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Synthesis and Characterization of Highly Pure Form of Sodium Salt of Anionic, Thiomalatogold(I) Complex with Antiarthritic Activity.
Analogs of Anionic, Thiomalatosilver(I) Complex with Antimicrobial Activity

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Sodium salt of anionic Au(I) complex with a trianion of thiomalic acid tma^{3-} (H_3tma=HOOCCH(SH)-CH_2COOH), known as an effective antiarthritic drug, was prepared in highly pure form by one-step synthesis from $NaAuCl_4$ and tma^{3-} in aqueous solution. The reaction consisted of a reduction of Au(III) by tma^{3-} and the following complexation of Au(I) with tma^{3-} ligand. The disulfide species of tma^{3-} formed by this reduction was removed by passing through an anion-exchange resin column and the contaminating NaCl by passing through a gel filtration column. The tma–Au(I) complex was also prepared by another reaction based on ligand exchange of the intermediate complex AuCl(thiodiglycol) with tma^{3-}. It was purified using the anion-exchange resin and gel filtration columns. The target compound, finally isolated in 30% yield in highly pure form, has been characterized by complete elemental analyses, TG/DTA, FT-IR, ^{1}H and ^{13}C NMR spectroscopies, and molecular weight was determined in aqueous solution by molmass measurement based on the cryoscopic method combined with dissociation degree determination based on the $[Na^+]$ measurement in equilibrium state using a Na^+-ion selective electrode. This Au(I) complex was an oligomer with a formula of $\{Na_2[Au(tma)]\cdot 1.75H_2O\}_n$ (n=3—10; MW=1260—4220). This polymerization degree, low in comparison with previously proposed data, was determined in the neutral aqueous solution without any other electrolytes under the concentration range C_{Na}=0.914—182.9 mmol dm^{-3}. The tma–Au(I) complex exists in an oligomeric form both in the solid and in aqueous solution. The properties of the oligomeric tma–Au(I) complex were compared with those of the previously reported complex and a commercially available sample, and also with those of the recently prepared, oligomeric tma–Ag(I) complex with antimicrobial activity.

In recent years, interest has increased in the coordination chemistry of Ag(I) and Au(I) with thiol ligands such as thiomalate, thioglucose, or thiosalicylate as a result of biological or medicinal activities.[1,2] In fact, bis(thiosulfato)argentate(I), $[Ag(S_2O_3)_2]^{3-}$ (STS) has been shown to possess an antiethylene activity resulting in delaying in senescence of ethylene-sensitive flowers such as carnation,[3] and the corresponding Au(I) complex, $[Au(S_2O_3)_2]^{3-}$ (Sanocrisin) to possess an antiarthritic activity, the molecular structure of which has been established.[4a] We have recently prepared sodium salt of the anionic, 1:1 complex of Ag(I) with a trianion of thiomalic acid tma^{3-} (H_3tma=HOOCCH(SH)CH_2COOH), which has been identified to be an oligomer with a formula of $\{Na[Ag(Htma)]\cdot 0.5H_2O\}_n$ (n=24—34; MW=6910—9790) in aqueous solution and has been shown to possess an effective antimicrobial activity against selected bacteria, yeast and mold.[5] Further, we have also recently prepared two types of anionic Ag(I) complexes with a dianion of thiosalicylic acid tsa^{2-} (H_2tsa=o-HS(C_6H_4)-COOH), one of which has been shown to be oligomeric species with a formula of $\{Na[Ag(tsa)]\cdot H_2O\}_n$ (n=21—27; MW=6320—8130) in aqueous solution and to possess a remarkable antimicrobial activity.[6] In connection with these bioinorganic compounds, we have also paid attention to the corresponding anionic Au(I) complex with thiomalate and thiosalicylate ligands. The sodium salt of a water-soluble, anionic and monomeric 1:2 complex of Au(I) with tsa^{2-} has been recently isolated as colorless needle crystals.[7] On the other hand, the Au(I) compound with tma^{3-}, called disodium aurothiomalate or gold(I) sodium thiomalate (Myocrisin), has been considered as polymeric species with a composition of Au(I) : $tma^{3-}=1:1$ molar ratio and also known as a commercially available, antiarthritic drug.[8—13] Crystals of such a compound suitable for X-ray measurements have remained elusive, so that its molecular structure is not known in detail, despite its extensive clinical use.

