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Review

The chemistry of cyano complexes of gold(I) with emphasis on the ligand scrambling reactions☆

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Dedicated in honor of Professor Anvarhusein A. Isab

Contents

Abstract

The gold(I) complexes, containing cyanide and some other ligand (L), {LAuCN} are stable in the solid state, while in solution they undergo dissociation to form ionic species. The X-ray and IR, studies show that some cyanogold(I) complexes exist as non-ionic complexes (LAuCN) and some as the ionic species $\{[Au(L_2)]^+[Au(CN)_2]^-\}$ in the solid state. In solution, the LAuCN complexes undergo ligand scrambling reactions exhibiting the equilibrium, $2[L–Au–CN] \rightleftarrows [AuL_2]^+ + [Au(CN)_2]^-$. Equilibrium constants (K_{eq}) for the scrambling equilibria are determined by integration of the ^{13}C and ^{31}P NMR spectra. The equilibrium constant is dependent on such factors as the initial concentration of the complex, ionic strength of the solution, temperature and polarity of the solvent, with polarity of the solvent showing major influence on K_{eq}. The order of ability of different L–Au–CN complexes undergoing disproportionation is: [≻C=SeAuCN] > [R_3PSeAuCN] > [≻C=SAuCN] > [R_3PAuCN] ≥ [R_3PSAuCN].

The reactions of gold drugs and their metabolites, with cyanide lead to the formation of intermediates, $[RSAuCN]^-$ and [Et_3PAuCN], which undergo disproportionation generating $[Au(CN)_2]^-$ that is readily taken up by red blood cells. The formation of aurocyanide is dependent on thiocyanate and occurs both by the myeloperoxidase dependent oxidation of thiocyanate and by a secondary reaction of hypochlorous acid

Abbreviations: Autm, gold(I) thiomalate; CEP, tris(2-cyanoethyl)phosphine; Cy, cyclohexyl; Et, ethyl; Imt, imidazolidine-2-thione; *i*-Pr, isopropyl; Me, methyl; Ph, phenyl; Tol, tolyl

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with thiocyanate. $[Au(CN)_2]^-$ is a common metabolite of the gold drugs in the blood and urine of chrysotherapy patients. The oxidation of $[Au(CN)_2]^-$ by OCl^- could lead to the formation of gold(III) metabolites.
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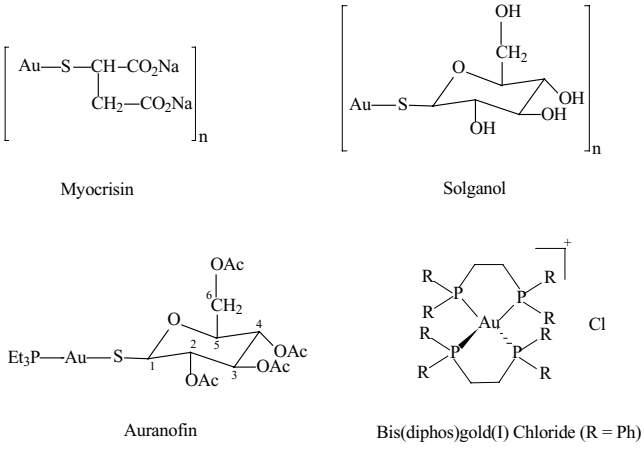
Keywords: Cyanogold(I) complexes; Ligand scrambling; Phosphine; Thione; Selenone; Equilibrium constant; Gold(I) metabolites

1. Introduction

Gold complexes are of considerable importance in the treatment of rheumatoid arthritis. The most widely used complexes are the water-soluble polymeric complexes, such as gold(I) thiomalate [myocrisin (Autm)] and gold(I) thioglucose [solganol (Autg)] and the monomeric complex, auranofin. Auranofin [(2,3,4,6-tetra-*o*-acetyl-1-thio-β-D-glucopyranosato-*S*)(triethylphosphine)gold(I)] ($Et_3PAuSATg$) is an orally active drug, while solganol and myocrisin are only active by injection [1–6]. Besides curing arthritis, a large number of phosphine gold(I) complexes especially, auranofin and $[Au(dppe)_2]Cl$ (dppe = 1,2-bis(diphenylphosphino)ethane) are also known to exhibit promising antitumor properties [7–11]. The structures of some important gold drugs are shown in Scheme 1.

The reactions of CN^- with gold(I) compounds are of therapeutic interest because the physiological distribution of Au(I) is believed to be affected by the cyanide present in the blood [12]. The polymeric nature of gold thiolates may limit their cellular uptake and thus their activity in vivo, while auranofin being monomeric does enter into RBCs immediately after its absorption and binds to glutathione (GSH) and hemoglobin (Hb) [13–15]. Graham et al. in 1984 were the first to investigate the activation of aurothiomalate (Autm) through interaction with cyanide [12]. It was observed that the cellular uptake of gold from Autm was slow in the absence of cyanide. Cyanide markedly increased the uptake of gold by red blood cells, 21.1% after incubation for 24 h [12]. Tobacco smoking is known to increase the concentrations of gold in red blood cells in patients treated with Autm [16,17]. The higher level of $[Au(CN)_2]^-$ in smokers is because of the inhalation of HCN from tobacco smoke [17]. Cyanide acts as a shuttle to carry gold into red blood cells [12]. Cyanide is produced naturally in the body by oxidation of SCN^- by the enzyme myeloperoxidase in polymorphonuclear leukocytes (PMN) [18,19].



Scheme 1. Structures of some important gold drugs.

The reactions of gold drugs and their metabolites with cyanide lead to the formation of intermediates, $[RSAuCN]^-$ and $[Et_3PAuCN]$, which undergo disproportionation generating $[Au(CN)_2]^-$ that is readily taken up by red blood cells [18–23]. Several studies describe the formation of $[Au(CN)_2]^-$ by disproportionation of L–Au–CN complexes in solution [24–34] according to the following equilibrium:

$$2[L\text{–}Au\text{–}CN] \rightleftarrows [AuL_2]^+ + [Au(CN)_2]^- \quad (1)$$

The very large formation constant of $[Au(CN)_2]^-$ ($\log \beta = 36.6$ [35] or 39 [36]) is believed to drive the reaction in the forward direction generating $[Au(CN)_2]^-$. Because of this very large formation constant the cyanide process has been exploited in the extraction of gold from its ores. Metallic gold is easily oxidized in the presence of cyanide with an oxidation potential of +0.60 V (Eq. (2)) [36,37]. Gold is precipitated by addition of zinc to the filtered solution of $[Au(CN)_2]^-$ [36,38]:

$$4Au + 8CN^- + 2H_2O + O_2 \rightarrow 4[Au(CN)_2]^- + 4OH^- \quad (2)$$

Because of the biological and commercial applications of cyanogold(I) complexes, it seems important to present a brief review of the progress made in this field. This review focuses on the structures of cyanogold(I) complexes and their scrambling equilibria in solution, and gives an insight to the possible biological implications of these complexes.

