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A gold(I) complex with a vitamin K_3 derivative: Characterization and antitumoral activity

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Abstract

Reaction of the vitamin K_3 derivative menadione sodium bisulfite thiosemicarbazone (NaK_3TSC) with chloro(triethylphosphine)gold(I) afforded the complex $[AuPEt_3(K_3TSC)]$. This compound consists of discrete molecules in which the metal is almost linearly coordinated to P and S. Preliminary *in vitro* screening showed significant anti-cancer activity, notably against the cisplatin-resistant cell line A2780cis.

Keywords: Gold(I) complex; Vitamin K_3; X-ray structure; Antitumoral activity

Vitamin K_3 (menadione) is a synthetic member of the vitamin K group, a loosely related set of fat-soluble derivatives of 2-methyl-1,4-naphthoquinone. Menadione sodium bisulfite (MSB) is a water-soluble derivative of vitamin K_3 that has significant anticancer properties [1].

Certain thiosemicarbazones and metal–thiosemicarbazone complexes also have antitumour activity [2], as do certain gold(I) phosphine derivatives [3] (it has been suggested that the latter are prodrugs acting as vehicles for their biologically active moieties [4]). MSB thiosemicarbazone (NaK_3TSC; Scheme 1) and a number of its complexes with metals have been reported to posses antibacterial activity [5]. To investigate the possibility that a complex of NaK_3TSC with a gold phosphine might inherit the biological properties of its component moieties, possibly in a synergistic manner, in this work we prepared the new complex $[AuPEt_3(K_3TSC)]$, determined its structure by X-ray crystallography, and initiated evaluation of its biological properties. Although complexes of thiosemicarbazones with organometallic derivatives of gold(III) have been described previously [6], $[AuPEt_3(K_3TSC)]$ is, as far as we know, the first gold(I) complex with a thiosemicarbazone ligand. $[AuPEt_3(K_3TSC)]$ (Fig. 1) consists of discrete molecules in which the gold(I) centre is coordinated almost linearly to the K_3TSC^- sulfur [Au–S = 2.319(1) Å] and the phosphine phosphorus [P–Au–S = 172.15(5)°]. Unlike that of most thiosemicarbazonates, the thiosemicarbazone chain of $[AuPEt_3(K_3TSC)]$ is not deprotonated, the charge of the K_3TSC^- anion being due to loss of Na^+ from the MSB moiety. Perhaps because of this, the configuration of the thiosemicarbazone chain is basically the same as in $NaK_3TSC \cdot 5H_2O$ [3]. Nevertheless, S-metallation does cause a partial shift towards the thiol form, lengthening the C(1)–S(1) bond from 1.696(2) to 1.718(6) Å and shortening C(1)–N(2) from 1.358(2) to 1.343(7) Å [the change in the C(1)–N(1) distance is close to the e.s.d.s.].

Intermolecular hydrogen bonds are observed between the hydrogen atoms of the carbothioamide group and two oxygen atoms in neighboring molecules, Fig. 2, one

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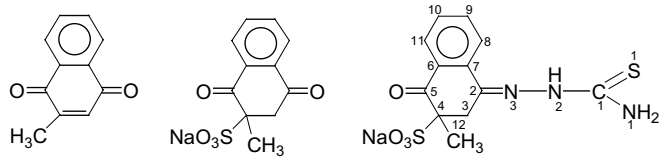

Scheme 1.

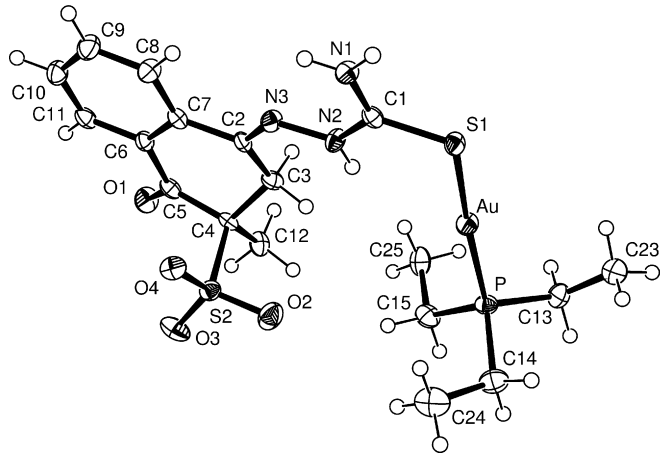

Fig. 1. X-ray crystal structure of the complex [$AuPEt_3(K_3TSC)$]. Principal metal–ligand bond lengths (Å) and angles (°): Au–P 2.2692(15), Au–S(1) 2.319(1), C(1)–S(1)–Au 106.9(2), P–Au–S(1) 172.15(5).

