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Potentiometric and ^{1}H NMR Studies on Silver(I) Interaction with S-methyl-L-cysteine, L-methionine and L-ethionine

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Introduction

Ag(I) ions exhibit high affinity for sulphur atoms and in their complexes with sulphur containing amino acid the metal–sulphur bond appears to be of critical importance [1, 2]. The involvement of the other two donors centres, *i.e.* NH_2 and COO^- is, however, still not clear [1]. We have, therefore, carried out systematic ^{1}H NMR and potentiometric studies on the Ag(I) S-methyl-L-cysteine system and the results are given in this communication. For comparison the formation constants and some NMR results of related Ag(I) complexes with methionine and ethionine are also presented.

Experimental

S-methyl-L-cysteine, L-methionine and L-ethionine were obtained from Fluka or the Sigma Chemical Co (SIGMA grade). $AgNO_3$ (analytical purity grade) was used as a source of Ag(I) ions.

Samples of 1:1 and 1:2 metal to ligand molar ratio were used for proton NMR measurements. The ligand concentration was 0.1 *M* in all cases. All spectra were recorded in D_2O on a 100 MHz JEOL-PS-100 spectrometer with t-butanol as an internal standard at 25 + 1 °C. The proton NMR spectra were recorded with a sweep of 270 Hz and a sweep time of 250 sec.

NMR spectra of the CH_2–CH proton unit in S-methyl-L-cysteine were treated as ABC type spectra and analyzed on a JEC-6 computer.

Metal complex formation constants were calculated from potentiometric titration curves, obtained at 25 °C and I = 0.10 *M* (K[NO_3]). Changes in both pH and pAg were followed using a glass electrode and a silver/silver chloride electrode respectively and twin Radiometer PHM64 pH meters. The electrode systems were calibrated in terms of hydrogen-ion and silver-ion concentrations. Formation constants were calculated from the experimental data with the help of the MINIQUAD computer program [3].

Two different titration techniques were used. In method I the Ag(I): ligand ratio was constant (between 1:1 and 1:2) and alkali was added to the silver–ligand mixture while changes in the concentration of free hydrogen ions and free silver ions were followed potentiometrically. In method II a solution of Ag[NO_3] was added by increments to a solution of the ligand at the pH at which the ligand was approximately half neutralized. Changes in pAg (large) and in pH (small) were followed potentiometrically and Ag[NO_3] was added until the Ag: ligand ratio reached 2:1. Potentiometric titrations using a glass electrode as the only indicator electrode can only detect Ag–S coordination as a second order effect. Since the equilibria between Ag(I) and sulphur containing aminoacids are known to be complicated a direct measurement of free silver ion concentration was found to be essential. Since the pH range covered in method II was generally small, this method permitted more precise calculations based on a limited range of complex species. For such species agreement between formation constants calculated by the two methods was good.

Results and Discussion

Nmr Results for the Ag(I) S-methyl-L-cysteine System

A detailed analysis of proton NMR spectra of free S-methyl-L-cysteine (SMC) has been published recently [4]. The chemical shift of the methyl protons (S–CH_3) is slightly pH dependent (Fig. 1) and appears to be very sensitive to the binding of the sulphur donor to metal ions [4].

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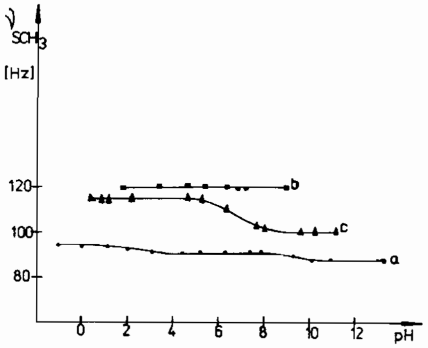


Fig. 1. pH dependence of the S–CH$_3$ proton chemical shift for free SMC (a), 1:1 (b), and 1:2 (c) Ag(I) to SMC molar ratio solutions.

