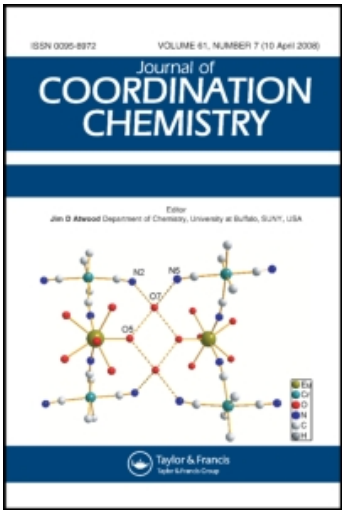

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Solution and solid state NMR studies of some selenium analogues of auranofin (an anti-arthritic gold drug)

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Solution and solid state NMR studies of some selenium analogues of auranofin (an anti-arthritic gold drug)

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Three mixed ligand complexes of gold(I) with phosphines and selenones, $[Et_3PAuSe{=}C<]Br$ as analogues of auranofin (Et_3PAuSR) have been prepared and characterized by elemental analysis, IR and NMR methods. A decrease in the IR frequency of the C=Se mode of selenones upon complexation is indicative of selenone binding to gold(I) via a selenone group. An upfield shift in ^{13}C NMR for the C=Se resonance of the selenones and downfield shifts in ^{31}P NMR for the R_3P moiety are consistent with the selenium coordination to gold(I). ^{13}C solid state NMR shows the chemical shift difference between free and bound selenone to gold(I) for ImSe and DiazSe to be ca 10 and 17 ppm respectively. Large ^{77}Se NMR chemical shifts (55 ppm) upon complexation in the solid state for $[Et_3PAuDiazSe]Br$ compared to $[Et_3PAuImSe]Br$ (10 ppm) indicates the former to be more stable and the Au–Se bond to be stronger than in the latter complex.

Keywords: Gold(I) complexes; Selenones; Triethylphosphine; Solid state NMR

1. Introduction

Current interest in the study of gold(I) phosphine complexes owes much to the successful use of auranofin (a gold(I) compound containing triethylphosphine and tetraacetylthioglucose ligands) for the treatment of rheumatoid arthritis [1,2]. In addition, auranofin and a number of phosphine–gold(I) complexes are also known to exhibit promising anti-tumor properties [3–5]. However, toxicity associated with the use of these gold(I) complexes is a serious disadvantage. Recent research has suggested that heavy metal toxicity can be reduced if selenium derivatives are employed [6]. Therefore, it will be of interest to report some selenium analogues of auranofin and the present studies describe the synthesis and characterization of some gold(I) complexes with Et_3P and selenones as *trans* ligands to gold(I). Some other reports

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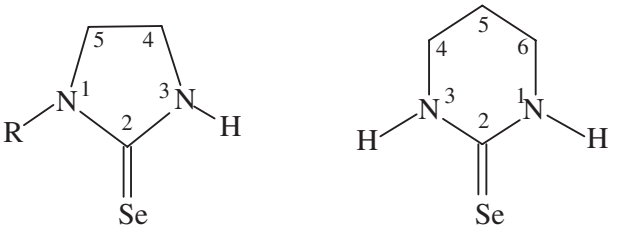
concerning (phosphine)gold(I)–selenium complexes are also available in the literature [7–10]. The structures of the selenones used in this study are described in scheme 1.



(a) (b, c)

(a) R = H; imidazolidine-2-selenone (ImSe)
(b) R = CH_3; *N*-methylimidazolidine-2-selenone (MeImSe)
(c) 1,3-diazinane-2-selenone (DiazSe)

2. Experimental

2.1. *Chemicals*

DMSO-d_6, $(CH_3)_2S$ and all solvents were obtained from the Fluka-Aldrich Chemical Co., Germany. $HAuCl_4 \cdot 3H_2O$ and Et_3P were obtained from the Strem Chemical Co. All the selenones were synthesized according to the procedure described in the literature [11,12]. Et_3PAuBr was prepared according to a published procedure [13].