2. Structures of cyanogold(I) complexes

2.1. X-ray studies

Gold(I) has a strong tendency to form linear and two coordinate complexes of the type L–Au–X, where L is a neutral Lewis base such as phosphine and thione, etc. and X is a halide or pseudohalide [39–41]. These complexes are usually stable in the solid state as well as in solution. However, when X is a CN^- ligand, these complexes undergo novel ligand scrambling reactions in solution [24–34] shown by the equilibrium (1). However, tris-(2-cyanoethyl)phosphine (CEP) and *N*,*N*′-dimethylthiourea (DmTu) form ionic complexes

Table 1
Bond lengths (pm) and bond angles of some known cyanogold(I) complexes

Compound	$d_{Au–C}$	$d_{L–Au}$	$d_{C–N}$	Bond angle of L–Au–CN (°)	References
Me_3PAuCN	200–206	226.8–227.9	99–106	178.4–178.8	[46]
CEPAuCN[a]	–	232.2, 231.4	98, 113	176 (CAuC), 168.3 (PAuP)	[42]
Et_3PAuCN	197	228.8	115	176.6	[25]
Ph_3PAuCN	200.3	227.8	113.6	177.0	[47]
Cy_3PAuCN	200.6	228.7	112.8	177.0	[41]
$(i\text{-Pr})_3PAuCN$	202	228.4	–	177.0	[48]
$CyPh_2PAuCN$	207.3	228.4	104	177.0	[49]
$(m\text{-Tol})_3PAuCN$	208.7	228.6	102	174.3	[49]
ImtAuCN[b]	196.4, 196.8	229.2, 229.3	–	173.6, 179.6	[43]
DmTuAuCN[a]	198.3, 198.4	228.5, 230.4	–	176.7 (CAuC), 169.7 (SAuS)	[43]
$[Au(CN)_2]^-$	198	–	117	176.7	[22,50]

[a] Known to exist in the ionic form.
[b] Exists as dimer.

$[Au(CEP)_2]^+[Au(CN)_2]^-$ and $[Au(DmTu)_2]^+[Au(CN)_2]^-$, respectively, both in solution as well as in the solid state [25,32,42,43]. The complexes (tetrahydrothiophene)iodogold(I) [44] and (pyridine)chlorogold(I) [45] also exist as ionic complexes in the solid state, i.e., as $[Au(THT)_2]^+[AuI_2]^-$ and $[Au(Py)_2]^+[AuCl_2]^-$, respectively. The bond lengths and bond angles of some cyanogold(I) complexes are given in Table 1.

It is observed that the L–Au–CN bond angle in all complexes is around 180° showing a linear geometry at the gold atom. As the Au–C bond length increases, the C–N bond length decreases. Et_3PAuCN with the smallest $d_{Au–C}$ of 197 pm has the longest $d_{C–N}$ of 115 pm, while an opposite trend is observed for $(m\text{-Tol})_3PAuCN$. These values provide a clear evidence for the existence of bock-bonding in the cyanogold(I) complexes. ImtAuCN has the lowest value of $d_{Au–C}$ compared to all R_3PAuCN complexes. This suggests that CN^- is a better π acceptor when it is *trans*, to a thione ligand than to R_3P, since phosphines are also among the π acceptor ligands. In most of the complexes, Au–Au distances around 330 pm (Cy_3/Ph_3–PAuCN are exceptions [41,47]) indicates only weak interactions [25,42,43,46] and therefore it seems appropriate to characterize these complexes as infinite metal–metal bonded structures. No inter- or intrametal coordination of C–N group was observed in any of the LAuCN complexes. On the other hand, in silver cyanide complexes (LAgCN), C–N group is bridging between two Ag atoms [51]. This could be because of greater affinity of Ag(I) compared to Au(I) towards nitrogen.

$[Au(CN)_2]^-$ is a linear and diagonal complex, with $d_{Au–CN} = 198$ pm [22].The structure of AuCN as determined by neutron diffraction measurements, consists of rows of linear AuCN chains with alternating Au–C = 206 pm and short Au–N = 182 pm. The Au atoms form sheets and are bonded to six other Au atoms at a distance of 339.6 pm. The Au–Au distance is within the range expected for an 'aurophilic attraction' between these atoms [52]. The structure of AgCN is very similar to that for AuCN, but the Ag–Ag distance in Ag sheets is considerably longer, 388 pm, so that there are no significant Ag–Ag interactions [52].

2.2. IR studies

The ν(CN) of AuCN appears around 2220 cm^{-1} [31,53]. Upon its complexation with various ligands, ν(CN) decreases to around 2100 cm^{-1}. The decrease in frequency indicates an increase in the ionic nature of the cyanide ligand. Recently, we observed that some [>C=SeAuCN] complexes showed two stretching bands (asymmetric and symmetric) for CN^- group, which are the characteristic of $[Au(CN)_2]^-$ (since the NC–Au–CN bond angle in $[Au(CN)_2]^-$ is found to be less than 180° [42,43]).

The crystal structures of the two complexes, [CEP–Au–CN] [42] and [DmTu–Au–CN] [43] show that they exist as ionic complexes, $[Au(CEP)_2]^+[Au(CN)_2]^-$ and $[Au(DmTu)_2]^+[Au(CN)_2]^-$, respectively, in the solid state. When IR spectra of these complexes were recorded, two bands corresponding to the CN^- stretch were observed [33]. For the other cyano(thione)gold(I) complexes, only one ν(CN) band was observed [53]. Thus, it is established that the complexes, which show only one CN^- stretch in IR exist as non-ionic complexes (i.e., as [L–Au–CN]), while those which possess two CN^- bands exist in the ionic form (i.e., as $[AuL_2]^+[Au(CN)_2]^-$). The IR spectrum of E_3PAuCN in solution also shows two bands for cyanide stretch [25]. The ν(CN) frequencies of some complexes are given in Table 2.

2.3. Thermal studies

Thermal studies have been reported only for a number of R_3PAuCN complexes. The thermal studies showed that R_3PAuCN complexes underwent decomposition in the temperature range of 200–600 °C, with the evolution of both *trans* ligands, R_3P and CN^-, leaving metallic gold as a residue (R = Me, Et, *i*-Pr, Cy, Ph, CE, *o*-Tol, *m*-Tol, *p*-Tol). Except in $(o\text{-Tol})_3PAuCN$, in all other complexes both R_3P and CN^- ligands evolved simultaneously. In $(o\text{-Tol})_3PAuCN$, the first step of decomposition was the

Table 2
IR frequencies, ν_{C-N} (cm^{-1}) of some cyanogold(I) complexes

Complex	ν(CN)	References
Et_3PAuCN	2138	[25,54]
Ph_3PAuCN	2141	[55]
$(NH_3)AuCN$	2142	[56]
$(Ph_3PCH_2)AuCN$	2142	[57]
DmTuAuCN	2140, 2068	[a]
ImtAuCN	2115	[53]
EtImtAuCN	2130	[53]
i-PrImtAuCN	2130	[53]
DiazAuCN	2130	[53]
ErSAuCN[b]	2066	[31]
ImSeAuCN	2048	[33]
DmSeuAuCN	2064	[34]
MeImSeAuCN	2136, 2096	[33]
EtImSeAuCN	2144, 2096	[33]
i-PrImSeAuCN	2146, 2106	[33]
PhImSeAuCN	2146, 2098	[33]
Et_2ImSeAuCN	2132, 2090	[33]
DiazSeAuCN	2060	[33]
MeDiazSeAuCN	2068	[34]
AuCN	2220	[31,53]
$K[Au(CN)_2]$	2140, 2068	[33,58]

[a] A.A. Isab and S. Ahmad, unpublished results.
[b] ErS: ergothionine.

evolution of phosphine and generation of AuCN, which in the second step undergoes a redox reaction to yield metallic gold. This behavior of (*o*-Tol)$_3$P was related to its largest value of cone angle (194°) [59]. The weight loss in each case corresponds to the release of only two ligands, which demonstrates that the complexes are two coordinate in the solid state. A simultaneous release of both the ligands (R_3P and CN) indicates that their binding capacity is almost of the same strength.

The DTA studies showed that for AuCN and for the complexes with R_3P = (*o*-Tol)$_3$P and (*m*-Tol)$_3$P, the decomposition step is exothermic, while for the rest of the complexes, it is endothermic [59]. The exothermic transitions in the cases of (*o*/*m*-Tol)$_3$PAuCN suggest that the decomposition occurs through the formation of AuCN.