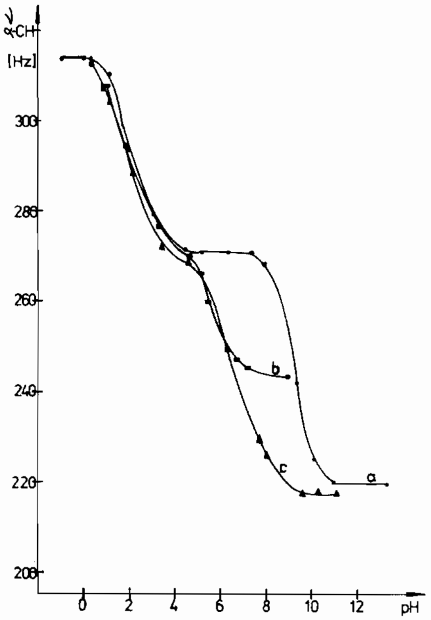


Fig. 2. pH dependence of the H_c proton chemical shift for free SMC (a), 1:1 (b), and 1:2 (c) Ag(I) to SMC molar ratio solutions.

In the 1:1 Ag(I) to SMC molar ratio solutions at pH up to 9 the chemical shift of S–CH$_3$ protons is almost constant and is shifted significantly downfield (*i.e.* 0.25 ppm) on coordination to Ag(I) (Fig. 1). This change in chemical shift suggests strongly that the SMC sulphur donor atom is involved in the binding of silver ions at the pH values studied.

The constant value of the S–CH$_3$ proton chemical shift between pH 2 and 9 in 1:1 molar ratio solutions suggests that the ligand is bound entirely through the sulphur since the shift does not depend on the deprotonation of the carboxyl ($pK_1 = 2.14$) or, apparently, the amine ($pK_2 = 9.22$) groups.

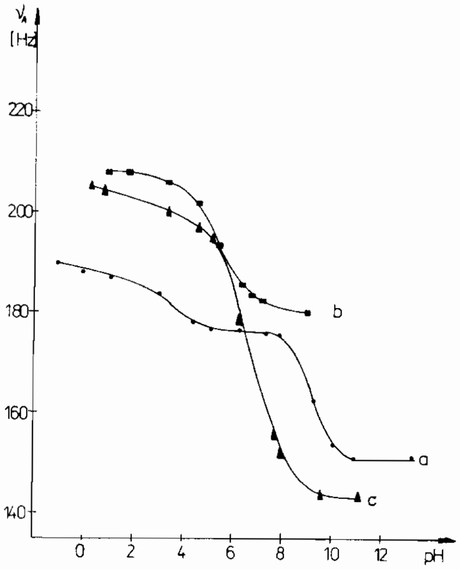


Fig. 3. pH dependence of the H_A proton chemical shift for free SMC (a), 1:1 (b), and 1:2 (c) Ag(I) to SMC molar ratio solutions.

A different pattern for the methyl proton chemical shift is observed for solutions of 1:2 Ag(I) to SMC molar ratio (Fig. 1). At low pH the downfield shift caused by metal ion coordination is similar to that found in 1:1 molar ratio solutions. However, above pH 4.5 when the amine group starts to dissociate (see Fig. 2) the S–CH$_3$ group undergoes an upfield shift in a sigmoidal pattern until, at pH > 9, it reaches a constant downfield shift value of only about 0.13 ppm in comparison to the S–CH$_3$ group of the free ligand (Fig. 1). This mode of change in the proton chemical shift of S–CH$_3$ for 1:2 solutions suggests that up to pH ~ 4.5 the SMC molecule is bound to Ag(I) via sulphur donor atoms to form a 1:2 Ag(I):SMC species (see also [1]). However, when the SMC amine group starts to dissociate at least one sulphur atom leaves the coordination sphere, probably as a result of amine group coordination (see below).

