Comparison of ^{13}C NMR Chemical Shifts of 2-Aminovaleric Acid, L-Methionine and DL-Selenomethionine and their Interactions with Aurothiomalate in Aqueous Solution

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Abstract

The ^{13}C NMR chemical shifts of DL-selenomethionine were measured and compared with L-methionine and 2-aminovaleric acid in neutral and basic aqueous solutions. The C_γ and C_δ carbons which are directly attached to the sulphur atom of L-methionine experience a shielding effect compared to the C_γ and C_δ of 2-aminovaleric acid resonances. However, shielding effects were observed on C_γ and C_δ resonances when S was substituted by Se, *i.e.*, on going from L-methionine to DL-selenomethionine. The interaction of L-methionine and DL-selenomethionine with aurothiomalate was also studied. The results show that L-methionine does not bind to gold(I) at any pH. However, there is a weak binding observed with DL-selenomethionine in basic aqueous solutions, as seen by ^{13}C NMR spectroscopy.

Introduction

Much of the current interest in the biological chemistry of gold results from the clinical uses of 1:1 gold(I)–thiolate compounds such as aurothiomalate ('Myocrisin'*) and aurothioglucose ('Solganol'*) as antiarthritic agents [1–3]. Both of these drugs, *i.e.* gold(I)–thiomalate (Au(tm)) and gold(I)–thioglucose (Au(tg)) exist as polymers (up to octamers) but these polymers can be dissociated in the presence of thiols, CN^- and thiones to form tm–Au–ligand complexes [4–8].

The complexation of metal ions by methionine (Met) has attracted considerable interest [9–11]. However, the coordination chemistry of DL-selenomethionine (Se-Met) has received much less attention, despite the fact that it is one of the few naturally occurring selenoamino acids and a component of at least one bacterial selenoenzyme [12].

*May and Baker Ltd trade names.

In the present paper, we report for the first time the ^{13}C NMR of Se-Met and compare the chemical shifts with Met and 2-aminovaleric acid. Also the interactions of Met and Se-Met with Au(tm) have been studied in aqueous solution using ^{13}C NMR spectroscopy.

Experimental

Chemicals

DL-Selenomethionine and gold(I)–thiomalate were obtained from ICN K and K Laboratories, Plainview, New York. Se-Met showed no significant impurities by ^1H NMR spectroscopy and was used as received. Au(tm) was analyzed as Au(tm)·0.33-glycerol·H_2O [5–7]. L-methionine (Met), 99.7% D_2O, 40% NaOH in D_2O, and 35% DCl in D_2O were obtained from the Fluka Chemical Co.

NMR Measurements

^{13}C NMR spectra were measured at 50.3 MHz on a Varian XL-200 spectrometer operating in the pulsed Fourier transform mode. The ^{13}C NMR measurements were made with coherent off-resonance ^1H decoupling or with broad-band ^1H decoupling. ^{13}C NMR chemical shifts were measured relative to the CH_2 resonance of internal glycerol, g_2, which occurs at 63.33 ppm from $SiMe_4$ [13].

pH Measurements

All pH measurements were made at 22 °C with a Fisher Accumet pH meter, model 620, equipped with a Fisher microprobe combination pH electrode. The symbol pH* is used to indicate the actual meter reading for D_2O solutions with no correction for deuterium isotope effects [14].

Resonance Assignments

The resonance assignments of Met, Se-Met and 2-aminovaleric acid are given in Table I. They are assigned as in Scheme 1.

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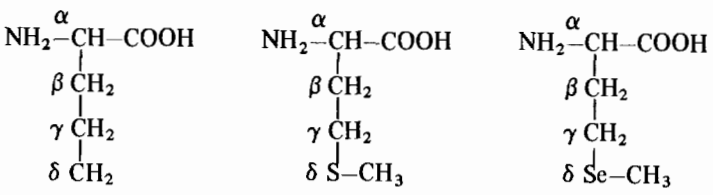
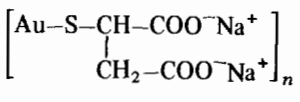
TABLE I. ^{13}C NMR Chemical Shifts of 2-Aminovaleric Acid, L-Methionine, DL-Selenomethionine and [Au(thiomalate)]:L (where L = L-methionine and/or DL-selenomethionine, in neutral and basic pH aqueous solution)

Ligand	pH*	CO_2^-	C_α	C_β	C_γ	C_δ	b_2	b_1	b_3	b_4	Rerefence
2-Aminovaleric acid	4.97	176.32	56.02	33.80	18.96	14.11					16
	12.97	185.06	57.10	38.17	19.56	14.54					16
L-Methionine	7.20	175.08	54.73	30.54	29.68	14.82					a, 15
	12.40	183.61	56.01	34.33	30.45	14.83					a, 15
L-Methionine:[Au(tm)]; 1:1	12.40	183.61	56.01	34.33	30.45	14.83	47.88	47.88	179.50	182.05	a
DL-Selenomethionine	7.40	175.16	55.61	31.80	20.13	4.16					a
	12.00	183.70	56.95	36.00	21.63	4.06					
DL-Selenomethionine:[Au(tm)]; 1:1	12.00	183.67	56.91	36.10	21.17	4.19	47.44	46.90	179.82	182.55	a

[a]This work.



