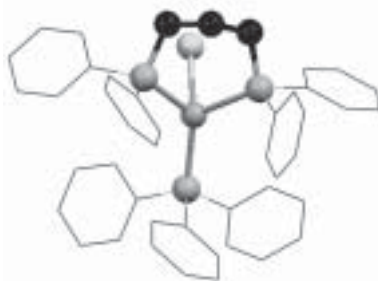


Figure 1. DFT molecular structure of $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$; ball and stick bonds for non-Ph atoms.

Experimental

The structural features of all compounds were analyzed as follows. Starting coordinates were obtained from the X-ray molecular structure of $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$ [7]. The

optimized geometry of this compound was obtained through energy minimization with the Accelrys program Cerius 2.4.6, subroutine DMol3 [9] on an Octane SGI computer. Standard local density was the Perdew and Wang (PWC) functional [10] using a double numeric basis set with polarization functions (DNP) [11] on all atoms. The same procedure was applied to (a) the cation $[\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)]^+$, obtained by eliminating the Cl^- anion from the $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$ Dmol3 minimized structure, and (b) $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{CN}$, obtained by replacing Cl^- with a CN^- moiety in $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$.

Results And Discussion

As seen in Table 1, comparison between X-ray and DFT molecular structures of $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$ show similar features, with the Au-P bonds shorter than Au-Cl, in agreement with X-ray structures of related Au(I)-phosphine compounds. For instance, $\text{Au}(\text{PPh}_3)_3\text{Cl}$ has Au-P bonds (average) 2.41 Å and Au-Cl = 2.71 Å [12]. The marked affinity of Au(I) for soft ligands such as phosphines explains such a difference.

Table 1. Structural data in the coordination sphere of $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{X}$ compounds, $\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2 = \text{DPPP}$.

	$\text{Au}(\text{PPh}_3)(\text{DPPP})\text{Cl}$		$[\text{Au}(\text{PPh}_3)(\text{DPPP})]^+$	$\text{Au}(\text{PPh}_3)(\text{DPPP})\text{CN}$
X	Cl ⁻		None	CN ⁻
Method	X-ray ¹	DFT	DFT	DFT
Au-P1	2.390(2)	2.541	2.509	2.576
Au-P2	2.386(2)	2.567	2.522	2.593
Au-P3	2.305(2)	2.465	2.463	2.475
Au-X	2.928(2)	2.613		2.221
P1-Au-P2	97.66(7)	89.3	94.1	88.0
P1-Au-P3	129.78(7)	132.8	134.0	127.7
P2-Au-P3	128.71(7)	116.2	127.5	113.0
P1-Au-X	83.31(7)	89.7		89.2
P2-Au-X	87.61(7)	90.2		94.0
P3-Au-X	112.95(7)	126.9		132.9
<Au-P>	2.360	2.524	2.498	2.548
∑P-Au-P	356.1	338.2	356.1	328.7
<P-Au-P>	118.7	112.7	118.7	109.6
∑P-Au-X	283.8	306.3		316.2
<P-Au-X>	94.6	102.1		105.4

Note: ¹Data obtained from ref [7]. Distances are provided in Å, angles in (°); <> stands for average value. Bold figures show data following the trend on metal geometry as the anion X is varied: the softer the anion, the more it is tetrahedral, or alternatively, the more ionic the complex, the more the geometry is trigonal planar.

In addition, Table 1 shows that the Σ P-Au-P angles is close to 360° from the X-ray structure, suggesting that the Cl⁻ anion is almost out of the coordination sphere. This pattern is very different from a pure tetrahedral structure, which would have Σ P-Au-P angles close to $3 \times 109.5^\circ = 328.5^\circ$.

In the tetrahedral $[\text{Au}(\text{PPh}_2\text{CH}_3)_4]^+$ cation there are marked differences among P-Au-P bond angles, as the sum of 3 P-Au-P bond angle range is $328\text{--}342^\circ$ [13], suggesting significant packing effects in the crystalline cell. Likewise, they may explain the different Au-Cl length in $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$ as obtained from X-rays (crystal, 2.928(2) Å) and DFT (isolated molecule, 2.613 Å).

We also analyze anion effects by replacement of Cl⁻ with the softer cyanide anion, which possesses marked affinity for M(I), M = Cu, Ag, Au. This is demonstrated in AgCN where it is impossible to remove the CN⁻ when reacting this salt with excess of PR₃, R = *p*-tolyl, and in fact, no more than 3 PR₃ groups enter the coordination sphere stabilizing Ag(PR₃)₃CN [2]. This feature is in contrast with weaker donor anions such as nitrate, since $[\text{Ag}(\text{PR}_3)_4]^+$ is easily obtained from silver nitrate.