2.2. *Synthesis of the complexes*

$[Et_3PAuSe{=}C<]Br$ complexes were prepared by the addition of an equimolar amount of selenone in acetonitrile to Et_3PAuBr solution in acetone [8]. After stirring for 15–20 min the resulting colorless solution was filtered and kept in the refrigerator. As a result, white crystalline products were obtained with 40–50 % yield. After preparation, the complexes were stored in a refrigerator. Elemental analyses of these complexes are given in table 1.

Table 1. Elemental analysis and characteristic IR frequencies (cm^{-1}) for $[Et_3PAuSe{=}C<]Br$ complexes.

Complex	Found (Calcd)			m.p. (°C)	ν(C=Se)
	C	H	N		
$[Et_3PAuImSe]Br$	19.87	3.41	5.00	129–130	578
	(19.29)	(3.89)	(5.15)		(558)*
$[Et_3PAuMeImSe]Br$	19.33	3.01	6.14	170 (decomp)	574
	(21.52)	(3.76)	(5.02)		(580)*
$[Et_3PAuDiazSe]Br$	21.25	3.9	4.49	160 (decomp)	594
	(21.52)	(4.15)	(5.02)		(602)*

*Values for free ligands.

2.3. *Spectroscopic measurements*

2.3.1. IR studies. Solid state IR spectra of the ligands and their gold(I) complexes were recorded on a Perkin Elmer FTIR 180 spectrophotometer using KBr pellets in the range 4000–400 cm^{-1}.

2.3.2. Solution NMR studies. ^{1}H NMR spectra were obtained in DMSO-d_6 solutions, on a Jeol JNM-LA 500 NMR spectrometer operating at a frequency of 500.00 MHz. ^{13}C NMR spectra were obtained at 125.65 MHz with ^{1}H broadband decoupling at 298 K. Conditions were: 32 K data points, 0.967 s acquisition time, 1.00 s pulse delay and 45° pulse angle. ^{13}C chemical shifts were measured relative to internal reference TMS. ^{31}P NMR spectra were recorded at 202.35 MHz, using a 0.269 s acquisition time, 5.00 s pulse delay and 6.20 μs pulse width (45°). Chemical shifts were measured relative to external 85% H_3PO_4. ^{77}Se NMR spectra were recorded at 95.35 MHz, using 160 millisecond acquisition time and a 2.00 s pulse delay. Chemical shifts were measured relative to external SeO_2 at 1301 ppm.

2.3.3. Solid state NMR studies. Natural abundance ^{13}C solid state NMR spectra were obtained on a JEOL LAMBDA 500 spectrometer operating at 125.65 MHz (11.74 T), at 25°C. Samples were packed into 6 mm zirconium oxide rotors. Cross polarization and high power decoupling were employed. Pulse delays of 7.0 s and a contact time of 5.0 ms were used in the CPMAS experiments. The magic angle spinning rates were from 2000 to 5000 Hz. Carbon chemical shifts were referenced to TMS by setting the high frequency isotropic peak of solid adamantane to 38.56 ppm. Solid state cross-polarization magic-angle spinning (CPMAS) $^{31}P\{^{1}H\}$ NMR spectra were obtained at ambient temperature on the same spectrometer operating at a frequency of 202.35 MHz. Contact times of 3 ms were used with a proton pulse width of 6 μs and a recycle delay of 10 s. Approximately 500 FIDs were collected and transformed with a line broadening of 50 Hz. Chemical shifts were referenced using an external sample of solid PPh_3 ($\delta = -8.40$ ppm from 85% H_3PO_4). CPMAS ^{77}Se spectra were obtained on the same instrument operating at 95.35 MHz. Contact times of 5 ms with a proton pulse width of 6.0 μs and a recycle delay of 12 s were used. Samples were spun at 3 and 5 kHz at the magic angle to determine the isotropic peak. Approximately 5000 scans were employed. ^{77}Se chemical shifts are referenced using an external ammonium selenate sample by setting its isotropic peak to 1040.2 ppm [14] relative to liquid Me_2Se at 23°C. The CPMAS spectra (selenone carbons, ^{31}P and ^{77}Se) containing spinning side-band manifolds were analyzed using a program based on the method of Maricq and Waugh [15] and developed by Durham University, UK, using an iterative method.

