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Complexes of Gold(I) and 5-Substituted Tetrazoles

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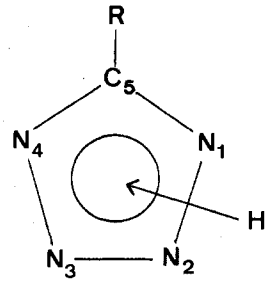
Metal complexes of substituted tetrazoles (see I for structure



I

and numbering convention) have been of interest lately to pharmaceutical investigators because of their ability to act as antiinflammatory agents.[2,3]

These complexes can exhibit several modes of coordination. They may bond in unidentate fashion through the N_1 or the N_2 position of the tetrazole ring or they can act as a bidentate ligand (I). Formation of π-bonded sandwich compounds analogous to ferrocene has never been observed. For complexes of 5-substituted tetrazole and Pd(II) and Pt(II), using proton NMR, both N_1 and N_2 bonded isomers were identified[4] in solution. Several single-crystal x-ray structural determinations have been reported for tetrazole complexes, including *cis*-bis[dimethyl(phenyl)phosphine]bis(5-methyltetrazolato)palladium(II),[5] $[(Me_2Ph)P][RCN_4]_2Pd$, the tetraphenylarsonium salt of tetrakis(1-isopropyltetrazol-5-ato)aurate(III), $[AsPh_4][Au(5\text{-}RCN_4)_4]$,[6] and the dimer of 5-trifluoromethyltetrazolatotriphenylphosphinesilver(I), $Ag_2(CF_3tet)_2(PPh_3)_2$.[7]

Since gold(I) complexes[8] and tetrazoles[9] have been shown to have antiinflammatory and antitumor[2] activity, the new triphenylphosphinegold(I)–tetrazole complexes containing tetrazoles, 5-substituted with groups of different electronegativities, reported below are being tested for antiinflammatory and anticancer activity.

Experimental Section

Chloroauric acid ($HAuCl_4 \cdot 3H_2O$) was purchased from Matheson Coleman and Bell. Triphenylphosphine was obtained from Aldrich Chemical Co. 5-Aminotetrazole monohydrate was purchased from Eastman Organic Chemicals. The methanol-d_4 was obtained from Bio-Rad Laboratories.

CH_2Cl_2, hexane, and pentane were purified by stirring with concentrated sulfuric acid. Methanol was purified by distillation. Other solvents were reagent grade.

Infrared spectra were recorded on either a Beckman IR-18A or a Perkin-Elmer 521 as KBr pellets and Nujol mulls. Proton NMR spectra were recorded on JEOL MH-100 and JEOL C-60HL spectrometers.

Preparations. Tetrazoles. The tetrazoles were prepared using standard literature preparations—5-phenyltetrazole by the method of Herbst and Wilson,[10] 5-trifluoromethyltetrazole by the method of Norris,[11] and 5*H*-tetrazole by the method of Henry and Finnegan.[12] 5-Dimethylaminotetrazole,[13] 5,5′-bitetrazole,[14] and bis(5-tetrazolyl)methane[15] were prepared according to the literature.

Chlorotriphenylphosphinegold(I). This complex was prepared by established methods.[16] The crude $AuClPPh_3$ was recrystallized from CH_2Cl_2/ethanol; mp 243 °C.

Acetatotriphenylphosphinegold(I). This compound was prepared by the method of Nichols.[17] The crude product was recrystallized *rapidly* from CH_2Cl_2/petroleum ether to yield white crystals, mp 186 °C.

5-Aminotetrazolatotriphenylphosphinegold(I). A 0.431-g (0.832-mmol) sample of $AuOAcPPh_3$ and 0.857 g (0.832 mmol) of 5-aminotetrazole monohydrate were dissolved in 25 ml of methanol and stirred for 30 min. The addition of 150 ml of water caused white 5-aminotetrazolatotriphenylphosphinegold(I) to separate from the solution. The crude product was air-dried and then recrystallized from methanol/water or rapidly from CH_2Cl_2/hexane. The procedure is the same for 5-phenyltetrazole and the 5-trifluoromethyltetrazolate anion.