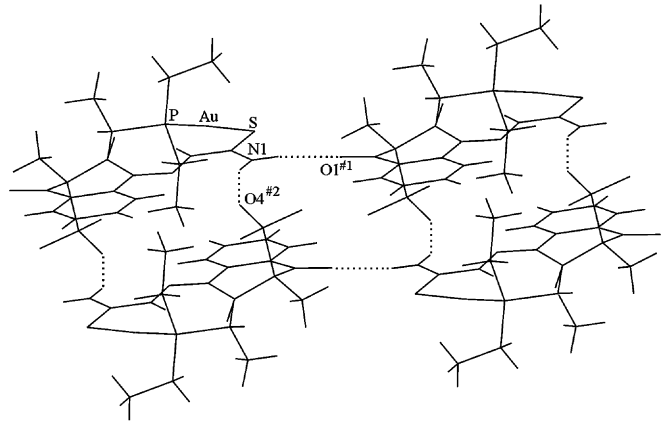

Fig. 2. Intermolecular hydrogen bonds (dotted line) in [$AuPEt_3(K_3TSC)$].

belonging to the bisulfite group and the other to the keto group [N(1)–H(1)···O(1)# = 2.890(6), # = x, $y+1$, z; N(1)–H(2)···O(4)#2 = 2.865(6), #2 = $-x$, $-y+1$, $-z$]. Additional hydrogen bonds, including the intramolecular N(1)–H···N(3) bridge typical of undeprotonated thiosemicarbazones, are included as Supplementary material. No gold–gold interactions are observed (Au···Au = 5.848 Å), probably due to the bulk of the ligands. Both the thiosemicarbazide chain and the naphthoquinone moiety are rather planar (rms = 0.0135 and 0.1210, respectively) and almost coplanar (dihedral angle 4.25°), the cyclic fragment is mainly distorted around the carbon atoms C(3) and C(4).

In keeping with the structural features of [$AuPEt_3(K_3TSC)$] described above, its IR and Raman spectra show bands at 395 and 367 (366) cm^{-1} that are absent from the spectra of the free ligand and can be ascribed to the ν(Au–P) and ν(Au–S) stretching modes, respectively [7].

The ^1H and ^{13}C NMR spectra of the ligand and the gold complex were recorded in DMSO-d_6 solution and elucidated by means of COSY ^1H–^1H and HMBC ^1H–^{13}C experiments. Only the signals corresponding to the thiosemicarbazide moiety are shifted from their positions in the free ligand. As expected, the ^1H spectrum of the complex shows a singlet at 11.36 ppm due to the −N(2)H proton, supporting the presence of this proton in solution. The N(1)H_2 protons give rise to two broad bands at 8.29 and 8.07 ppm in the spectrum of the free ligand and at 9.47 and 9.04 ppm in the spectrum of [$AuPEt_3(K_3TSC)$]. The difference in magnetic behaviour between these two protons is attributable to the rotation of the amine group around the C(1)–N(1) bond being restricted by both the partial multiplicity of this bond and the intramolecular N(1)–H···N(3) hydrogen bond (vide supra). The two N(1)H signals coalesce and shift upfield when the ligand spectrum is recorded at 343 K and that of [$AuPEt_3(K_3TSC)$] at 370 K, the higher coalescence temperature for [$AuPEt_3(K_3TSC)$] probably being due to a slight increase in C(1)–N(1) bond order upon S-metallation (cf. the solid state results discussed above). This metallation also affects the C(1) signal, which shifts from 178.9 ppm in the free ligand to 171.2 ppm in the complex. The shielding of this nucleus is in keeping with the presence of a gold–sulphur bond and the resulting partial thione-to-thiol evolution of K_3TSC^- in [$AuPEt_3(K_3TSC)$] [8].