Changes in the αCH proton chemical shift on the metal coordination are also different for solutions of 1:1 and 1:2 metal to ligand molar ratio (Fig. 2). In both solutions at pH values up to 4 the αCH proton undergoes very slight change in the presence of metal ions (Fig. 2). Thus, it is probable that the carboxyl group of SMC is not involved in any direct bond formation with silver ion. The dissociation of the amine group on the other hand is affected significantly by the presence of Ag(I) ions. The silver ions promote the deprotonation of the SMC–NH_3^+ group markedly, causing it to occur about 3 pH units below the values obtained for the free ligand (Fig. 2). This result therefore also indicates that amine group coordinates to the silver ion at pH values above

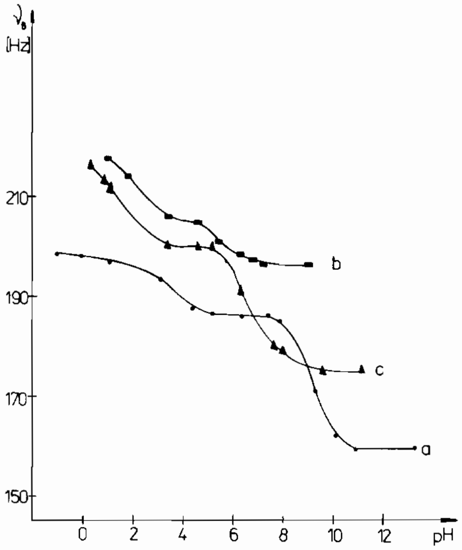
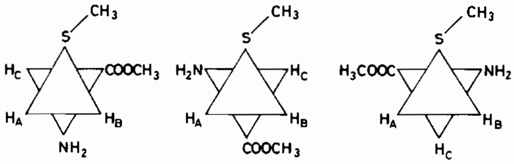


Fig. 4. pH dependence of the H_B proton chemical shift for free SMC (a), 1:1 (b), and 1:2 (c) Ag(I) to SMC molar ratio solutions.

4.5. Changes in αCH proton chemical shift observed for 1:1 and 1:2 solutions at pH > 7 are also different (Fig. 2). Coordination of silver ions to the $-NH_2$ group of SMC in a species formed in 1:1 solution causes a considerable downfield shift of the αCH proton resonance of about 0.25 ppm as compared to free ligand. In species formed at higher pH in 1:2 solutions silver ions also coordinate to $-NH_2$ but the chemical shift of αCH proton is close to that of free SMC (Fig. 2). The differences between the species formed in 1:1 and 1:2 solutions may be also seen if one considers the pH dependence of βCH_2 proton chemical shifts (Fig. 3, 4).

Thus the chemical shift variations of SMC protons can be interpreted as showing that, at pH values >4.5, the ligand coordinates to Ag(I) ions via both sulphur and nitrogen donors atoms. With pH values of less than 2 in both 1:1 and 1:2 solutions Ag(I) ion is bound to the sulphur donors only to form 1:1 $[AgH_2L]$ or 1:2 $[Ag(H_2L)_2]$ molar ratio complexes. In the pH range of 2–4 the carboxyl groups dissociate but sulphur remains as the only coordination site for Ag(I) ions and AgHL or $[Ag(HL)_2]$ species are formed. The deprotonation and coordination of the amine group to Ag(I) ions at pH > 4.5 leads to the removal of sulphur donor atoms from the coordination sphere only in the 1:2 complex, *e.g.* the $[Ag(HL)_2]$ species, when deprotonated ($[AgL_2]$), has one sulphur and one nitrogen bound to the metal ion. The species formed in 1:1 solution at pH > 4.5 has also sulphur and amine donors bound to silver. The resulting complex could be [AgL] with tetrahedral coordination around the silver ion. If, however, linear coordination is assumed the resulting



I II III

Fig. 5. Representation of the rotamers.

complex would have to be dimeric ($[Ag_2L_2]$) since the amount of bound sulphur does not appear to decrease when the pH increases above 4.5. Thus the differences found in the chemical shift patterns of Ag(I)–SMC complexes at higher pH values may result from differences in the stoicheiometry of the species formed and not from the different donor centres around each silver ion. The formation of dimers will be concentration dependent, the dimer concentration dropping rapidly as the solution becomes more dilute. Since comparatively concentrated solutions are required for NMR studies this technique is well suited to the qualitative detection of dimers.

