

A ^{13}C NMR study of the interactions of Ag^{13}CN and $\text{Ag}(\text{CN})_2^-$ with thiomalic acid, L-methionine and DL-selenomethionine

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Abstract. Complexation of Ag^+ as AgNO_3 , solid AgCN and $\text{Ag}(\text{CN})_2^-$ by labeled and unlabeled L-methionine, DL-selenomethionine and d,l-thiomalate were studied by nuclear magnetic resonance methods. The ^{13}C NMR indicates that only Ag^+ react with the both L-methionine, DL-selenomethionine at neutral and higher pH via CO_2^- and S or Se atom forming a chelate. The $\text{Ag}(\text{CN})_2^-$ and AgCN do not bind to either of these two ligands at any pH. The Ag^{13}CN , which is an insoluble polymer, can react with thiomalate to form chelate complexes at neutral pH. Various structures for the chelate formations are proposed.

Keywords: L-methionine, DL-selenomethionine, d,l-thiomalate, AgNO_3 , AgCN and $\text{Ag}(\text{CN})_2^-$, ^{13}C NMR

1. Introduction

There is considerable interest devoted to the reactions of the dicyanoaurate (I) ion, $\text{Au}(\text{CN})_2^-$, because it exhibits anti-HIV activity [1]. It is also an important metabolite of chrysotherapy agents (anti-arthritis gold drugs) [2,3].

Although, the formation constant for $\text{Au}(\text{CN})_2^-$ is known to be about 10^{36} [4], this important metabolite is known to react with thiols where one of the cyanide can be exchanged with addition of thiomalate (tmS^-) [5] and with glutathione [6]. However, little is known about the reactivity of $\text{Ag}(\text{CN})_2^-$ complex, although the coordination chemistry of the thiocyanate group has been exploited extensively, and the crystal structures of a large number of thiocyanate compounds are known [7–9]. Recently, Stocker et al. [10] studied the complexation of thiourea and its derivatives with AgCN where monomer and dimer complexes are formed which are separated and studied by X-ray spectroscopy.

The formation constant of $\text{Ag}(\text{CN})_2^-$ is about 10^{21} [4], which is much less than that of $\text{Au}(\text{CN})_2^-$. Since $\text{Au}(\text{CN})_2^-$ can react with thiols, it is possible that $\text{Ag}(\text{CN})_2^-$ may also react with thiols in aqueous solution. In this paper we present the interaction of thiomalic acid (tmS^-), L-methionine (Met) and $^{13}\text{C}\text{-CH}_3\text{-L-Met}$, DL-selenomethionine (SeMet) and $^{13}\text{C}\text{-CH}_3\text{-DL-SeMet}$ with AgCN and $\text{Ag}(\text{CN})_2^-$, as studied by carbon-13 NMR spectroscopy.

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2. Experimental

2.1. Chemicals

L-methionine (Met), thiomalate (tmS^-), AgCN and $\text{KAg}(\text{CN})_2$ and other reagents were obtained from Fluka Chemical company. DL-selenomethionine (SeMet) was obtained from Sigma-Aldrich Chemical Company. The K^{13}CN , $^{13}\text{C}\text{-CH}_3\text{-L-Met}$ and $^{13}\text{C}\text{-CH}_3\text{-DL-SeMet}$ were obtained from Isotec Chemical Company, USA. Ag^{13}CN was prepared as described in the literature [10].

2.2. NMR measurements

All NMR measurements were carried out on a Jeol JNM-LA 500 NMR spectrophotometer at 297 K. The ^{13}C NMR spectra were obtained at 125.65 MHz with ^1H broadband decoupling. The spectral conditions were: 32k data points, 0.967 s acquisition time, 1.00 s pulse delay and 45° pulse angle.

2.3. Solution preparations

Experiment 1: 0.10 M L-Met was prepared in 1.0 cm^3 D_2O . The pH^* was adjusted to neutral, acidic and basic as shown in Table 1. 1 equivalent of solid (0.0168 g) AgNO_3 (or and with 1 equivalent of $\text{KAg}(\text{CN})_2$) was added to the above solution and pH^* was adjusted as indicated in the same table. There were no precipitates observed at neutral pH^* and acidic medium but some ppts were observed at the basic medium. Similar experiments were repeated with SeMet. The results are summarized in Table 1.