The remaining tetrazole complexes were prepared using similar procedures. The complexes containing 5*H*-tetrazole and 5-dimethylaminotetrazole were prepared using a 1.5 molar excess of tetrazole. Various ratios of $Au(OAc)PPh_3$ were used with 5,5′-bitetrazole and bis(5-tetrazolyl)methane but the only complex obtained had replaced the acidic hydrogen of each tetrazole with a gold complex. In order to obtain complete reaction, it was necessary to stir the reaction containing bis(5-tetrazolyl)methane for 24 h.

Reactions. Methyl Iodide. The reaction of methyl iodide with the 5-aminotetrazolatogold(I) complex was carried out as follows. 5-Aminotetrazolatotriphenylphosphinegold(I) was placed in an NMR tube and dissolved in MeOH-d_4. Five drops of CH_3I was added and NMR observations were begun. After a period of time iodotriphenylphosphinegold(I) formed and separated from solution. This caused the resonances to broaden. However, when the reaction was performed in methanol, the methanol was allowed to evaporate, and the resulting 1- and 2-methyl-5-aminotetrazoles were dissolved in MeOH-d_4 and filtered into an NMR tube, a sharp spectrum was obtained.

Analyses. Chemical analyses and molecular weight determinations were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921. The analytical data are presented in Table I.

Results and Discussion

The 5-substituted tetrazolatotriphenylphosphinegold(I) complexes gave analytical results shown in Table I. The complexes are stable toward moisture and are stable indefinitely in air. Molecular weight determinations indicate the compounds are monomeric in chloroform (Table I). The infrared spectra[18] showed the presence of the tetrazole due to characteristic vibrations of the skeletal ring at 1000–1200 cm^{-1} and the particular bands of the substituent in the 5 position such as the N–H stretch at 3300–3400 cm^{-1} for the 5-aminotetrazole and the C–F vibrations for the 5-trifluoromethyltetrazole between 1100 and 1200 cm^{-1}.

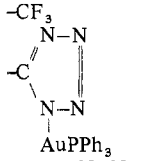
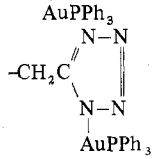
The proton NMR spectrum of the tetrazole complexes showed the expected value for the ratio of protons (Table II). There is also a slight shift of the PPh_3 protons as the R group of the tetrazole becomes more electronegative. As the R group becomes more electronegative, electron density is withdrawn from the tetrazole ring. Molecular orbital calculations on three neutral 5-substituted tetrazoles (R = NH_2, H, and CF_3) confirm that the electron density on the nitrogens of the tetrazole ring decreases as R becomes more electronegative.[19] The electron densities are shown in Table III. The resulting shift of electron density away from P and Au toward the tetrazole would account for the deshielding of the phenyl protons.

It was also observed that when halogenated solvents are used for recrystallization, major contamination is observed. If the impure 5-aminotetrazolegold(I) complex is recrystallized from $MeOH/H_2O$, the resulting complex has a sharp melting point at 178 °C. This melting point is also observed in a fast recrystallization with $CHCl_3$/hexane or CH_2Cl_2/hexane. However, slow recrystallization in halogenated solvents leads to materials with melting points varying from 178 to 130 °C with increasing yellowish coloration. As the melting point is lowered, new lines could be observed in the x-ray powder pattern. The yellowish crystals were separated and found to

Table I. Analytical Results

Compd	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	Mol wt ($CHCl_3$) Calcd	Mol wt ($CHCl_3$) Found	mp, °C
$Au[5\text{-}N(CH_3)_2CN_4]PPh_3$	44.14	44.30	3.71	3.84	12.26	12.28			177
$Au(5\text{-}NH_2CN_4)PPh_3$	41.99	41.91	3.16	3.21	12.89	12.84	543	545	178
$Au(5\text{-}HCN_4)PPh_3$	43.19	42.90	3.06	3.04	10.61	10.54			142
$Au(5\text{-}PhCN_4)PPh_3$	49.67	49.62	3.34	3.32	9.27	9.54	604	563	166
$Au(5\text{-}CF_3CN_4)PPh_3$	40.27	40.21	2.54	2.54	9.39	9.14	596	588	154
$(PPh_3)Au\text{-}CN_4\text{-}CN_4\text{-}Au(PPh_3)$	43.27	42.98	2.86	2.80	10.63	10.81			284
$(PPh_3)Au\text{-}CN_4\text{-}CH_2\text{-}CN_4\text{-}Au(PPh_3)$	43.83	43.67	3.02	2.96	10.49	10.46			233

Table II. 100-MHz ^1H NMR Data for 5-Substituted Tetrazolegold(I) Complexes, $(PPh_3)Au(CN_4R)$

-R	$\delta(PPh_3)^{a,b}$	$\delta(R)^{a,b}$
$-N(CH_3)_2$	7.51	3.09 (CH_3)
$-NH_2$	7.43	4.62 br (NH)
-H	7.50	8.63 (CH)
-Ph	7.56	
$-CF_3$	7.56	
	7.56	
	7.56	4.72 (CH_2)

[a] Ppm downfield from TMS. [b] Measured in $CDCl_3$.