3. NMR studies and the ligand scrambling reactions of cyanogold(I) complexes

In solution, cyanogold(I) complexes are usually characterized by using ^{13}C, ^{15}N and ^{31}P NMR spectroscopy. All LAuCN type complexes studied so far are observed to undergo ligand scrambling reactions in solution according to Eq. (1) [24–34]. Ligand scrambling reactions were first observed in cyano-thiolatogold(I) complexes [24] and for Et_3PAuCN complex [25]. Later, they were reported for a variety of cyano(phosphine)gold(I) complexes [26–28]. Recently, we observed these reactions in Cy_3PSe–Au–CN [29], Cy_3PS–Au–CN [30] and for a series of cyano(thione/selenone)gold(I) complexes [31–34].

3.1. Cyano(phosphine)gold(I) complexes

The ^{31}P NMR spectra of most of the $R_3PAu^{13}C^{15}N$ complexes revealed two signals at room temperature, one each from $[R_3PAu^{13}C^{15}N]$ and $[Au(R_3P)_2]^+$ species [25–28]. The appearance of two signals suggested that R_3PAuCN complexes underwent scrambling reactions according to Eq. (3):

$$2[R_3PAuCN] \rightleftarrows [Au(R_3P)_2]^+ + [Au(CN)_2]^- \quad (3)$$

The ^{31}P NMR spectral data for some complexes are listed in Table 2a (see supplementary material). The ^{31}P NMR of $[Au(R_3P)_2]^+$ in all complexes appeared as a single sharp resonance whereas, the resonance for $[R_3PAu^{13}C^{15}N]$ was a doublet of doublets due to $^2J(^{31}P–^{13}C)$ and $^3J(^{31}P–^{15}N)$ couplings [28]. [(*m*-Tol)$_3$PAu^{13}C^{15}N] and [(*p*-Tol)Ph$_2$PAu^{13}C^{15}N] revealed these resonances at 233 K, while for $[Ph_3PAu^{13}C^{15}N]$ they could be resolved at 213 K. Only one resonance was observed in the cases of [(*o*-Tol)$_3$PAu^{13}C^{15}N], [CEPAu^{13}C^{15}N] and [(1-naphtyl)$_3$PAu^{13}C^{15}N].

The ligand exchange in R_3PAuCN complexes was related to the basicity of phosphines and their steric bulk. The basicity of phosphines is measured in terms of electronic parameter, ν(CO) for the complex $[R_3PNi(CO)_3]$ while, the steric factor is expressed in terms of cone angle (θ) [60]. The ν(CO) values and cone angles of the phosphines are compared in Table 2b (see supplementary material). It has been observed that $R_3PAu^{13}C^{15}N$ complexes with ν(CO) values of R_3P equal to or less than 2067 cm^{-1} show fast exchange between $[R_3PAu^{13}C^{15}N]$ and $[Au(R_3P)_2]^+$ at room temperature. The complexes with ν(CO) values of R_3P greater than 2067 cm^{-1} exhibited separate resonances at low temperature. In the cases of [(*o*-Tol)$_3$PAu^{13}C^{15}N] and [(naphthyl)$_3$PAu^{13}C^{15}N], the steric factor plays an important role. The (*o*-Tol)$_3$P has a cone angle of 194°, which makes it difficult to form $[Au\{(o\text{-Tol})_3P\}_2]^+$ species. The same is true for (naphthyl)$_3$P [28].

The ^{13}C and ^{15}N NMR spectra of R_3P–$Au^{13}C^{15}N$ complexes also showed two resonances in the low field region corresponding to the equilibrium (1) [26,28]. In ^{15}N NMR, two resonances could only be observed for $[Me_3P–Au^{13}C^{15}N]$ and $[Et_3P–Au^{13}C^{15}N]$. The ^{13}C and ^{15}N chemical shifts for CN^- and coupling constants of the $[R_3P–Au^{13}C^{15}N]$ complexes are given in Table 2c (see supplementary material).

The ^{13}C and ^{15}N chemical shifts are found to have opposite dependence on the basicity of phosphine ligands in $R_3PAu^{13}C^{15}N$ complexes. The ^{15}N NMR resonance shifts upfield, while ^{13}C NMR resonance shifts downfield with the increase in the basicity of the phosphine. This opposite behavior can be explained on the basis of bock-bonding between gold(I) and CN^- group. The π-bonded species involves a transfer of electron density from a filled metal d orbital into the π^* antibonding molecular orbitals centered on the carbon of the cyanide group [61]. The donation

of electron density from gold(I) to phosphines increases the double bond character of the Au–C bond resulting in a deshielding effect at carbon atom. Similarly, the reduction in the C–N bond order in the π-bonded species would be expected to be accompanied by an upfield shift of the ^{15}N resonance.

In the ^{31}P and ^{13}C NMR spectra of $R_3PAuSCN$ complexes, resonances of $[Au(R_3P)_2]^+$ and $[Au(SCN)_2]^-$, respectively, were not observed suggesting that these complexes do not undergo ligand scrambling reactions [62]. This could be due to the lower stability constant value of $Au(SCN)_2]^-$ ($\log\beta = 17.0$ [63]) compared to that of $[Au(CN)_2]^-$ ($\log\beta = 36.6$ [35]).

3.2. Cyano(phosphine-sulfide/selenide)gold(I) complexes

The observation of two resonances in the ^{13}C and ^{15}N NMR of $[Cy_3P{=}S/Se{-}Au^{13}C^{15}N]$ is consistent with the fact that these complexes undergo disproportionation in solution as shown in Eq. (3). The ^{31}P NMR at 297 K showed only one resonance, indicating that the $[Cy_3P{=}S/Se{-}AuCN]$ complexes are undergoing rapid exchange with $[Au(CN)_2]^-$ and $[(Cy_3P{=}S/Se)_2Au]^+$. However, two distinct resonances were observed in the ^{13}C and ^{15}N NMR of these complexes. The ^{13}C and ^{15}N NMR spectra of $Cy_3P{=}S{-}AuCN$ are shown in Fig. 1. In an expansion of downfield region of the spectrum (Fig. 1a), it was observed that the resonance due to '^{13}C' of $[Cy_3P{=}S{-}AuCN]$ is a doublet with $^1J(^{13}C{-}^{15}N) = 9$–11 Hz, while the $[Au(CN)_2]^-$ resonance appeared as a triplet with an average coupling constant of 6.5 Hz. The $^{13}C{-}^{15}N$ coupling in $[Au(CN)_2]^-$ follows the AA′XX′ spin system rather than A_2X_2 system. The simple triplet appearance of ^{13}C spectrum arises due to the fact that $^2J(^{13}C{-}^{13}C) \gg {}^4J(^{15}N{-}^{15}N)$ and the inner lines of AB sub-spectrum are so close together that they cannot be resolved and the outer lines lie below the limit of detection. So only the sum of the coupling constants $[^1J(^{13}C{-}^{15}N) + {}^3J(^{13}C{-}^{15}N)]$ is extracted from the separation of the outer lines of the triplet and they lie in the range of 5–10 Hz [28–30]. The ^{13}C and ^{15}N parts are identical in appearance as expected from AA′XX′ system [29,30]. A comparison of the ^{13}C, ^{15}N and ^{31}P chemical shifts of $Cy_3P{-}Au{-}CN$, $Cy_3P{=}Se{-}Au{-}CN$ and $Cy_3P{=}S{-}Au{-}CN$ is given in Table 3 [28–30].