2-Aminovaleric acid Met Se-Met



Au(tm)

$-CH = b_1$ and $-CH_2 = b_2$
$-CH-CO_2^- = b_3$ and $-CH_2-CO_2^- = b_4$

and $-CH = g_1$ and $-CH_2 = g_2$ for glycerol

Scheme 1.

Results and Discussion

Comparison of ^{13}C NMR Chemical Shifts of 2-Aminovaleric Acid, L-Methionine and DL-Selenomethionine

The ^{13}C NMR chemical shifts of Met, Se-Met and 2-aminovaleric acid are given in Table I. The ^{13}C NMR resonance assignments for Met [15] and 2-aminovaleric acid are reported in the literature [16].

When the sulphur is substituted, as going from 2-aminovaleric acid to methionine, the C_γ resonance is deshielded because of the electronegativity of sulphur and is shifted from 18.96 ppm to 29.68 ppm. The other resonances are shifted in a range of between 1 to 3 ppm. The C_δ resonance which is also directly bonded to sulphur does not experience any significant change.

When sulphur is substituted by selenium (going from Met to Se-Met) the two carbons which are directly bonded to selenium (*i.e.*, C_γ and C_δ) experience the biggest shift. Selenium is less electronegative than sulphur, which in turn has a shielding effect on these two resonances and both resonances shift to higher field by approximately 10 ppm. The other resonances remain almost unshifted by the substitution of sulphur by selenium.

Interaction of Gold(I)–Thiomalate with Met and Se-Met

A 20 mM Au(tm) solution was prepared in D_2O. The solution was pale yellow in colour at pH* 7.20 and the chemical shifts of Au(tm) for $b_2 = b_1 = 47.88$ ppm, $b_3 = 179.29$ and $b_4 = 181.69$ were observed. When one equivalent of Met was added as a solid to the Au(tm) solution, no colour change was observed and no chemical shift changes for any resonance were seen. When the pH* was increased from 7.20 to 12.40, the colour of the solution was still pale yellow and no chemical shift change was seen, except that deprotonation of the NH_2 group caused a shift of the $-CO_2^-$ and C_α resonances of Met. When the pH* was lowered from 12.00 to acidic, the solution became viscous, indicating that polymerization of

Au(tm) occurs, as reported earlier [5]. This observation indicates that Met does not bind to Au(tm) at any pH*.

The above experiment was repeated but instead of Met, Se-Met was used. At a 1:1 ratio of Au(tm):Se-Met, at pH* 7.20, no colour change of the Au(tm) solution and no chemical shifts change of either Se-Met or Au(tm) were seen.

When the pH* was increased from 7.20 to 12.00, the solution was still pale yellow in colour; however, the b_2 resonance shifted from 47.88 to 47.44 pm, whereas, the b_1 resonance shifted from 47.88 to 46.90 ppm, as shown in Fig. 1. Smaller chemical shift changes were observed for C_γ and C_δ resonances of Se-Met at higher pH* values. These data show that Se-Met binds to Au(tm) at high pH* values only.

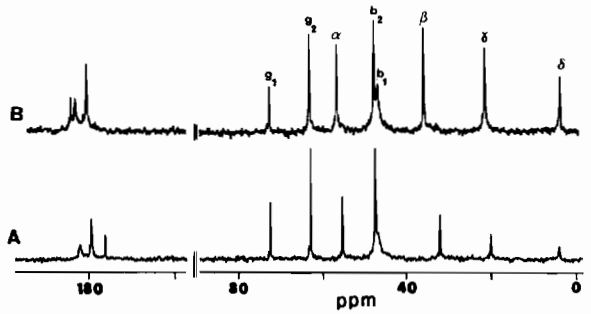


Fig. 1. The 50 MHz ^1H noise-decoupled ^{13}C NMR spectra of 20 mM Au(tm):DL-selenomethionine at (A) pH* 7.20 and (B) pH* 12.00.

The formation constants of $CH_3Hg(II)$ with Se-Met [19] and Met [10] have been reported in the literature. The log K_f value for Se-Met for selenoether is 3.73, whereas the log K_f for Met is 1.94 for the thioether group. These results indicate that the selenoether group forms more stable complexes with the 'soft' $CH_3Hg(II)$ than the analogous thioether group. These formation constants are compared in acidic solution because in basic solution $CH_3Hg(II)$ also forms the CH_3HgOH complex.