Experiment 2: 0.20 M L-methionine (0.0250 g unlabel Met + 0.0050 g $^{13}\text{C}\text{-CH}_3\text{-Label Met}$) was prepared in 1.0 cm^3 D_2O . The pH^* was adjusted to neutral, acidic and basic as shown in Table 2. 1 eq. of (0.0336 g) AgNO_3 was added to the above solution and pH^* was adjusted as indicated in the same table. There were no precipitates observed at neutral pH^* and acidic medium but some ppts were observed at the basic medium. Similarly 0.0250 g SeMet was mixed with 0.042 g $^{13}\text{C}\text{-CH}_3\text{-Label SeMet}$ which is equivalent to 0.20 M 1.0 cm^3 solution. Followed by 1 equivalent addition of AgNO_3 as a solid to each solution. The results are summarized in Table 2. In this experiment, the $\text{KAg}(\text{CN})_2$ interactions with Met

Table 1

^{13}C NMR measurements of a pH^* titration of L-Met, SeMet itself and in the presence of AgNO_3 and $\text{Ag}(\text{CN})_2^-$ at a 1 : 1 (0.10 M) ratio each separately

Ligand	pH^*	$\text{Ag}(\text{CN})_2^-$	CO_2^-	$\alpha\text{-CH}$	$\beta\text{-CH}_2$	$\gamma\text{-CH}_2$	$-\text{CH}_3$	^{77}Se
Met	0.90	–	172.28	52.68	29.45	29.65	14.89	–
Met : AgNO_3	0.90	–	172.07	51.99	29.40	29.65	14.08	–
Met	7.0	–	175.05	54.70	29.63	30.46	14.73	–
Met : AgNO_3	7.0	–	177.91	55.71	34.39	32.68	18.53	–
Met : $\text{Ag}(\text{CN})_2^-$	6.90	149.66	174.99	54.74	29.68	30.50	14.81	–
SeMet	0.90	–	171.27	53.54	30.90	19.84	4.22	70.05
SeMet : AgNO_3	1.12	–	172.27	54.89	31.08	20.03	4.88	70.05
SeMet	7.0	–	175.25	55.53	31.68	20.05	4.08	70.77
SeMet : AgNO_3	7.0	–	178.47	56.99	36.65	25.20	9.24	57.97
SeMet : $\text{Ag}(\text{CN})_2^-$	7.1	149.75	174.88	55.64	31.79	20.33	4.41	68.81
$\text{Ag}(\text{CN})_2^-$	7.0	149.96	–	–	–	–	–	–

Table 2

^{13}C NMR measurements of a pH* titration of L-Met, SeMet itself and in the presence of AgNO_3 at a 1 : 1 (0.20 M) ratio for both Met and SeMet each reactions

Ligand	pH*	CO_2^-	$\alpha\text{-CH}$	$\beta\text{-CH}_2$	$\gamma\text{-CH}_2$	$-\text{CH}_3$	^{77}Se	$^1\text{J}(^{77}\text{Se}-^{13}\text{C})$
Met	0.90	172.28	52.68	29.45	29.65	14.89	–	–
Met : AgNO_3	0.90	173.88	52.89	30.01	30.88	15.05	–	–
Met	7.50	175.15	54.74	29.67	30.56	14.77	–	–
Met : AgNO_3^{a}	7.05	181.70	55.87	30.58	34.02	15.15	–	–
Met : AgNO_3^{b}	–	177.37	55.37	30.66	34.28	15.23	–	–
Met	12.40	182.0	55.84	33.90	30.42	15.01	–	–
Met : AgNO_3	High pH* ppts							
SeMet	8.92	178.38	56.14	33.47	20.74	4.30	68.48	30
SeMet	12.21	183.71	57.01	36.21	21.77	4.15	66.33	30
SeMet : $\text{Ag}^{+\text{c}}$	13.45	183.08	57.29	36.19	24.16	6.88, 6.84 (doublet)	54.18	22

^aMet– AgNO_3 at pH* 7 gave a ppts. therefore, solution was decanted and ran ^{13}C NMR spectrum.

^bppts of Met– AgNO_3 were dissolved in DMSO-d_6 and ran spectrum.

