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

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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 "AuP_3" 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 geometria 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 geometria 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 descripta 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, (PR_3)AuX, $X^- =$ anion, in contrast with its homologue Ag(I) which prefers tetrahedral geometries, at least in the solid state, as in $Ag(PR_3)_3X$, $\{Ag[(PR_3)]_2X\}_2$, $[Ag(PR_3)X]_4$ and $[Ag(PR_3)_4]X$ [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), (PEt_3)AuL, whose anion L is a thio-glucose derivative.

In contrast with Au^+, the Au^+ cation is unstable but can be generated *in situ* from reduction by thiodiglycol of the Au(III) species $Na[AuCl_4]$ 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]:

$$Au(PPh_3)Cl + Ph_2P(CH_2)_3PPh_2 \rightarrow Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl \qquad (1)$$

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 $[Au(Ph_2P(CH_2)_nPPh_2)]Cl$, n = 2, 3 [8]. The antitumor activity of $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ (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.
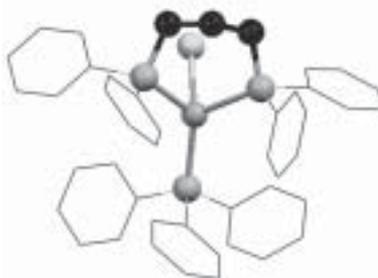

Figure 1. *DFT molecular structure of Au(PPh₃)(Ph₂P(CH₂)₃PPh₂)Cl; ball and stick bonds for non-Ph atoms.*

Experimental

The structural features of all compounds were analyzed as follows. Starting coordinates were obtained from the X-ray molecular structure of $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ [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 $[Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)]^+$, obtained by eliminating the Cl^- anion from the $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ Dmol3 minimized structure, and (b) $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)CN$, obtained by replacing Cl^- with a CN^- moiety in $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$.

Results And Discusion

As seen in Table 1, comparison between X-ray and DFT molecular structures of $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ 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, $Au(PPh_3)_3Cl$ 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 $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)X$ compounds, $Ph_2P(CH_2)_3PPh_2 = DPPP$.*

	$Au(PPh_3)(DPPP)Cl$		$[Au(PPh_3)(DPPP)]^+$	$Au(PPh_3)(DPPP)CN$
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: [1]Data 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 $\sum$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 $\sum$P-Au-P angles close to 3x109.5° = 328.5°.

In the tetrahedral [Au(PPh$_2$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 328-342° [13], suggesting significant packing effects in the crystalline cell. Likewise, they may explain the different Au-Cl length in Au(PPh$_3$)(Ph$_2$P(CH$_2$)$_3$PPh$_2$)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 PR$_3$, R = *p*-tolyl, and in fact, no more than 3 PR$_3$ groups enter the coordination sphere stabilizing Ag(PR$_3$)$_3$CN [2]. This feature is in contrast with weaker donor anions such as nitrate, since [Ag(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 Au(PPh$_3$)(Ph$_2$P(CH$_2$)$_3$PPh$_2$)CN versus 112.7° for Au(PPh$_3$)(Ph$_2$P(CH$_2$)$_3$PPh$_2$)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 Au(PPh$_3$)(Ph$_2$P(CH$_2$)$_3$PPh$_2$)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 Au(PPh$_3$)(Ph$_2$P(CH$_2$)$_3$PPh$_2$)CN as the isolated molecule is studied. The only example of non-linear terminal cyanide derivative studied with X-rays is the trimetallic cation [(Ph$_3$P){AgS$_3$WOCu}(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 Au(PPh$_3$)(Ph$_2$P(CH$_2$)$_3$PPh$_2$)CN.
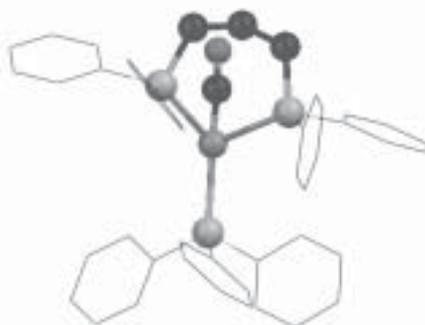
Figure 2. *DFT molecular structure of Au(PPh$_3$)(Ph$_2$P(CH$_2$)$_3$PPh$_2$)CN*

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 NO$_3$⁻, ClO$_4$⁻ or BF$_4$⁻, 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 $[Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)]^+$ (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 $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)X$ molecules, a strong (soft) donor as cyanide penetrates markedly the coordination sphere establishing the most tetrahedral geometry with <P-Au-P> = 109.6° and <P-Au-X> = 105.4°, which are close to the tetrahedral angle corresponding to 4 equal ligands (109.5°). The weaker donor chloride ($X^- = Cl^-$) is slightly displaced from the coordination sphere with consequent strengthening of Au-P bonds (<Au-P> is 2.524 Å for Cl^- and 2.548 Å for CN^-). Accordingly, a more pyramidal geometry is stabilized for Cl^-, with <P-Au-P> = 112.7° or <P-Au-X> = 102.1°. When the anion is completely out of the coordination sphere, the DFT analysis of $[Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)]^+$ shows further strengthening of Au-P bonds (<Au-P> = 2.498 Å) and a geometry (<P-Au-P> = 118.7°) very close to the trigonal planar "AuP_3" system (<P-Au-P> = 120°). X-ray and DFT data for $Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)Cl$ 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 $[Au(PPh_3)_4]^+$, 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 Å and 2 of 2.61 Å, whereas tetrakis(triphenylphosphine)-gold(I) tetraphenylborate acetonitrile solvate [15] has 2 Au-P bonds of 2.56 Å and 2 of 2.50 Å.
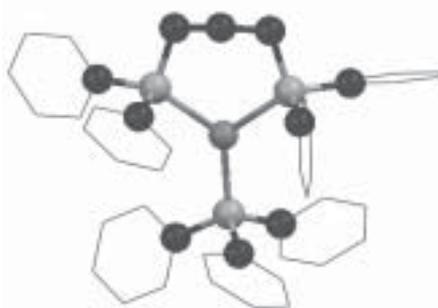

Figure 3. DFT molecular structure of $[Au(PPh_3)(Ph_2P(CH_2)_3PPh_2)]^+$

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