The ^{31}P spectrum shows a single resonance at 39.4 ppm that is characteristic of triethylphosphine gold(I) compounds with a gold–sulphur bond [9]. The presence of this bond in solution is also confirmed by the positions of the triethylphosphine signals in the ^1H and ^{13}C NMR spectra [10].

In a preliminary screening experiment we evaluated the *in vitro* activity of the ligand and the gold complex against the cisplatin-sensitive cell line A2780 and the cisplatin-resistant line A2780cis [5] (see Table 1). Cisplatin was used as the control compound. NaK_3TSC had very little effect on the viability of cisplatin-sensitive cells, and about 14 times less effect on the cisplatin-resistant line. By contrast, the gold complex was as cytotoxic as cisplatin for A2780,

Table 1
In vitro cytotoxicity of NaK_3TSC and [$AuPEt_3(K_3TSC)$]

Compound	Cell line	IC_{50} (μM)
Cisplatin	A2780	0.51 ± 0.09
NaK_3TSC	A2780	273 ± 23
[$AuPEt_3(K_3TSC)$]	A2780	0.45 ± 0.08
Cisplatin	A2780cis	4.2 ± 0.6
NaK_3TSC	A2780cis	3732 ± 167
[$AuPEt_3(K_3TSC)$]	A2780cis	0.40 ± 0.06

and ten times more so for A2780cis. This possibly means that the formation of the uncharged complex facilitates the delivering of the K_3TSC^- anion to its biological target. We are currently exploring the biological effects of analogues with modified thiosemicarbazone ligands and for gold centres with an oxidation state other than I.

In conclusion, we have synthesized the new compound $[AuPEt_3(K_3TSC)]$, characterized its structure, and explored its *in vitro* cytotoxic activity. This seems to be the first gold(I) complex containing a thiosemicarbazone ligand. In the solid state, the gold atom is coordinated to the sulfur atom of the thiosemicarbazone and the phosphorus atom of the phosphine in an almost linear S–Au–P arrangement. NMR data suggest that this arrangement probably remains intact in DMSO solution. Preliminary screening for antitumour activity suggests that whereas the K_3TSC^- ligand has very little effect, that of $[AuPEt_3(K_3TSC)]$ is very significant and is not reduced by resistance to cisplatin.

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Appendix A. Supplementary data

Supplementary data associated with this article (details of the synthesis and characterization of $[AuPEt_3(K_3TSC)]$, and antitumoral test data) can be found, in the online version, at doi:10.1016/j.jinorgbio.2006.07.006.

References

[1] S.A. Akman, M. Dietrich, R. Chlebowski, P. Limberg, J.B. Block, Cancer Res. 45 (1995) 5257–5262.
[2] H. Beraldo, D. Gambino, Mini Rev. Med. Chem. 4 (2004) 159–165.
[3] M.J. McKeage, L. Maharaj, S.J. Berners-Price, Coord. Chem. Rev. 232 (2002) 127–135.
[4] E.R.T. Tiekink, Gold Bull. 36 (2003) 117–124.
[5] Q. Li, H. Tang, Y. Li, M. Wang, L.-F. Wang, C.-G. Xia, J. Inorg. Biochem. 78 (2000) 167–174.
[6] J.S. Casas, M.V. Castaño, M.C. Cifuentes, J.C. García-Monteagudo, A. Sánchez, J. Sordo, U. Abram, J. Inorg. Biochem. 98 (2004) 1009–1016.
[7] M.M. El-Etri, W.M. Scovell, Inorg. Chem. 29 (1990) 480–484.
[8] J.S. Casas, A. Sánchez, J. Sordo, A. Vázquez-López, E.E. Castellano, J. Zukerman-Schpector, M.C. Rodríguez-Argüelles, U. Russo, Inorg. Chim. Acta 216 (1994) 169–175.
[9] M.T. Coffer, C.F. Shaw III, M.K. Eidsness, J.W. Watkins, R.C. Elder, Inorg. Chem. 25 (1986) 333–339.
[10] A.L. Hormann, C.F. Shaw III, D.W. Bennett, W.M. Reiff, Inorg. Chem. 25 (1986) 3953–3957.