3. Results and discussion

The IR frequencies for the ν(C=Se) mode of free selenones and for [$Et_3PAuSe{=}C<$]Br complexes are given in table 1. The ν(C=Se) vibration of selenones [16] is somewhat shifted towards lower frequency upon complexation, as observed for other selenone complexes [17,18]. The ν(NH) band, which appears around 3200 cm^{-1} in the free ligands, is shifted to higher wave numbers upon coordination to gold(I). The presence

Table 2. ^{31}P, ^{1}H and ^{13}C NMR chemical shifts (ppm) of the ligands and their gold(I) complexes.

Complex and/or Ligand	δ ^{31}P	δ ^{1}H (N–H)	C-2	C-4	C-5	C-6
Et_3PAuBr	38.05[a]	–	–	–	–	–
ImSe	–	8.48	177.09	44.94	44.94	–
$[Et_3PAuImSe]Br$	38.84	8.96	172.80	45.09	45.09	–
MeImSe	–	8.47	178.67	42.07	50.35	35.06[b]
$[Et_3PAuMeImSe]Br$	38.44	8.66	177.44	42.38	50.64	35.27[b]
DiazSe	–	8.23	169.14	40.10	18.76	40.10
$[Et_3PAu\text{-}DiazSe]Br$	39.78	8.95	161.94	40.30	18.24	40.30

[a]δ ^{31}P of $Et_3PAuCl = 34.52$ ppm. [b]N–C1 carbon.

of a band around 3200 cm^{-1} in the free ligands as well as in the complexes indicates the existence of the selenone form of the ligands in the solid state.

In the ^{31}P NMR spectra of $[Et_3PAuSe{=}C<]Br$ complexes in DMSO-d_6, a sharp singlet was observed for the Et_3P ligand. The ^{31}P NMR chemical shifts of the complexes are given in table 2. It is observed that the ^{31}P resonance of the complexes appears downfield compared to that of Et_3PAuBr. This is related to the Π accepting ability of phosphines from gold(I) in these complexes. The donation of electron density by selenones to gold(I) increases back donation from gold(I) towards phosphines, which would increase the double bond character of the Au–P bond resulting in a deshielding effect at phosphorus. The smallest shift in $[Et_3PAuMeImSe]Br$ suggests that MeImSe is the least basic of the selenones.

In ^{1}H NMR the N–H signals were broadened upon coordination and shifted downfield from their positions in the free ligands. The deshielding is related to an increase in Π electron density in the C–N bond upon complexation [19,20]. The appearance of a N–H signal in the ^{1}H NMR of all the ligands after complexation shows that they coordinate to gold(I) in the selenone form in solution. ^{1}H NMR chemical shifts of the N–H protons of the ligands and their gold(I) complexes are given in table 2.

The ^{13}C chemical shifts of the ligands and complexes are also given in table 2. In all complexes, the C-2 resonance is shifted upfield compared to its position in the free ligands in accordance with the data observed for other complexes of gold(I) with selenones [17]. Upon coordination to a metal via the selenium atom, the carbon–selenium double bond character is reduced and that of the carbon–nitrogen single bond is increased resulting in an upfield shift for the C-2 resonance [7,17]. This suggests that in these complexes gold(I) is bonded to selenones through the selenium atom only. The other resonances are only slightly shifted. Due to an increase in the Π character of the C–N bond, a minor deshielding effect is observed at C-4/6. In the case of bonding through nitrogen, a considerable shift of the C-4 resonance would have been observed. A comparison of the shift differences for the C-2 resonance of the complexes (table 2) shows that the greatest shift is observed for the DiazSe ligand. Thus it would be expected that DiazSe would form the most stable complex with gold(I) among the selenones. The MeImSe complexes with the smallest shifts should be least stable. The data for the complexes presented in this study would provide a basis for understanding and predicting the interaction of gold(I) with other phosphine and selenone ligands. Earlier, we have reported $[Et_3PAuImt]Cl$ and $[Et_3PAuDiaz]Cl$ complexes [21]. The chemical shift differences between free and bound ^{13}C resonances are 5.95 and 6.38 ppm, respectively, which are similar to the complexes studied here.