^cStill at such a high pH* the ppts. were not dissolved, so the solution was decanted and ran the NMR. The ppts were attempted to dissolve in DMSO-d_6 but the ppts turned immediately black and therefore no attempt was made to run the spectrum.

Table 3

^{13}C NMR measurements of a pH* titration of $^{13}\text{C}\text{-CH}_3\text{-L-Met}$, $^{13}\text{C}\text{-CH}_3\text{-SeMet}$ itself and in the presence of AgNO_3 at a 1 : 1 (0.05 M each) ratio each separately

Ligand	pH*	CO_2^-	$\alpha\text{-CH}$	$\beta\text{-CH}_2$	$\gamma\text{-CH}_2$	$-\text{CH}_3$	^{77}Se	$^1\text{J}(^{77}\text{Se}-^{13}\text{C})$
Met	0.90	172.28	52.68	29.45	29.65	14.89	–	–
Met : AgNO_3	0.84	172.53	52.56	29.34	29.34	14.68	–	–
Met	7.0	175.05	54.70	29.63	30.46	14.73	–	–
Met : AgNO_3	7.54	178.38	56.04	35.00	32.43	17.92	–	–
Met	12.40	182.00	55.84	33.90	30.42	15.01	–	–
Met : AgNO_3	13.81	183.68	56.10	34.99	30.57	14.94	–	–
SeMet	0.90	171.27	53.54	30.90	19.84	4.22	70.00	30
SeMet : AgNO_3	0.95	172.68	53.49	30.90	19.80	4.44	70.05	28
SeMet	7.0	175.25	55.53	31.68	20.05	4.08	70.77	30
SeMet : AgNO_3	7.0	176.82	56.58	31.93	20.29	4.35	69.15	28
SeMet	12.21	183.71	57.01	36.21	21.77	4.15	66.33	30
SeMet : AgNO_3	12.52	183.47	57.01	36.00	22.41	4.48	63.00	29

and SeMet were not studied because in the previous experiment it was found that it does not react with either of these ligands.

Experiment 3: 0.05 M L-methionine (0.0075 g $^{13}\text{C}\text{-CH}_3\text{-Label Met}$) was prepared in 1.0 cm^3 D_2O . The pH* was adjusted to neutral, acidic and basic as shown in Table 3. 0.0084 g AgNO_3 was added to the above solution and pH* was adjusted as indicated in the same table. At such a low concentration after addition of AgNO_3 still some ppts were observed. Similarly 0.0075 g SeMet $^{13}\text{C}\text{-CH}_3\text{-Label SeMet}$ was prepared in 1.0 cm^3 solution and 1 equivalent of solid AgNO_3 was added again some ppts were observed. The results are summarized in Table 3. We used labeled ligands to see if we can identify $^1\text{J}(^{77}\text{Se}-^{13}\text{C})$

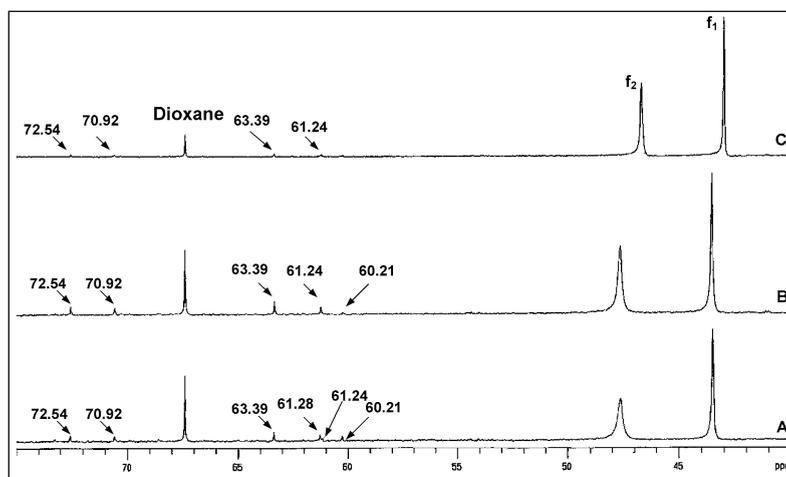


Fig. 1. The ^{13}C NMR spectra of low-field region of 0.30 M L : M (1 : 1) ratio at $\text{pH}^* 7$, of (A) thiomalate : Ag^{13}CN ; (B) thiomalate : AgCN and (C) thiomalate : $\text{Ag}(\text{CN})_2^-$.