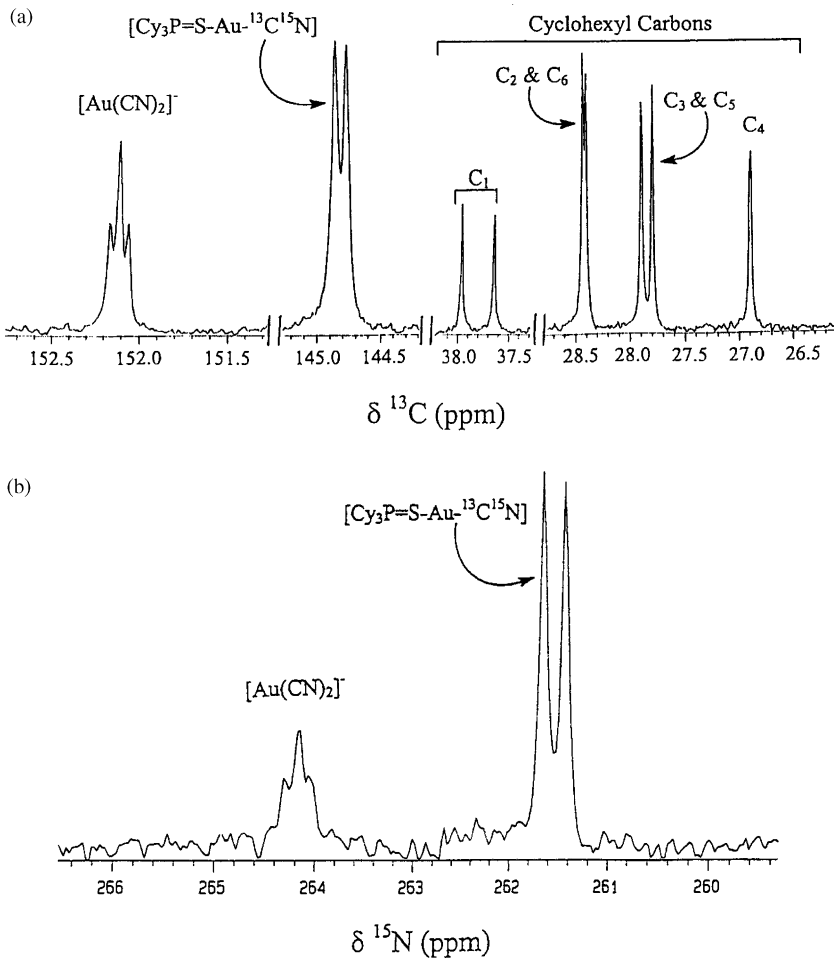


Fig. 1. The 125.65 MHz $^{13}C\{^1H\}$ NMR spectrum (a) and 50.55 MHz $^{15}N\{^1H\}$ NMR spectrum (b) of 0.025 M $[Cy_3PS{-}Au^{13}C^{15}N]$ in CD_3OD.

Table 3
^{13}C (CN carbon), ^{15}N and ^{31}P NMR chemical shifts (ppm) for Cy_3P–Au–CN, Cy_3P=Se–Au–CN and Cy_3P=S–Au–CN complexes in CD_3OD

Complex	$\delta(^{13}C)$	$\delta(^{15}N)$	$\delta(^{31}P)$[a]	Reference
Cy_3P–AuCN	160.29	264.35	56.27	[28]
Cy_3P=Se–AuCN	146.44	260.65	63.02	[29]
Cy_3P=S–AuCN	144.85	261.55	66.62	[30]

[a] ^{31}P chemical shifts relative to H_3PO_4.

3.3. Cyano(thione/selenone)gold(I) complexes

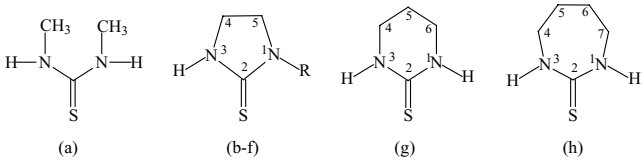
The ligand scrambling reactions of the cyano(thione/selenone)gold(I) complexes in DMSO were investigated by ^{13}C and ^{15}N NMR spectroscopy. The structures of the thiones and selenones studied so far are described in Schemes 2 and 3, respectively.

In the CN region of ^{13}C and ^{15}N NMR of all [≻C=S/Se–Au–CN] complexes, two intense resonances were observed, which demonstrates that they undergo a similar type of ligand scrambling reaction as observed for R_3PAuCN complexes, i.e.:

$$2[\succ C{=}S/Se{-}Au{-}CN] \rightleftarrows [Au(\succ C{=}S/Se)_2]^+ + [Au(CN)_2]^- \quad (4)$$

The $[Au(CN)_2]^-$ resonance appeared as a triplet (or a broad singlet) with an average coupling constant of 5.9 Hz and the other resonance was a doublet from the $^{13}C^{15}N$ of [≻C=S/Se–Au–CN]. Typical ^{13}C and ^{15}N NMR spectra for a representative complex [Imt–Au–$^{13}C^{15}N$] are shown in Fig. 2. Separate resonances for the thione/selenone ligands in [≻C=S/Se–Au–CN] and $[Au(\succ C{=}S/Se)_2]^+$ species could not be observed either due to their rapid exchange or the chemical shifts of the two species are overlapped so that they cannot be resolved. However, we were able to resolve these resonances for one of the complexes, Imt–Au–CN at 240 K in methanol. The ≻C=S and C-4/5 resonances of Imt–Au–CN and $[Au(\succ C{=}S)_2]^+$ which were observed as average resonances at 298 K, were clearly separated into two peaks at 240 K (Fig. 2c). Thus, we were able to detect both species, $[Au(\succ C{=}S)_2]^+$ and $[Au(CN)_2]^-$ formed as a result of the scrambling of Imt–Au–CN. The analogous species in the scrambling of some R_3P–Au–CN complexes, $[Au(R_3P)_2]^+$ could be detected at room temperature by ^{31}P NMR [25–28].

The ^{13}C and ^{15}N chemical shifts for CN^- and coupling constants of all [≻C=S/Se–Au–CN] complexes are given in Tables 3a and 3b (see supplementary material). In the ^{15}N NMR of ImtAuCN in DMSO, the $[Au(CN)_2]^-$ resonance appeared at 284.1 ppm with an average coupling constant of 5.9 Hz, while that of [Imt–Au–$^{13}C^{15}N$] was observed at 281.2 ppm. In methanol, they were observed at 264.7 and 262.2 ppm, respectively. In water $[Au(CN)_2]^-$ resonance was observed around 267 ppm with a J_{C-N} value of 11.1 Hz [64]. This shows that ^{15}N chemical shift is highly dependent on the nature of the solvent. Since the chemical shifts of $[Au(CN)_2]^-$ and [LAuCN] species are very close in methanol, therefore for some R_3PAuCN complexes only average resonances were observed in ^{15}N NMR [27,28].

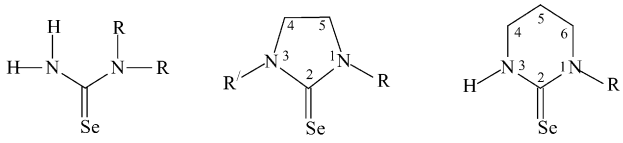


(a) N,N′-dimethylthiourea (DmTu)
(b) R = H; Imidazolidine-2-thione (Imt)
(c) R = CH_3; N-methylimidazolidine-2-thione (MeImt)
(d) R = C_2H_5; N-ethylimidazolidine-2-thione (EtImt)
(e) R = C_3H_7; N-propylimidazolidine-2-thione (PrImt)
(f) R = *i*-C_3H_7; N-(*i*-propyl)imidazolidine-2-thione (*i*-PrImt)
(g) 1,3-Diazinane-2-thione (Diaz)
(h) 1,3-Diazipane-2-thione (Diap)

Scheme 2.

In the scrambling reactions of cyano(phosphine)gold(I) complexes [26,28], it was observed that with increasing basicity of phosphines, the $\delta(^{13}C)$ for CN also increased due the increased π bond character in Au–C bond, while the $\delta(^{15}N)$ was decreased. A comparison of Tables 2c, 3a and 3b shows that CN group appears most upfield in the thione complexes. When a sulfur or selenium atom binds to an electron rich d^{10} center, the second lone pair on the donor atom may produce a significant π repulsion [65]. Due to lower electron density on gold(I), back-bonding by CN is reduced and an upfield shift is observed in ^{13}C NMR.