We have also studied the interaction of Hg(II) with Met and Se-Met [20] and conclude that Se-Met binds to Hg(II) more strongly than Met.

Methionine is present in almost all proteins and enzymes. In the present studies, we have shown that gold(I)–thiomalate does not bind to it. However, Et_3PAuCl (which is a potential drug and synthetic precursor of auranofin, another antiarthritic drug) [21] does bind to the multibinding sites of bovine serum albumin and one of the weak binding sites was suggested to be methionine [22].

Table II shows the difference in chemical shifts between the b_1 resonance of Au(tm) in the presence of various ligands. The following conclusion can be drawn from Table II: when the ligand(s) is added to the Au(tm) solution, the *trans*-effect which can be seen on the b_1 resonance is in the order: CN^- > thiols > thiones > selenother > thioether.

TABLE II. Differences in the ^{13}C NMR Chemical Shifts (Δ) of the b_1 Resonance of Gold(I)–Thiomalate in the Presence of Various Ligands (ppm)

Ligand	b_1	Δ	pH	Reference
[Au(tm)]	47.88		7.20	this work
CN^-	43.47	4.41	7.40	17
Thiols[a]	44.88–43.88	3–4	7.20	6
Thione	46.59[b]	1.29	7.20	7
	45.93[c]	1.95	7.20	18
Selenoether[d]	46.90	0.98	12.00	this work
Thioether[e]	47.88	0.00	12.40	this work

[a]Various thiols, see ref. 6 for details. [b]1,3-Diazinane-2-thione. [c]Imidazolidine-2-thione. [d]DL-Selenomethionine. [e]L-Methionine.

Conclusions

(1) When sulphur is substituted by selenium, e.g. methionine to selenomethionine, the carbons bonded directly to selenium experience a shielding effect and shift to higher field.

(2) Gold(I)–thiomalate (an antiarthritic drug) binds very weakly to selenomethionine at high pH*; however, it does not bind to methionine at any pH*.

(3) The b_1 resonance of gold(I)–thiomalate shifts to higher field after additions of various ligands. This high-field shift is due to electron donation by the ligand to the 6s and 6p orbitals of gold(I). The *trans*-effect as seen from the ^{13}C NMR spectrum of the b_1 resonance is as follows: CN^- > thiols > thiones > selenoether > thioether.

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References

1 P. J. Sadler, *Struct. Bonding (Berlin), 29*, 171 (1976).
2 C. F. Shaw, III, *Inorg. Perspect. Biol. Med., 2*, 287 (1979).
3 D. H. Brown and W. E. Smith, *Chem. Soc. Rev., 9*, 217 (1980).
4 D. T. Hill, B. M. Sutton, A. A. Isab, M. T. Razi, P. J. Sadler, J. M. Trooster and J. M. Calis, *Inorg. Chem., 22*, 2936 (1983).
5 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 1657 (1981).
6 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 135 (1982).

7 A. A. Isab, *J. Chem. Soc., Dalton Trans.*, 1049 (1986).
8 G. Lewis and C. F. Shaw, III, *Inorg. Chem., 25,* 58 (1986).
9 L. D. Pettit, K. F. Siddiqui, H. Kozłowski and T. Kowalik, *Inorg. Chim. Acta, 55,* 87 (1981).
10 M. T. Fairhurst and D. L. Rabenstein, *Inorg. Chem., 14,* 1413 (1975).
11 D. F. S. Natusch and L. J. Porter, *J. Chem. Soc. A,* 2527 (1971).
12 H. E. Ganther, in R. A. Zingaro and W. C. Cooper (eds.), 'Selenium', Van Nostrand Reinhold, New York, 1974, p. 546.
13 A. A. Isab, *J. Inorg. Biochem., 30,* 69 (1987).
14 P. A. Glasoe and F. A. Long, *J. Phys., Chem., 64,* 188 (1960).
15 W. J. Horsley, H. Sternlicht and J. C. Cohen, *J. Am. Chem. Soc., 92,* 680 (1970).
16 D. L. Rabenstein and T. L. Sayer, *J. Magn. Reson., 24,* 27 (1976).
17 G. G. Graham, J. R. Bales, M. C. Grootveld and P. J. Sadler, *J. Inorg. Biochem., 25,* 163 (1985).
18 A. A. Isab, *Inorg. Chim. Acta, 135,* 19 (1987).
19 A. A. Isab and A. P. Arnold, *J. Coord. Chem., 14,* 73 (1985).
20 A. A. Isab, *Inorg. Chim. Acta, 91,* L35 (1984).
21 M. T. Coffer, C. F. Shaw, III, M. K. Eidness, J. W. Watkins, II and R. C. Elder, *Inorg. Chem., 25,* 333 (1986).
22 A. A. Isab, A. L. Hormann, M. T. Coffer and C. F. Shaw, III, *J. Am. Chem. Soc., 110,* 3278 (1988).