By replacing Cl⁻ with CN⁻ a lengthening of Au-P bonds is obtained, as shown in Table 1, in agreement with the softer character of CN⁻ (in comparison with Cl⁻). That is, a competitive effect is present with the cyanide showing stronger bonding to Au(I) than Cl⁻ with consequent withdrawal of P atoms from the coordination sphere. Another noticeable change is in the P-Au-P angle (average value of 109.6° for $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{CN}$ versus 112.7° for $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$). Therefore a more tetrahedral character can be induced in Au(I) by substituting Cl⁻ with appropriate (softer) anions. This DFT study shows that in $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{CN}$ (Fig.2) the cyanide moiety is not linear as the bond angle Au-C-N is 156.8° . Several examples of this feature in the solid state show additional interaction with other units, e.g. from oligomerization due to interaction of the N lone pair with other units. This is not the case in the DFT structure of $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{CN}$ as the isolated molecule is studied. The only example of non-linear terminal cyanide derivative studied with X-rays is the trimetallic cation $[(\text{Ph}_3\text{P})\{\text{AgS}_3\text{WOCu}\}(\text{CN})]^+$ [14] where the cyanide binds the Cu atom and has a Cu-C-N bond angle of 160° , which is of the same order in $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{CN}$.

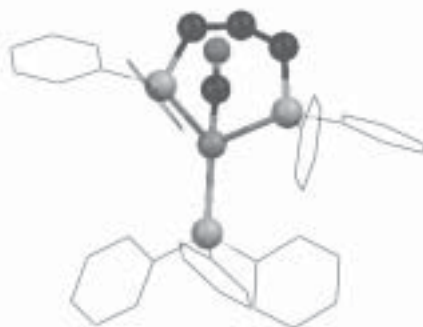


Figure 2. DFT molecular structure of $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{CN}$

The opposite structural effect than that caused by CN⁻ in the coordination sphere, that is shortening of Au-P bonds and widening of P-Au-P angles, can be also obtained. For instance, replacing Cl⁻ with weaker donors as NO₃⁻, ClO₄⁻ or BF₄⁻, should point only one atom towards

the metal (O, O and F, respectively). We preferred to analyze the most extreme situation, corresponding to an anion completely out of the coordination sphere, for instance BPh_4^- , and therefore we performed a DFT study for the cation $[\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)]^+$ (Fig.3), see Table 1. In comparison with the cyanide and chloride structures there are shorter Au-P bonds due to the increased s bond character (33%) at the metal because a pure “ AuP_3 ” system implies a sp^2 hybrid. However, a perfectly planar geometry is not obtained through DFT in the minimization process, possibly because of a flattened shape at the bottom of the energy minimization curve.

To conclude, a clear trend emerges when the anion X^- is varied in $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{X}$ molecules, a strong (soft) donor as cyanide penetrates markedly the coordination sphere establishing the most tetrahedral geometry with $\langle\text{P-Au-P}\rangle = 109.6^\circ$ and $\langle\text{P-Au-X}\rangle = 105.4^\circ$, which are close to the tetrahedral angle corresponding to 4 equal ligands (109.5°). The weaker donor chloride ($\text{X}^- = \text{Cl}^-$) is slightly displaced from the coordination sphere with consequent strengthening of Au-P bonds ($\langle\text{Au-P}\rangle$ is 2.524 \AA for Cl^- and 2.548 \AA for CN^-). Accordingly, a more pyramidal geometry is stabilized for Cl^- , with $\langle\text{P-Au-P}\rangle = 112.7^\circ$ or $\langle\text{P-Au-X}\rangle = 102.1^\circ$. When the anion is completely out of the coordination sphere, the DFT analysis of $[\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)]^+$ shows further strengthening of Au-P bonds ($\langle\text{Au-P}\rangle = 2.498 \text{ \AA}$) and a geometry ($\langle\text{P-Au-P}\rangle = 118.7^\circ$) very close to the trigonal planar “ AuP_3 ” system ($\langle\text{P-Au-P}\rangle = 120^\circ$). X-ray and DFT data for $\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}$ show good agreement, although in the crystal the Au-Cl bond appears lengthened with consequent strong Au-P bonds. This feature is probably associated with packing effects that are known to be important in Au-phosphine compounds as shown by $[\text{Au}(\text{PPh}_3)_4]^+$, which was studied crystallographically in 2 different systems. Thus, tetrakis(triphenylphosphine)-gold(I) tetraphenylborate ethanol solvate [15], shows 2 Au-P bond lengths of 2.60 \AA and 2 of 2.61 \AA , whereas tetrakis(triphenylphosphine)-gold(I) tetraphenylborate acetonitrile solvate [15] has 2 Au-P bonds of 2.56 \AA and 2 of 2.50 \AA .

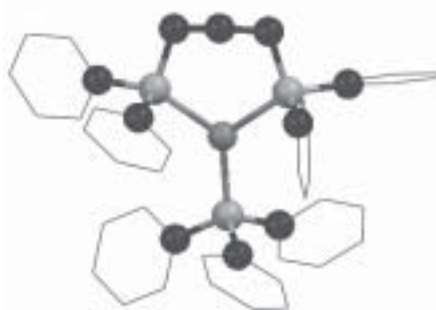


Figure 3. DFT molecular structure of $[\text{Au}(\text{PPh}_3)(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)]^+$

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