Conformational analysis of the Ag(I)–SMC complexes also suggests structural differences between species formed in 1:1 ($[Ag_2L_2]$ – and 1:2 ($[AgL_2]$) solutions when the amine groups become coordinated. Assuming the rotamers as given in Fig. 5, the isomer distribution was calculated according to the Feeney approximation [5]. The populations are presented in Table I. A comparison of the population distribution for all complexes formed shows that, in the dimeric $[Ag_2L_2]$ complex, rotamer III is more stable and rotamer II is less stable than corresponding isomers in the $[AgL_2]$ complex. Molecular models therefore suggest that distinct stabilization of rotamer III in the $[Ag_2L_2]$ complex results from the dimeric structure of that complex.

The species found in 0.1 *M* solution may therefore be represented by the following scheme:

$$\begin{tikzcd}
\mathrm{Ag(I)} + \mathrm{SMC}(H_2L^+) \arrow[d, shift left] \arrow[d, leftarrow, shift right] & & & \\
{[Ag(H_2L)]^{2+}} \arrow[rr, rightleftharpoons] \arrow[d, shift left] \arrow[d, leftarrow, shift right] & & {[Ag(H_2L)_2]^{3+}} \arrow[d, shift left] \arrow[d, leftarrow, shift right] & \mathrm{pH} < 2 \\
{[Ag(HL)]^+} \arrow[rr, rightleftharpoons] \arrow[dr, shift left] \arrow[dr, leftarrow, shift right] & & {[Ag(HL)_2]^+} \arrow[d, shift left] \arrow[d, leftarrow, shift right] & \\
{[Ag_2L_2]} \arrow[r, rightleftharpoons] & {[AgL]} \arrow[r, rightleftharpoons] & {[AgL_2]^-} & \mathrm{pH} > 4.5 \\
& 1:1 \text{ ratio} & 1:2 \text{ ratio} &
\end{tikzcd}$$

Ag(I) Complexes with Methionine and Ethionine

The proton chemical shift pattern obtained for the solutions containing Ag(I) and methionine or ethionine is very similar to that found for Ag(I) SMC system. For example, the pH dependence of

TABLE I. Rotamer Populations of SMC in Free and Coordinated Ligands.

SMC				Ag(I)–SMC 1:2				Ag(I)–SMC 1:1			
pH	p_I	p_{II}	p_{III}	pH	p_I	p_{II}	p_{III}	pH	p_I	p_{II}	p_{III}
2 M DCl	0.03	0.66	0.31	0.35	0.19	0.48	0.33	1.05	0.20	0.45	0.35
1 M DCl	0.09	0.57	0.34	0.88	0.20	0.46	0.34	1.84	0.17	0.47	0.36
1.15	0.12	0.59	0.29	1.12	0.15	0.46	0.39	4.67	0.20	0.36	0.44
2.04	0.10	0.59	0.31	2.15	0.14	0.39	0.47	5.74	0.06	0.46	0.48
3.12	0.07	0.60	0.33	4.62	0.15	0.38	0.47	6.36	0.06	0.48	0.46
4.45	0.07	0.61	0.32	5.20	0.11	0.56	0.33	6.83	0.05	0.50	0.44
5.23	0.09	0.59	0.32	6.31	0.13	0.56	0.31	7.22	0.05	0.54	0.41
6.36	0.07	0.63	0.30	7.68	0.06	0.67	0.27	9.01	0.00	0.52	0.48
7.43	0.09	0.60	0.31	8.03	0.08	0.69	0.23				
7.96	0.08	0.62	0.30	9.61	0.06	0.72	0.22				
9.35	0.10	0.58	0.32	10.24	0.00	0.64	0.36				
10.10	0.12	0.54	0.34	11.14	0.07	0.74	0.19				
10.99	0.15	0.53	0.32								
13.30	0.12	0.56	0.32								

TABLE II. Complex Formation Constants of S-methyl-L-Cysteine (SMC), L-Methionine and L-Ethionine with Ag(I) at 25 °C and I = 0.10 mol dm^{-3} (K[NO$_3$]). Standard deviations (σ values) are given in parentheses.