Table 3. ^{77}Se chemical shifts (ppm) of the ligands and their complexes in DMSO-d_6 (^{77}Se chemical shifts from 1301 ppm from SeO_2 in D_2O as external reference).

Complex	Chemical shift (δ)	Chemical shift of free ligands (δ)
[Et_3PAuImSe]Br	90.94	88.79
[Et_3PAuMeImSe]Br	89.77	88.00
[Et_3PAuDiazSe]Br	212.65	214.93

As shown in table 3, there is not much difference between free and bound resonances for ^{77}Se NMR in solution.

The room temperature ^{77}Se CPMAS spectra of two of the complexes are shown in figure 1. The spectra show a set of spinning sidebands arising from the large shielding anisotropy. Selenium is considered as an isolated nucleus; the interaction with ^{13}C at natural abundance is below the detection limit and with a line broadening of 50 Hz, we were unable to resolve the two bond P–Se coupling ($^2J_{P-Se}$). Hence we could not perform spinning side-band analysis to obtain tensor parameters corresponding to the two spin states of phosphorus, which would yield sum and difference of the shielding tensor and dipolar tensor. We assume that ^{77}Se chemical shift anisotropy is substantially greater than the dipolar coupling constant over the P–Se distance of 4.7 Å. Moreover, at the rotor speed of 4.5 kHz used, we were, most probably, spinning out the dipolar coupling. The fact that we were able to get a good fit for the ^{77}Se spinning sideband manifold intensities with the calculated intensities justifies the above assumption.

The principal components of the ^{77}Se, ^{31}P and ^{13}C (selenone carbon) chemical shift tensors σ_{ii} were calculated from spinning sideband intensities employing an iterative computer program. Nuclear magnetic shielding tensors of the ligands and the complexes are shown in table 4, along with the anisotropy, which is related to the breadth of the chemical shift tensor, and the asymmetry factor, which describes the shape of the powder pattern [22]. The ^{13}C and ^{31}P chemical shift tensors are believed to have an error of $\pm$ 1 ppm, and that of ^{77}Se is $\pm$ 4 ppm.

It is seen that the ^{77}Se isotropic shift moves 9.6 ppm and 55.1 ppm to high frequency upon complexation for complexes [Et_3PAuImSe]Br and [Et_3PAuDiazSe]Br, respectively. Negative chemical shift anisotropy has been reported [12] for the ligand ImSe, indicating a possible swap of σ_{11} and σ_{33}. Hence, when tensor components are considered, a shielding of 270 ppm is observed for the ^{77}Se shielding tensor σ_{11}, while 102 ppm and 199 ppm deshielding were observed for the shielding tensors σ_{22} and σ_{33}, respectively, on complexation of ImSe. The greater paramagnetic contribution, due to possible π bonding between Se and Au, leads to less shielding along the Se–Au axis [23]. Hence the molecular axis containing the Au–Se bond may be associated with the principal value σ_{33} of the ^{77}Se chemical shift tensor in [Et_3PAuImSe]Br. The ^{77}Se chemical shift tensors in complex [Et_3PAuDiazSe]Br, show deshielding by 79 ppm, 35 ppm and 52 ppm respectively for σ_{11}, σ_{22}, and σ_{33}, compared to that in DiazSe. This suggests that the molecular axis containing the Au–Se bond is not along any principal axes of the tensors. From the above data for the two complexes, we infer that they do not have similar crystal structures.