Table III. Calculated Electron Charges for 5-Substituted Tetrazoles

-R	H on N_1 N_4	H on N_1 N_3	H on N_2 N_4	H on N_2 N_3
$-NH_2$	0.356	0.121	0.328	0.139
-H	0.299	0.111	0.291	0.129
$-CF_3$	0.291	0.094	0.278	0.107

be Ph_3PAuCl. Synthetic mixtures could be prepared which matched the melting points for some of the recrystallized Ph_3PAu(5-amtet) (5-amtet = 5-aminotetrazole) samples.

The presence of Ph_3PAuCl and Ph_3PAu(5-amtet) seems to indicate that an oxidative addition followed by a reductive elimination[20] occurred between the $CHCl_3$ (or CH_2Cl_2) and Ph_3PAu(5-amtet) during the recrystallization. This would result in samples of Ph_3PAu(5-amtet) contaminated with Ph_3PAuCl. (See eq 1.) Further work on these reactions is

$$(PPh_3)Au(5\text{-amtet}) + CH_2Cl_2 \rightarrow (PPh_3)\underset{\displaystyle CH_2Cl}{\overset{\displaystyle Cl}{\overset{|}{\underset{|}{Au}}}}(5\text{-amtet})$$
$$\rightarrow (PPh_3)AuCl + \text{1- and 2-chloromethyl-5-aminotetrazole} \quad (1)$$

in progress.

A similar reaction was used in an attempt to determine the mode of coordination of the tetrazole to gold(I). 5-Aminotetrazolegold(I) complex was treated with methyl iodide. This reaction should yield iodotriphenylphosphinegold(I) and either 1-methyl- or 2-methyl-5-aminotetrazole. The position of the methyl on the tetrazole ring could be identified by the proton NMR data and used to elucidate the position of coordination of the tetrazole to the gold. If 5-aminotetrazole is methylated in basic solution,[10] a mixture of 1- and 2-methyl-5-aminotetrazole is obtained, presumably due to the formation of the resonance-stabilized tetrazolate ion. For the results of the methyl iodide exchange reaction to be meaningful, therefore, it would be necessary to obtain only one methyl isomer of the 5-aminotetrazole. The reaction did indeed give the iodotriphenylphosphinetetrazolegold(I) complex[21] which was identified by its melting point and ir spectra. However, a mixture of 1- and 2-methyl-5-aminotetrazole was obtained in about the same ratio as in the methylation of 5-aminotetrazole.[10] This could indicate that the 5-aminotetrazole gold(I) complex is a mixture of the N_1- and N_2-bound isomers, but it seems more likely that the resonance-stabilized tetrazolate ion is displaced from the gold prior to methylation.

The work with the bidentate tetrazoles was undertaken to see if these ligands would form anionic complexes.

$$(PPh_3)AuOAc + \text{bistet}^{2-} \rightarrow [(PPh_3)Au(\text{bistet})]^-$$

As the Experimental Section indicates, only binuclear complexes were obtained even though models show that a favorable size bite for the chelate is possible.

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Registry No. $Au[5\text{-}N(CH_3)_2CN_4]PPh_3$, 59054-10-3; $Au(5\text{-}NH_2CN_4)PPh_3$, 59054-12-5; $Au(5\text{-}HCN_4)PPh_3$, 59054-11-4; $Au(5\text{-}PhCN_4)PPh_3$, 59054-09-0; $Au(5\text{-}CF_3CN_4)PPh_3$, 12706-31-9; $(PPh_3)Au\text{-}CN_4\text{-}CN_4\text{-}Au(PPh_3)$, 59054-08-9; $(PPh_3)Au\text{-}CN_4\text{-}CH_2\text{-}CN_4\text{-}Au(PPh_3)$, 59054-07-8; methyl iodide, 74-88-4; $AuOAcPPh_3$, 24169-88-8.

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