		SMC	*L-Methionine*	*L-Ethionine*
$\log \beta_{HL}$		8.948(3)	9.058(1)	9.084(5)
$\log \beta_{H_2L}$		10.79(5)	11.21(1)	10.87(2)
$\log \beta_{AgLH}$	Method I	11.53(1)	12.21(3)	12.4(1)
	Method II	11.55(1)	12.36(3)	12.71(1)
$\log \beta_{Ag(LH)_2}$	Method I	?	24.60(4)	23.93(5)
	Method II	23.10(6)	23.80(1)	24.13(2)
$\log \beta_{AgL}$	Method I	5.42(1)	5.22(1)	?
	Method II	5.72(6)		
$\log \beta_{AgL_2}$	Method I	9.62(2)	?	9.66(1)

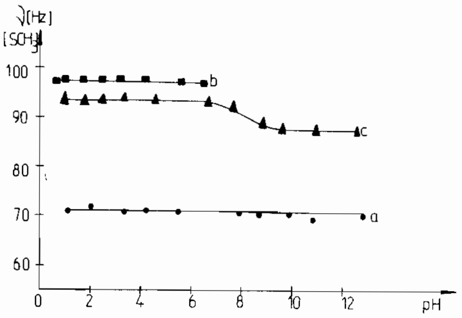


Fig. 6. pH dependence of the S–CH$_3$ proton chemical shift for free Met (a), 1:1 (b), and 1:2 (c) Ag(I) to Met molar ratio solutions.

S–CH$_3$ proton chemical shift (Fig. 6) is almost the same as found in Fig. 1 for the Ag(I)–SMC system. The species formed in solutions containing Ag(I) and methionine or ethionine would, therefore, be expected to be similar to those presented in the scheme for the Ag(I) SMC system [2].

Potentiometric Studies

Calculated complex formation constants, for both hydrogen ions and silver(I) complexes, are given in Table II. Figures in brackets are estimated standard deviations. While these reflect the precision of the measurements rather than their accuracy they do give an indication of the importance of the species concerned. Since they are only measurements of precision, the ranges of values for silver complex formation constants calculated by methods I and II do not always overlap although they are acceptably close.

The hydrogen ion complex formation constants reported in Table II are in good agreement with literature values and reflect the electron withdrawing properties of the thioether group. The major ligand species in the pH range of 3–8 will be HL, with the amine group protonated. Since the pH range studied in method II is pH 4.5 to 5.5, the protonated complexes would be expected to be major species. Silver complex formation constants were calculated from measurements in dilute solutions (about 10^{-3} mol dm^{-3}) – significantly more dilute than the solutions used for the NMR studies (about 0.1 mol dm^{-3}). As a result binuclear species were not significant in any of the refinements which were most acceptable statistically. However, trial calculations on test solutions using more concentrated solutions (up to 0.05 mol dm^{-3} ligand) demonstrated that the $[M_2(HL)_2]$ species was significant with methionine at higher concentrations.

Quantitative titrations of 0.1 *M* ligand solutions were not realistic since the background electrolyte required to keep the ionic strength constant would make comparison of results with those determined in 0.1 *M* solutions difficult or meaningless. Since the aim of this study was to investigate the donor centres used in silver complexes, the absence of quantitative data on possible dimers was not considered a serious disadvantage – particularly in view of the practical difficulties which would have to be overcome.

The potentiometric results given in Table II support the species distributions deduced from the NMR data if binuclear species are omitted. Formation constants for the reactions:

$$Ag^+ + HL \rightarrow [AgHL]^+$$

and

$$Ag^+ + 2HL \rightarrow [Ag(HL)_2]^+$$

are approximately log $K_{AgHL} = 3.0$ and log $K_{Ag(HL)_2} = 6.0$. Values reported for the formation constants of Ag^+ complexes of saturated (alkylthio) acetic acids are approximately log $K_{AgL} = 3.9$ and log $K_{AgL_2} = 6.9$ [6]. Allowing for the destabilising effect of the cationic $-NH_3^+$ group in the protonated amino acids studied, the reasonable agreement found supports the idea of comparable bonding in the two systems, *i.e.* Ag–S coordination only.

Once the amine group is deprotonated the formation constant would be expected to show an increase in size if $Ag-NH_2$ coordination is present. However, formation of a mononuclear complex with bidentate coordination would preclude linear coordination around the silver ion. The actual increase found demonstrates that such coordination is indeed possible, particularly when the solution is sufficiently dilute to discourage binuclear complex formation.

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