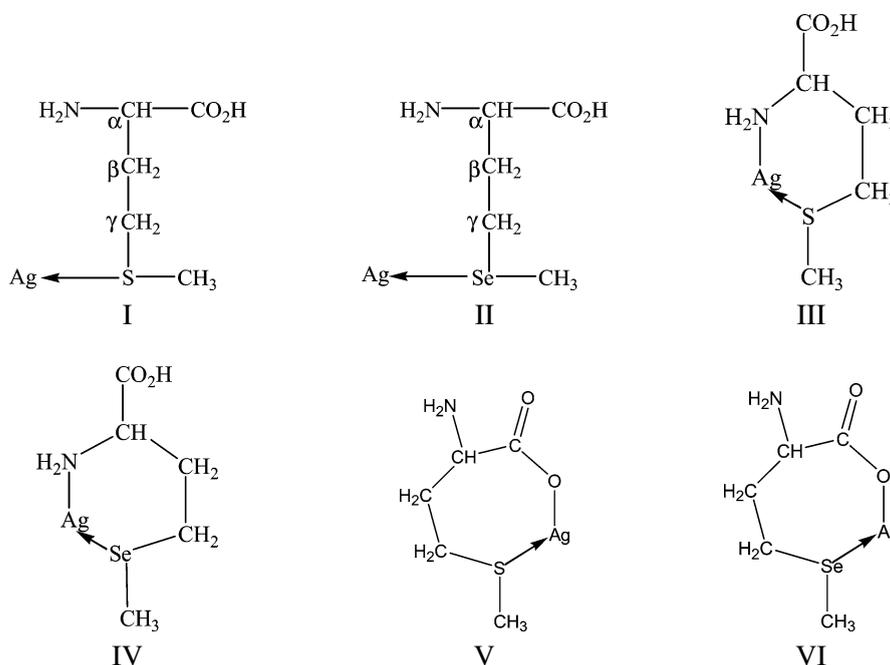
for the SeMet or $^1\text{J}(^{109}\text{Ag}-^{13}\text{C})$ for the Met which will give information about the nature of the bonding between $\text{Ag}(\text{I})$ and Met or SeMet.

Experiment 4: 0.30 M thiomalate (tmS^-) was prepared in D_2O and added 1 eq of Ag^{13}CN as a solid. Ag^{13}CN itself is insoluble in water [10]; however, in the presence of tmS^- it dissolved completely. The pH^* titration was carried out as indicated in Fig. 1. Same experiment was repeated with unlabeled AgCN to see the reproducibility of the experiment as indicated in Fig. 1B. Fresh new sample of 0.30 M thiomalate (tmS^-) was prepared in D_2O and added 1 equivalent of $\text{KAg}(\text{CN})_2$ as a solid, the spectrum of the experiment is shown in Fig. 1C.

3. Results and discussion

The AgCN is an insoluble polymer and does not react with thioether and selenoether type ligands under study [10]. There is no change in the chemical shifts of Met and SeMet in the presence of $\text{Ag}(\text{CN})_2^-$, therefore it can be concluded that $\text{Ag}(\text{CN})_2^-$ does not interact with either of these two ligands as noted in Table 1. However, AgNO_3 does react with these two ligands at neutral and at higher pH^* . The possible structures of the Ag complexes formed with Met and SeMet are shown in scheme 1. As noted in Table 1, the chemical shift difference between free and bound CO_2^- carbon is 2.86 ppm at neutral pH^* , however, only 0.20 ppm difference was observed in the acidic medium. Similarly, a chemical shift difference of 3.22 ppm for the CO_2^- carbon was observed for SeMet and its Ag^+ complex at neutral pH^* and 1.00 ppm difference was observed in the acidic medium. Since both CO_2^- and $\gamma\text{-CH}_2$ carbon resonances are affected on complexation, we may infer that both Se (and S) and CO_2^- groups are involved in bonding to $\text{Ag}(\text{I})$ ion. Therefore, we can rule out structures I and II.