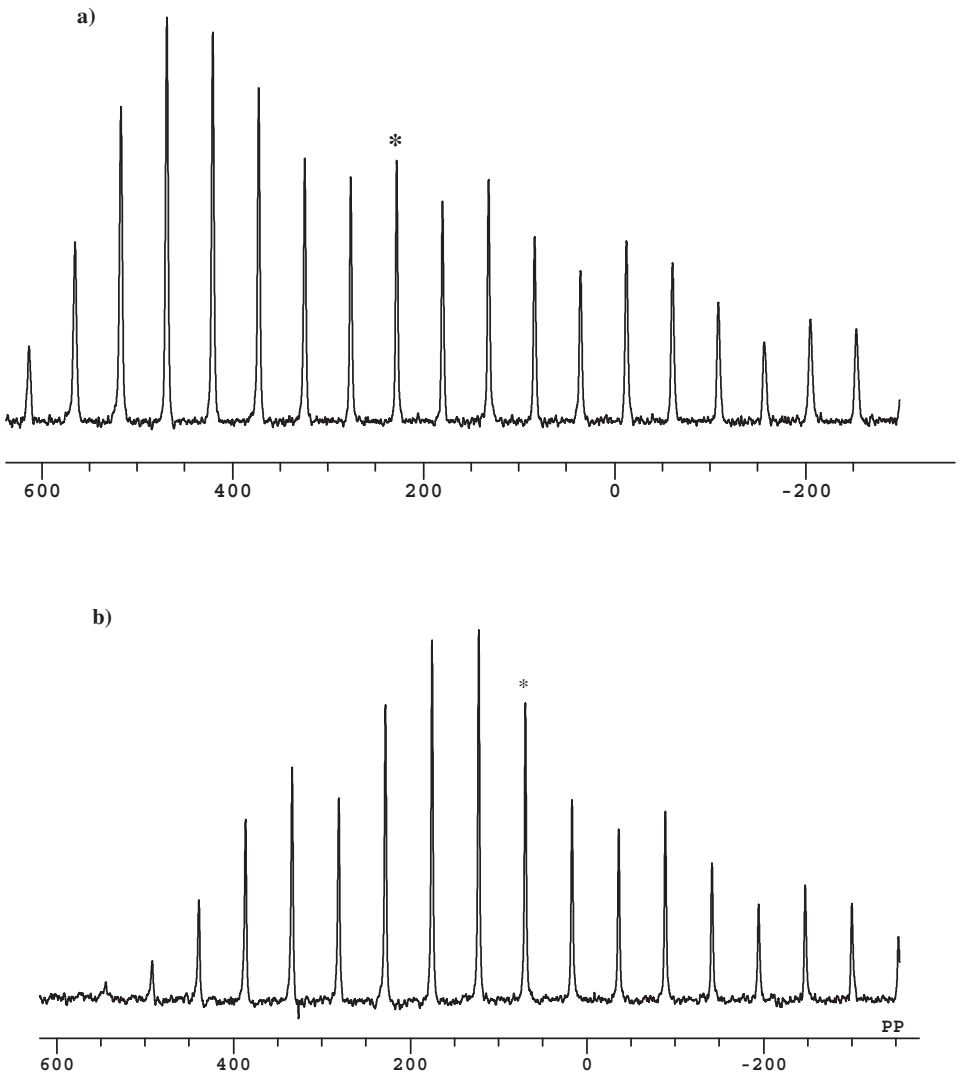


Figure 1. ^{77}Se CPMAS spectra of (a) [Et_3PAuDiazSe]Br and (b) [Et_3PAuImSe]Br. The asterisk denotes isotropic peaks.