The steric factors were known to influence the kinetics of the scrambling reactions, for example, for Cy_3PAuCN due to its larger size the equilibrium was established after several weeks [26]. Even for more bulky phosphines (*o*-Tol)$_3$P and



(a) R = H; Selenourea (Seu)
(b) R = CH_3; N,N-Dimethylselenourea (DmSeu)
(c) R = R′ = H; Imidazolidine-2-selenone (ImSe)
(d) R = H, R′ = CH_3; N-methylimidazolidine-2-selenone (MeImSe)
(e) R = H, R′ = C_2H_5; N-ethylimidazolidine-2-selenone (EtImSe)
(f) R = H, R′ = *i*-C_3H_7; N-(*i*-propyl)imidazolidine-2-selenone (*i*-PrImSe)
(g) R = H, R′ = C_6H_5; N-phenylimidazolidine-2-selenone (PhImSe)
(h) R = R′ = C_2H_5; N,N′-diethylimidazolidine-2-selenone (Et_2ImSe)
(i) R = H; 1,3-Diazinane-2-selenone (DiazSe)
(j) R = CH_3; N-methyl-1,3-Diazinane-2-selenone (MeDiazSe)

Scheme 3.

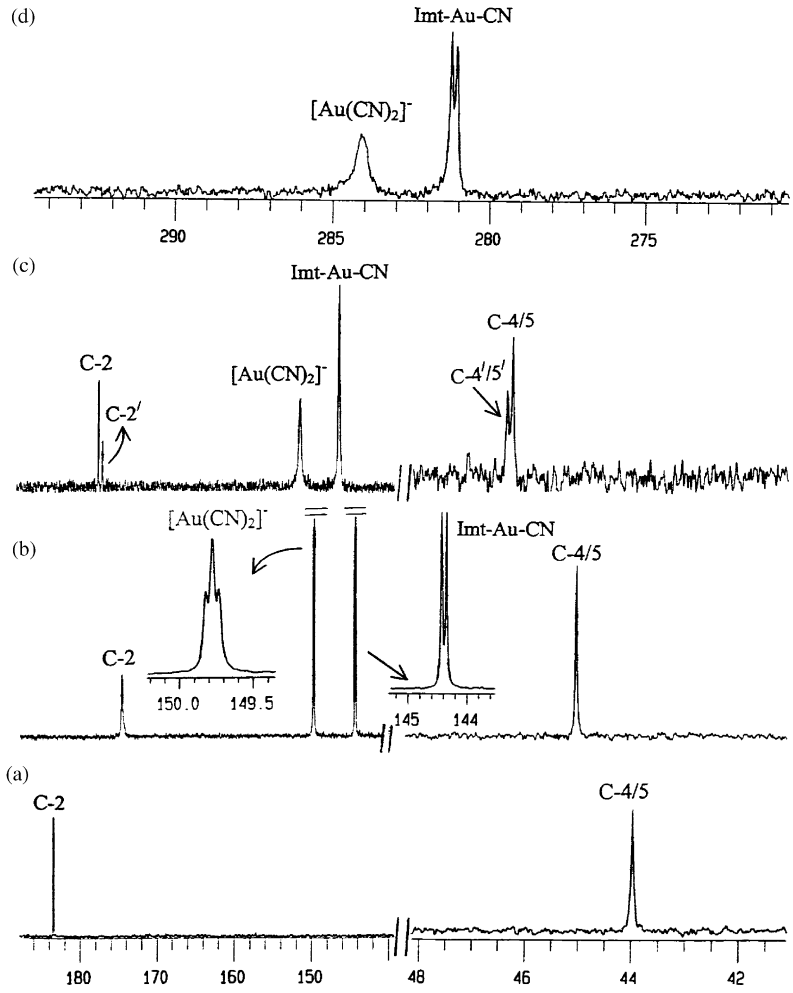


Fig. 2. (a) The 125.65 MHz ^{13}C NMR spectrum of Imt in DMSO-d_6. (b) ^{13}C NMR spectrum of Imt–Au–$^{13}C^{15}N$ at 298 K in DMSO-d_6. (c) ^{13}C NMR spectrum of Imt–Au–$^{13}C^{15}N$ at 240 K in methanol (C-2 of the thione is enriched to 2% and C′ are the resonances corresponding to $[Au(Imt)_2]^+$). (d) The 50.55 MHz ^{15}N NMR spectrum of Imt–Au–$^{13}C^{15}N$ in DMSO-d_6.

(naphthyl)$_3$P, no scrambling was observed [28]. However, for the thione and selenone complexes a rapid scrambling was observed, which could be due to the smaller size of the ligands.

Recently, we observed that LAgCN complexes do not undergo disproportionation reactions as observed for LAuCN complexes [66]. The possible reason is the lower value of stability constant for $[Ag(CN)_2]^-$ ($\log\beta = 20$ [58]) compared to that for $[Au(CN)_2]^-$ ($\log\beta = 36.6$ [35]).

4. Determination of equilibrium constant (K_{eq})

Equilibrium constants (K_{eq}) were calculated using relative intensities (I) of cyanide resonances of $[LAu^{13}C^{15}N]$ and $[Au(^{13}C^{15}N)_2]^-$ complexes in the ^{13}C NMR [32,33], which gave the relative concentrations of all three species because of the stoichiometric relationship, $I[Au(^{13}C^{15}N)2]^- = I[Au(\succ C{=}S)_2]^+$:

$$K_{eq} = \frac{(I[Au(^{13}C^{15}N)_2]^-)(I[Au(L)_2]^+)}{(I[LAu^{13}C^{15}N])^2} \quad (5)$$

Delay times of 30–50 s were used to record the ^{13}C and ^{31}P NMR spectra of all the complexes so that the spectra could be integrated quantitatively. Each K_{eq} value was the result of several measurements. The average K_{eq} values thus calculated for various complexes are compared in Table 4.

In the scrambling reactions of cyanogold(I) complexes of phosphines, it was observed that the basicity of the phosphine is the most important factor, which affects K_{eq} [26], although K_{eq} is also affected by the external factors such as ionic strength [26,32]. An increase in K_{eq} was observed with an increase in basicity of the phosphine. As given in Table 4, the K_{eq} values for the cyanogold(I) complexes of selenones are found to be much larger than for the complexes of other ligands. The larger K_{eq} values suggest that selenones are more basic towards gold(I) compared with phosphines and thiones. It seems that greater donation of electron density to

Table 4
Comparison of K_{eq} values of some cyanogold(I) complexes in DMSO-d_6

R_3PAuCN[a,b]	K_{eq}	[⩾ C=SAuCN][c]	K_{eq} (±S.D.)	[⩾ C=SeAuCN][d]	K_{eq} (±S.D.)
Ph_3PAuCN	0.112	$DmTuAu^{13}C^{15}N$	0.98 ± 0.03	SeuAuCN[e]	4.40 ± 0.07
Me_3PAuCN	0.37	$ImtAu^{13}C^{15}N$	0.630 ± 0.005, 0.45[a] ± 0.01	DmSeuAuCN[e]	5.28 ± 0.08
Et_3PAuCN	0.24	$MeImtAu^{13}C^{15}N$	0.56 ± 0.02	ImSeAuCN	2.95 ± 0.05
$(i\text{-}Pr)_3PAuCN$	0.29	$EtImtAu^{13}C^{15}N$	0.62 ± 0.01	MeImSeAuCN	2.90 ± 0.08
Cy_3PAuCN	0.49	$PrImtAu^{13}C^{15}N$	0.59 ± 0.01	EtImSeAuCN	2.76 ± 0.06
		$i\text{-}PrImtAu^{13}C^{15}N$	0.55 ± 0.01	*i*-PrImSeAuCN	3.12 ± 0.02
$R_3PXAuCN$[a,f]		$DiazAu^{13}C^{15}N$	0.91 ± 0.01	PhImSeAuCN	4.28 ± 0.05
$Cy_3PSAuCN$	0.147	$DiapAu^{13}C^{15}N$	0.96 ± 0.01	$Et_2ImSeAuCN$	2.84 ± 0.07
$Cy_3PSeAuCN$	1.81	$ErSAu^{13}C^{15}N$[a,g]	1.08	DiazSeAuCN	3.64 ± 0.06
				MeDiazSeAuCN[e]	3.33 ± 0.03