The structures III and IV would require only $\alpha\text{-CH}$ and Se attached groups (i.e. $\gamma\text{-CH}_2$ and $-\text{CH}_3$) would be affected. Since we do not observe any substantial changes in the shifts of these carbons upon complexation, we can rule out structures III and IV. Therefore, the only possibilities of binding are proposed in the following structures V and VI, where CO_2^- and $\gamma\text{-CH}_2$ resonances are shifted the most. We have earlier reported the interactions of Met and SeMet with $\text{Hg}(\text{II})$ [11] and with $\text{CH}_3\text{Hg}(\text{II})$ [12]



Scheme 1. Possible structures of Ag–Met and Ag–SeMet complexes.

in aqueous solution. The chemical shift difference between free and bound $-\text{CH}_3$ of SeMet show of about 9.22 ppm, however for Met the difference is around 4 ppm. Our recent study of solution and solid state ^{13}C NMR between thiourea (TU) and selenourea (SeU) with $\text{Hg}(\text{II})$ show that for $\text{Hg}(\text{TU})_2\text{Cl}_2$ and $\text{Hg}(\text{SeU})_2\text{Cl}_2$, it is 6.9 and 9.7 ppm respectively indicating the softer nature of Se which binds more strongly to Hg compared to S atom [13].

Figure 1A shows the ^{13}C resonances of thiomalate (tmS^-) (0.30 M) solution in D_2O and after adding 1 eq of Ag^{13}CN as a solid. Ag^{13}CN itself is insoluble in water [10], however, in the presence of tmS^- it dissolved completely. The pH^* was below 4 which was adjusted to 6.90. The free tmS^- ^{13}C NMR resonances at pH^* 7 appeared at $f_1 = 42.17$, $f_2 = 45.42$, $f_3 = 181.07$ and $f_4 = 180.36$ ppm. At 1 : 1 ratio of tmS^- : Ag^{13}CN they appeared at 47.66 ppm (with broadening), 43.52, 183.36 and 180.26 ppm respectively. The $^{13}\text{CN}^-$ resonance is very broad at 148.88 ppm and a small sharp resonance appeared at 120.04 ppm. Six new resonances in the high-field region appeared at 72.54, 70.92, 63.39, 61.28, 61.24 and 60.21 ppm.

Figure 1B shows the 1 : 1 equivalent of unlabel AgCN : tmS^- , where the pH was maintained at 7.0. The CN^- resonance was very broad. Two carboxylate resonances appeared at 183.28 ppm and 180.25 ppm, and a new resonance appeared at 171.85 ppm. In the high field region b1 and b2 resonances appeared at 47.68 and 43.57 ppm respectively. Again five new resonances appeared at 72.54, 70.92, 63.39, 61.24 and 61.21 ppm. All these five resonances are of very low intensity.

Figure 1C shows the spectrum of 1 : 1 ratio of $\text{Ag}(\text{CN})_2^-$: tmS^- at pH^* 6.90. Again the CN^- resonance was very broad. Two carboxylate resonances appeared at 182.69 ppm and 180.39 ppm respectively. In the high field region b1 and b2 resonances appeared at 46.72 and 43.07 ppm respectively. Again four new resonances appeared at 72.54, 70.92, 63.39 and 61.24 ppm. All these four resonances of with very low intensity. Figure 2A,B,C is the expansion of the low field region. Several attempts were made