The selenone ^{13}C isotropic shifts for the complexes move to lower frequency upon complexation. Studies of the chemical shift tensors of carbonyl carbon have shown [24] that the principal axis of the tensor σ_{33} is perpendicular to the carbonyl sp^2 plane and the principal axes associated with σ_{22} and σ_{11} components are ca 10° and 80° off the C=O bond, respectively. For the selenone carbon in [Et_3PAuImSe]Br, we observe a very large shielding of 39 ppm for the component σ_{11} relative to the free ligand, and this can be assigned to the axis perpendicular to the sp^2 plane. Both σ_{22} and σ_{33} components in [Et_3PAuImSe]Br are deshielded by ca 5 to 6 ppm upon complexation. In [Et_3PAuDiazSe]Br, the selenocarbonyl carbon chemical shift tensors are shielded by 33 ppm, 11 ppm and 6 ppm, respectively, for the components σ_{11}, σ_{22}

Table 4. Chemical shift tensors.[a]

Complex	δ_{iso}	σ_{11}	σ_{22}	σ_{33}	$\Delta\sigma$	η
^{13}C Tensors						
ImSe[b]	175.0	−271	−187	−67	162	0.78
[Et$_3$PAuImSe]Br	165.5	−232	−193	−72	141	0.41
DiazSe[b]	174.1	−257	−204	−61	170	0.47
[Et$_3$PAuDiazSe]Br	157.2	−224	−193	−55	153	0.31
^{31}P Tensors						
[Et$_3$PAuImSe]Br	47.2	−74	−56	−12	52	0.51
[Et$_3$PAuDiazSe]Br	48.0	−70	−60	−14	51	0.30
^{77}Se Tensors						
ImSe[b]	59.8	604	−57	−725	−999	0.99
[Et$_3$PAuImSe]Br	69.4	−455	−159	405	712	0.63
DiazSe[b]	173.1	−541	−390	412	878	0.26
[Et$_3$PAuDiazSe]Br	228.2	−620	−425	360	882	0.33

[a]Isotropic shielding, $\sigma_i = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3$; $\Delta\sigma = \sigma_{33} - 0.5(\sigma_{11} + \sigma_{22})$; $\eta = 3(\sigma_{22} - \sigma_{11})/2\Delta\sigma$. [b]From Ref. [12].

and σ_{33} relative to the free ligand DiazSe. The σ_{11} component, showing large shielding, can be assigned to the axis perpendicular to the sp^2 plane as in the previous case.

The ^{31}P shielding anisotropies in [Et$_3$PAuImSe]Br and [Et$_3$PAuDiazSe]Br are rather small in comparison to that in four-coordinate systems [25]. The ligand change on the other side of gold seems to have minimal effect on the ^{31}P tensors.

As noted earlier, ^{77}Se NMR (table 3) in solution shows no significant difference between free and bound resonances; however, solid state ^{77}Se NMR shows a significant difference. It is interesting to note that thiourea, which is much less basic than CN^- and thiols, was able to replace both the ligands Et$_3$P and $SATg^-$ simultaneously from gold(I) in auranofin (Et$_3$PAuSATg, where $SATg^- = 2,3,4,6$-tetra-*o*-acetyl-1-thio-β-*D*-glucopyranosato-*S*) forming [Et$_3$P–Au–Tu]$^+$ and Tu–Au–SATg complexes [26–28]. Therefore it can be concluded that both *trans* ligands to gold(I) can easily be replaced by S-containing ligands like glutathione, ergothionine, etc. This fast replacement of ligands from gold(I) may be one of the causes of side effects of the gold(I) drugs. Selenone-containing ligands are softer bases than thiones towards gold(I) and complexation of these ligands with gold(I) will involve a stronger Au–Se bond. Therefore, exchange with other ligands will be slower and consequently they may be better alternative drugs and less toxic than S-containing analogues.

In conclusion, ^{13}C solid state NMR shows the chemical shift difference between free and bound selenone to gold(I) for ImSe and DiazSe to be ca 10 and 17 ppm respectively. The ^{77}Se NMR shows a 10 and 55 ppm difference, respectively, for the same compounds indicating [Et$_3$PAuDiazSe]Br is more stable and the Au–Se bond is stronger than for [Et$_3$PAuImSe]Br. This observation indicates that exchange with other ligands (thiols or thiones) will be slower in the human body. These properties may lead to better alternative drugs that are less toxic than Et$_3$P–Au–SR species.

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