[a] Values in methanol.
[b] From [26].
[c] From [32].
[d] From [33].
[e] From [34].
[f] From [30].
[g] From [31].

gold(I) would result in a stronger Au–CN bond. This should lead to an easier formation of $[Au(CN)_2]^-$, resulting in a larger value of K_{eq}. In the case of R_3PAuCN complexes, π accepting ability of phosphines stabilizes the Au–P bond and thus would result in a lower value of K_{eq}. These results reveal that AuCN complexes with the better sigma donating ligands undergo dissociation more easily, compared to those containing pi acceptor ligands. Thus, the order of ability of different L–Au–CN complexes undergoing disproportionation is: [⩾C=SeAuCN] > $[R_3PSeAuCN]$ > [⩾C=SAuCN] > $[R_3PAuCN] \geq [R_3PSAuCN]$.

Equilibrium constant values have also been determined for some ligand exchange reactions at $[Au(CN)_2]^-$ in aqueous solutions at 25 °C. For example, the equilibrium constant for cysteine competition, $K_{eq} = ([Au(Cys)_2]^-)(CN)^2/([Au(CN)_2]^-)(Cys)^2$, has a value of 6.0×10^{-3} at pH 7.4 [67]. The K_{eq} value for iodide displacement of one cyanide from $[Au(CN)_2]^-$ is 7.9×10^{-2} and for replacement of both cyanides is 3.16×10^{-3} (Eqs. (6) and (7)) [68]:

$$[Au(CN)_2]^- + H^+ + I^- \rightleftarrows [Au(CN)I]^- + HCN \quad (6)$$

$$[Au(CN)_2]^- + 2H^+ + 2I^- \rightleftarrows [AuI_2]^- + HCN \quad (7)$$

The displacement of CN by a thione, 1-methylpyridine-2-thione (Eq. (8)) is a markedly disfavored process with the K_{eq} value equal to 7.37×10^{-9} ($\log K = -8.13$) [63]. These results show that the affinity of thiolate and iodide ions to gold(I) should be greater than that of a thione. Thus, the replacement of CN from $[Au(CN)_2]^-$ depends on the strength of incoming ligand and stability of the resulting complex:

$$[Au(CN)_2]^- + mpt \rightleftarrows [Au(CN)(mpt)] + CN^- \quad (8)$$

5. Effect of various factors on equilibrium constant

The effect of several factors on the magnitude of K_{eq} has been examined for two representative complexes, Et_3PAuCN and Imt–Au–CN. The first extrinsic factor examined was the initial concentration of the complex, $[Et_3PAuCN]_0$ or $[Imt–Au–CN]_0$. A plot of K_{eq} versus $[Imt–Au–^{13}C^{15}N]_0$ shows that K_{eq} value increases consistently with increasing $[Imt–Au–^{13}C^{15}N]_0$ (Fig. 3) [32]. A similar observation was recorded for Et_3PAuCN [26]. Thus, an increase in initial concentration generates more ionic species resulting in a larger K_{eq} value.

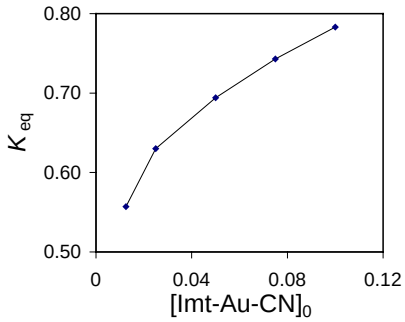


Fig. 3. K_{eq} vs. $[Imt–Au–CN]_0$ at 298 K and at the concentrations of 0.0125–0.10 M in DMSO.

The effect of ionic strength is explained by Fig. 4, which shows a plot of K_{eq} versus the concentration of NH_4NO_3. Since ionic complexes are generated by the scrambling process therefore an increase in ionic strength leads to an increase in the activity coefficients for $[Au(Imt)_2]^+$ and $[Au(CN)_2]^-$ with a subsequent increase in K_{eq}. A decrease in K_{eq} at $[NH_4NO_3]$ greater than 0.8 M is perhaps due to ion pairing [32]. The increase in K_{eq} observed by increasing ionic strength is more than that observed by changing concentration.

When K_{eq} values were plotted against temperature, an inverse correlation was observed (Fig. 5). A decrease in K_{eq} with increasing temperature indicates that the scrambling reaction is exothermic in forward direction (Eq. (4)) according

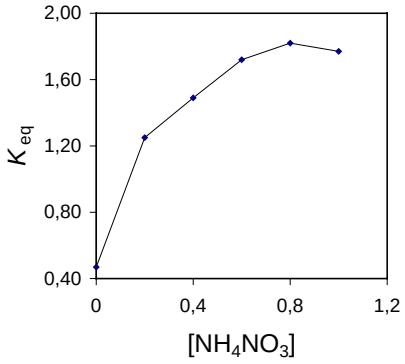


Fig. 4. K_{eq} vs. $[NH_4NO_3]$ (0.20–1.0 M) for 0.05 M Imt–Au–$^{13}C^{15}N$ at 298 K in methanol.

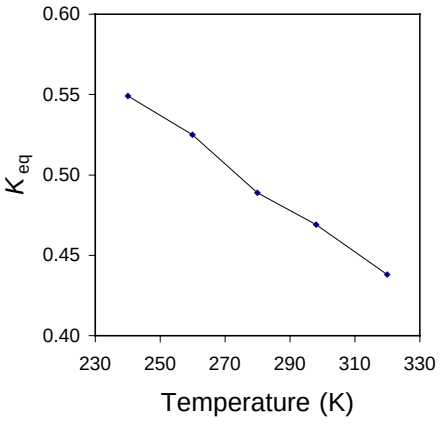


Fig. 5. K_{eq} vs. temperature for 0.05 M Imt–Au–$^{13}C^{15}N$ in methanol.

to van't Hoff equation, $\ln K = -\Delta H^{\circ}/RT + C$ [69]. ΔH° for this reaction can be obtained if $\ln K$ is plotted versus $1/T$ in the above equation. Such a plot is shown in Fig. 6 and the ΔH° value obtained from this plot is −1.81 kJ/mol [32].

Polarity of the solvent should also have a significant effect on K_{eq} because the increased solvation of the ionic species generated as a result of the scrambling process should ultimately result in larger K_{eq} value. The K_{eq} values

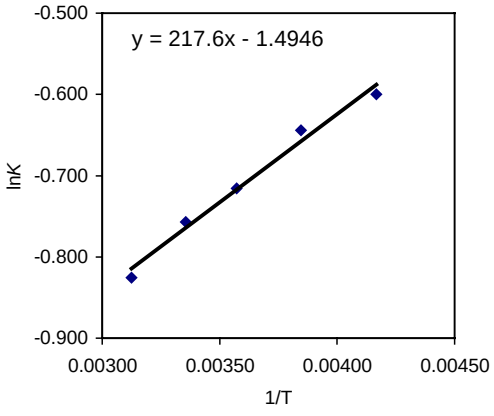


Fig. 6. A plot of $\ln K$ vs. $1/T$ for Imt–Au–$^{13}C^{15}N$ in methanol.

Table 5
K_{eq} values for the scrambling of Imt–Au–$^{13}C^{15}N$ in different solvents at 298 K

Solvent	μ (Debye)	K_{eq}
DMSO	3.9	0.63
Acetonitrile	3.44	0.34
Methanol	2.87	0.45
Acetone	2.69	0.19

Values taken from [70].

for Imt–Au–$^{13}C^{15}N$ obtained in different solvents using 0.025 M solution of the complex are shown in Table 5 [32]. The K_{eq} values are consistent with the polarity of the solvent except methanol. Methanol being a protic solvent solvates the anion [70], $[Au(CN)_2]^-$ (which is more stable) strongly and thus would result in larger K_{eq}.