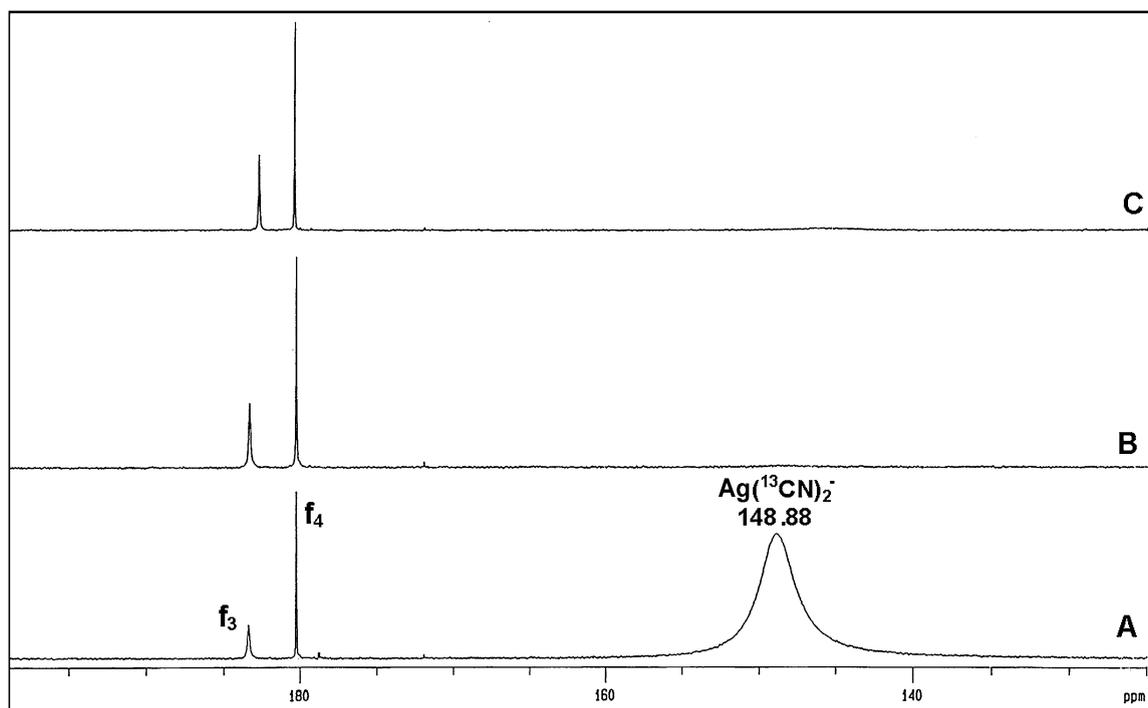


Fig. 2. A, B and C are the same as in Figs 1A, 1B and 1C but corresponding to high-field region (130 to 190 ppm).

to increase the intensity of 72.54, 70.92, 63.39, 61.28, 61.24 and 60.21 ppm resonances by changing the concentrations of tmS^- and or the concentrations of Ag^{13}CN or $\text{Ag}(\text{CN})_2^-$ but the intensities of these resonances remained the same indicating the equilibrium concentration of the product does not increase appreciably when the concentrations of the reactants was increased. This perhaps indicates the equilibrium constant for these reactions are very small and lie towards the reactants.

Although AgCN is known to be a polymer [10] and insoluble in water at any pH, the addition of thiomalate was able to dissolve it even in the acidic pH. Stocker et al. [10] have prepared series of complexes of thiourea and its derivatives with AgCN . AgCN was able to form complexes with various stoichiometries bonding to AgCN via sulphur atom of the ligands.

The above three experiments which were repeated twice to check reproducibility shows interesting features, e.g. in all three experiments the CN^- region is very broad except in Fig. 2A because here labeled Ag^{13}CN was used. This broadening is due to the formation of various species like $\text{RS-Ag-}^{13}\text{CN}^-$. The ^{13}C NMR chemical shift difference between $\text{Au}(\text{CN})_2^-$ and $\text{RS-Au-}^{13}\text{CN}^-$ is very small only 1.13 to 1.88 ppm [14,15]. Therefore one would expect the similar difference between Ag^{13}CN and $\text{RS-Ag-}^{13}\text{CN}^-$ species. The bonding to Ag with oxygen is well established in $\text{PPh}_3\text{-Ag-NO}_3$ complex where two oxygen of nitrate is bonded to Ag [16]. The six resonances newly identified may be due to the structures VII to IX proposed in Scheme 2, which clearly indicate $-\text{CH}$ and $-\text{CH}_2$ of tmS^- ligand in the 3 different environments. Unfortunately it is not possible to assign any resonances individually because of very low concentrations of the cyclic products proposed in structures VII to IX.

Xie et al. [17] have recently reported $[\text{Ag}_3(1,5\text{-bis}(2\text{-pyridylthio)pentane})_2(\text{NO}_3)_2]\text{NO}_3(\text{CH}_3\text{CN})$ type complex where Ag(I) is weakly bonded to oxygen of the nitrate. Nomiya et al. [18] have recently reported the complexation of hinokitiol (4-isopropyltropolone) ligand with Ag(I) ion. This ligand bonded



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