6. Biochemical pharmacology of the cyanogold(I) metabolites

6.1. Formation of aurocyanide

The formation of aurocyanide from antirheumatic gold(I) complexes occurs by the myeloperoxidase dependent oxidation of thiocyanate [19]. Myeloperoxidase uses hydrogen peroxide to oxidize chloride and thiocyanate to hypochlorous acid and hypothiocyanite, respectively. Upon addition of H_2O_2 to myelopeoxidase, thiocyanate and aurothiomalate, the absorbance spectrum of the gold complex changed to that of aurocyanide, which has the characteristic peaks at 204, 211, 231 and 240 nm [18,71]. There was a progressive increase in the conversion of aurothiomalate to aurocynide by lowering of pH. The rate of aurocyanide production also increased in the presence of chloride, which indicates that hypochlorous acid accelerates the formation of cyanide [19]. Because thiocyanate is a major physiological substrate of myeloperoxidase, this appears to be the dominant route by which aurocyanide is formed from gold complexes in vivo. The aurocyanide formed inhibits the oxidative burst of polymorphonuclear leukocytes and monocysts, so that superoxide and hydrogen peroxide are no longer generated, thereby depriving myeloperoxidase of a substrate for the production of hypohalous acid. The inhibition of the oxidative burst of PMN may decrease the progression of the arthritis disease [19,72].

In the absence of thiocyanate, the myeloperoxidase, hydrogen peroxide, chloride system oxidized aurothiomalate to hydroxo and aquo complexes of Au(III) as demonstrated by the broad peak at 218 nm [73], which can be described by Eq. (9):

$$\text{Autm} + \text{OCl}^- \rightarrow [\text{Au(X)}_4]^- + \text{Htm} \quad (\text{X} = \text{OH}^-, \text{Cl}^-) \quad (9)$$

Addition of thiocyanate to the Au(III) complexes led to the loss of the broad peak at 218 nm [19] indicating that they had reacted with thiocyanate. However, conversion to

aurocyanide did not occur. Thus, Au(III) is unable to oxidize thiocyanate to cyanide with the concomitant formation of aurocyanide.

6.2. Cellular distribution and uptake of $[Au(CN)_2]^-$

The dicyanoaurate(I) anion, $[Au(CN)_2]^-$ has been identified as a common metabolite of the gold drugs in the blood and urine of chrysotherapy patients [23,74]. Model studies show that $[Au(CN)_2]^-$ is formed in vitro when CN^- reacts with the gold drugs or with the gold–protein metabolites such as the albumin–gold–triethylphosphine complex, AlbS–Au–PEt_3 [20,21]. Interaction of gold(I) thiolates with CN^- shows that CN^- binds to gold(I) releasing thiols as free ligands in solution [20,21,75,76]. For instance, cyanide converts Autm primarily to a mixed ligand complex, $[tm–Au–CN]^-$, when one equivalent of cyanide is added. With the addition of the second equivalent of cyanide, thiomalate is displaced and the very stable complex, $[Au(CN)_2]^-$ is formed [20,24]. The principal reactions are:

$$Autm + HCN \rightarrow [tm–Au–CN] \quad (10)$$

$$[tm–Au–CN]^- + HCN \rightarrow [Au(CN)_2]^- + Htm \quad (11)$$

At lower CN: Autm ratios, the oligomeric species such as NC–$(Autm)_n$–Au–CN are also possible. Small amounts of both aurocyanide and a bisthiomalate complex, $[Au(tm)_2]^-$, were present in equilibrium with a marked excess of the mixed complex [20]. This observation indicated the occurrence of the following equilibrium:

$$2[tm–Au–CN] \rightleftarrows [Au(tm)_2]^- + [Au(CN)_2]^- \quad (12)$$

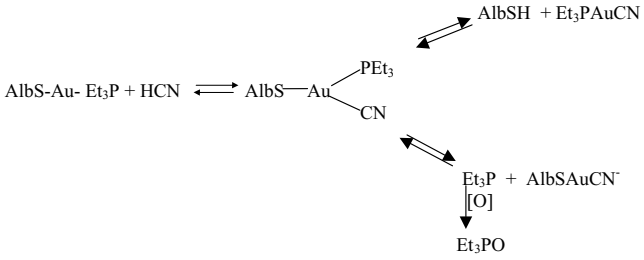
The formation of $[Au(SR)_2]^-$ and $[Au(CN)_2]^-$ was also observed, when Autg (gold(I) thioglucose) and Au(cap) (gold(I) captopril) were reacted with cyanide [75–77].

In the case of auranofin ($Et_3PAuSATg$), both the ligands can be replaced by cyanide thereby generating $[Au(CN)_2]^-$ [78]. But no systematic study on the reaction of auranofin with cyanide has been carried out. However, the reaction of AlbS–Au–PEt_3 with HCN has been studied in detail. The study of AlbS–Au–PEt_3 with HCN was carried out, since SATg ligand of auranofin is readily displaced and auranofin is metabolized to AlbS–Au–PEt_3. The reaction of HCN with AlbS–Au–PEt_3 yields irreversibly formed products, Et_3PO, $[Au(CN)_2]^-$ and $[AlbSAuCN]^-$. Et_3PAuCN was also observed as a transient equilibrium product. Its formation can be explained via a simple ligand exchange reaction:

$$AlbS–Au–PEt_3 + HCN \rightleftarrows Et_3PAuCN + AlbSH \quad (13)$$

The results of the study are described by Scheme 4.

Aurocyanide is rapidly taken up by polymorphonuclear leukocytes and red blood cells and could affect the function of these cells [79]. In RBCs, hemoglobin and glutathione are the main protein target for gold. The experiments



Scheme 4.

showed that most of the gold in RBCs is bound to glutathione. Although, the concentration of cyanide is very low in RBCs (0.3–1 μM) [80,81], there is a high formation constant between cyanide and gold(I), 10^{39} [36] and therefore bis(glutathione)gold(I) and dicyanogold(I) are likely to be found in RBCs. The mechanism by which $[Au(CN)_2]^-$ is transported through the cell membrane is still a subject of current research [19,22,23]. However, the most convincing mechanism is the one in which gold(I) complexes undergo ligand exchange reactions to bind to sulfhydryl groups immobilized on or in the membrane [82]. A series of such exchange reactions then passes the gold across the membrane and into the cells, where it may react with molecules containing sulfhydryl groups such as glutathione [82]. The displacement of CN^- from $[Au(CN)_2]^-$ by thiols in the model systems have already been studied, where the reaction may be written as [24]:

$$[Au(CN)_2]^- + RSH \rightarrow [RSAuCN]^- + HCN \quad (14)$$

Additional free CN^- will inhibit the loss of cyanide from $[Au(CN)_2]^-$ and in turn inhibit the dicyanogold(I) uptake. The value of stability constant significantly decreases when cyanide is replaced by another group, for example, $[Au(CN)I]^-$ ($\log\beta = 28.9$), [Au(CN)(mpt)] ($\log\beta = 30.9$), $[Au(mpt)_2]^+$ ($\log\beta = 17.9$) [63].

6.3. Redox and ligand exchange reactions of $[Au(CN)_2]^-$

$[Au(CN)_2]^-$ contains two tightly bound cyanide ligands, which render it relatively unreactive towards ligand exchange reactions with potential gold binding ligands [22]. However, the formation of $[RSAuCN]^-$ has been reported by partially displacing CN^- from $[Au(CN)_2]^-$ with thiols such as cysteine and glutathione in aqueous solution (Eq. (14)), although the formation constant of $[RSAuCN]^-$ is less than $[Au(CN)_2]^-$ [24]. The reaction of 1-methylpyridine-2-thione (mpt) with $[Au(CN)_2]^-$ was found to be very slow ($k = 1.4\,M^{-1}\,s^{-1}$); rate increases linearly with increasing $[Au(CN)_2]^-$ concentration [63]. Ligand exchange reactions at $[Au(CN)_2]^-$ with sulfur donors that have higher affinities than mpt should be much faster.

Bovine serum albumin (BSA) reacts weakly with $[Au(CN)_2]^-$ forming BSA–$[Au(CN)_2]^-$ adducts (BSA +

$[Au(CN)_2^-]_n \rightleftarrows BSA\text{–}n[Au(CN)_2^-]$). The equilibrium binding constant at pH 7.4 is $K_1 = (5.5 \pm 1.1) \times 10^4$ [22] The easily reversed association of intact dicyanoaurate(I) with albumin and the unfavorable reaction at cysteine-34 are consistent with the proposed roles of $[Au(CN)_2]^-$ as, a cellularly accumulated metabolite [12] and a urinary excretion product [74].

The oxidation of gold(I) metabolite, $[Au(CN)_2]^-$, by hypochlorite, OCl^- (an immunologically generated oxidant) generates gold(III) metabolites [23]. The reactions of $[Au(CN)_2]^-$ were studied using UV-Vis and ^{13}C NMR spectroscopy at pH 7.4. On addition of hypochlorite, the characteristic spectrum of $[Au(CN)_2]^-$ (λ_{max} = 204, 211, 230, 240 nm) was replaced by an intense, broad band at 287 nm. The intensity of 287 nm band increased as the pH was lowered to 2 with HCl and it decreased with increasing pH by addition of NaOH. The intensity of the 287 nm band at pH 2 is consistent with the species, $[Au(CN)_2Cl_2]^-$ [83]. The reversible, pH-dependent changes occurred by the oxidation of $[Au(CN)_2]^-$ can be described by Eqs. (15) and (16):

$$[Au(CN)_2]^- + OCl^- \rightarrow [Au(CN)_2X_2]^- \quad (X = OH^-, Cl^-) \tag{15}$$

$$[Au(CN)_2Cl_2]^- \underset{H^+}{\overset{OH^-}{\rightleftarrows}} [Au(CN)_2(OH)Cl]^- \underset{H^+}{\overset{OH^-}{\rightleftarrows}} [Au(CN)_2(OH)_2]^- \tag{16}$$

In the ^{13}C NMR, the initial 156 ppm of $[Au(CN)_2]^-$ was replaced by resonances at 121.0 ppm {$[Au(CN)_2(OH)Cl]$} and then by 122.7 ppm {$[Au(CN)_2(OH)_2]$}, increasing amounts of OCl^- were added to the solution. These chemical shift changes towards the chemical shift of $[Au(CN)_4]^-$ (δ_C = 106 ppm) are consistent with the direction of the gold(I) to gold(III). The transformation of the species resonating at 121 ppm, to the one resonating at 122.7 ppm is associated with a ligand exchange reaction (Eq. (16)). Additional hydroxide is also generated according to the half reaction for reduction of the hypochlorite ion:

$$OCl^- + H_2O + 2e^- = 2OH^- + Cl^- \tag{17}$$

When a solution exhibiting only the 122.7 ppm band {due to $[Au(CN)_2(OH)_2]$}, was adjusted to pH 2 with HCl, a new resonance appeared at 119 ppm and was assigned to $[Au(CN)_2Cl_2]^-$. Chloride was completely replaced by cyanide on its further addition. The reaction was anticipated to proceed through $[Au(CN)_3Cl]^-$ to $[Au(CN)_4]^-$.

It was found that the tetracyanoaurate complex, $[Au(CN)_4]^-$ could undergo reduction with glutathione (GSH) releasing $[Au(CN)_2]^-$. It was observed in ^{13}C NMR that the resonances due to the starting material $[Au(CN)_4]^-$ (106 ppm) and the final product $[Au(CN)_2]^-$ (156 ppm) are present in addition to the intermediates. The reduction of $[Au(CN)_4]^-$ occurs according to Eq. (18):

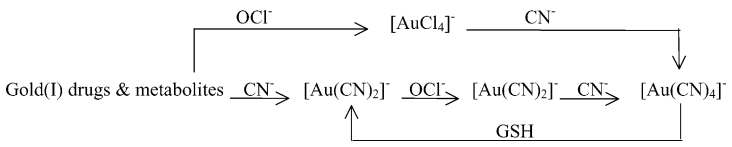
$$[Au(CN)_4]^- + 2GSH \rightarrow [Au(CN)_2]^- + 2HCN + 2GSSG \tag{18}$$

This oxidation and reduction process demonstrates that there is a potential redox cycle involving dicyanoaurate(I) and di- or tetracyanoaurate(III) species that could be established in vivo during chrysotherapy when macrophages are stimulated to undergo the oxidative burst (Scheme 5).

The operation of such a cycle is consistent with observations that while relatively low concentrations of gold are achieved during chrysotherapy (10 μM Au), the changes in tissue levels of essential metals, thiols, proteins, in responding patients are much larger than can be accounted for on the basis of a stoichiometric reaction with the gold present [1]. The formation of gold(III) species in vivo raises the possibility that, like the gold(I) species that are converted to dicyanoaurate, they might be converted to the homoleptic tetracyanoaurate(III) complex by immunogenerated hydrogen cyanide [23,84].

6.4. Medicinal use of cyanogold(I) complexes

Dicyanogold(I), $[Au(CN)_2]^-$ inhibits proliferation of HIV (human immunodeficiency virus) in cultured T-9 cells at levels as low as 20 nM and may have a promise in treating AIDS in combination with other drugs [79]. A rapid and nearly completely uptake of dicyanogold(I) by RBCs and its high tolerance in humans suggests that this material may provide a useful therapy for the treatment of AIDS [82]. A number of cyano(trialkylphosphine)gold(I) complexes were also tested against HIV, but were sufficiently cytotoxic that the MT-4 cells died at concentrations (∼1 μM) below the onset of antiviral activity [1]. $[Au(CN)_2]^-$ and Et_3PAuCN are also known to possess antitumor activity [10,85]. Gold(I) being a soft Lewis acid prefers to bind sulfur containing proteins rather than to DNA bases when administered. Therefore, cyanogold(III) complexes, which can bind strongly to DNA bases can be tested for antitumor activity and would hopefully be better antitumor agents compared to cyanogold(I)



Scheme 5.

complexes. In the light of close chemical similarity between the compounds of Pt(II) and Au(III), there is a possibility that both may use DNA as a target site. However, the complexes should also contain the groups which are labile, so that their displacement by DNA bases is thermodynamically favorable.

7. Conclusions

Cyanogold(I) complexes exist either as non-ionic complexes, LAuCN or as the ionic species $[AuL_2]^+[Au(CN)_2]^-$, in the solid state. K_{eq} for ligand scrambling is dependent on; the basicity and steric bulk of the ligand, solvent polarity and ionic strength of the solutions. The data about equilibrium constants, presented in this work constitute an important step towards characterizing ligand exchange reactions on gold(I) complexes, that are conducive basis for the detailed understanding of the dynamics of gold(I) in biological systems. The kinetics of ligand exchange reactions still require further details since it has not been studied as extensively as the thermodynamics. Ligand exchange reactions of $[Au(CN)_2]^-$ with sulfhydryl groups provide a possible mechanism by which $[Au(CN)_2]^-$ is transported across the cell membrane. Similar to the oxidation of OCl^-, oxidative addition of $[Au(CN)_2]^-$ with the oxidizing agents like Cl_2 and Br_2 can provide a good comparison. Since three and four coordination is also possible gold(I), therefore it will be interesting to prepare and characterize the tri- and tetra-coordinate cyanogold(I) complexes.

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