It has been believed that the disodium aurothiomalate in solution exists in aggregate form.[12] However, there are some vague points in this description; is the disodium aurothiomalate itself monomeric or polymeric in the solid ? Does the monomeric aurothiomalate polymerize in aqueous solution or does the polymeric one further polymerize in aqueous solution? Further, its solution molecular weight has been reported with some different values, e.g. as about 6 of the degree of polymerization for its 10^{-2} mol dm^{-3} aqueous solution in the presence of 0.5 mol dm^{-3} NaCl, the measurement method of which has been unpublished,[1a] and as an eluate with an apparent molecular weight of ca. 10000 Daltons from Sephadex G-100-120 in pH 8.6 Tris buffer.[14] These polymerization degrees look significantly depending upon the experimental conditions. However, there is also a problem whether a purity of the compound used for measurements has been confirmed. In fact, almost all of the compounds used for the reported measurements were not freshly prepared, but were commercially available ones which have been contaminated with another chemicals such as glycerol.[8] The pharmacopoeia of the tma–Au(I) compound or gold(I) sodium thiomalate, clinically used as therapeutic drugs, has actually reported that it is a mixture of compounds with the different countercation-composition such as $(Na^+)_2$ and $(Na^+)(H^+)$.[15]

We have prepared the sodium salt of tma–Au(I) complex in highly pure form by two different methods: (1) one is by a one-step synthesis from $NaAuCl_4$ and tma^{3-} in aqueous solution, which consists of a reduction of Au(III) by tma^{3-} and the following complexation of the Au(I) with tma^{3-} ligand, and (2) the other is by another reaction of tma^{3-} with the intermediate complex AuCl(thiodiglycol), which has been formed in aqueous solution by the reaction of $NaAuCl_4$ with thiodiglycol.[16] Both methods have required some purifications for isolation of pure tma–Au(I) complex. We have overcome them by passing the crude materials in aqueous solution through an anion-exchange resin column and subsequently through a gel filtration column. The pure species obtained by (1) with a formula of $\{Na_2[Au(tma)]\cdot 1.75H_2O\}_n$ ($n=3$—10) has been characterized with complete elemental analyses, TG/DTA measurements, FT-IR, ^{1}H and ^{13}C NMR spectroscopies, and molecular weight determination in aqueous solution which has been recently applied for both oligomeric tma^{3-}–Ag(I) and tsa^{2-}–Ag(I) complexes.[5,6]

Herein we reported the preparation of the tma–Au(I) complex, its characterization, and solution properties compared with those of the previously reported tma–Au(I) complex.[8a,8b,8c] Furthermore we compared the properties of the tma–Au(I) complex with those of the recently prepared Ag(I) analogue.[5]

Experimental

Chemicals. All chemicals were reagent grade and were used without further purification: thiomalic acid, $NaAuCl_4\cdot 2H_2O$, NaOH, EtOH, Et_2O (Wako); disodium aurothiomalate monohydrate (Aldrich); 99.8% D_2O (Merck); thiodiglycol (Tokyo Kasei); Sephadex G-10 (Pharmacia); DE-52 Cl^--form anion-exchange resin (Whatman).

The anion-exchange resin in the column has been pretreated with 0.5 mol dm^{-3} hydrochloric acid to show the eluent (with water) pH ≈4, next with 0.5 mol dm^{-3} NaOH aqueous solution to show the eluent (with water) pH ≈7, and finally with 1.0 mol dm^{-3} NaCl aqueous solution and washed thoroughly with water, before use. The Sephadex G-10, which has been swelled with water and packed in the gel filtration column, has been washed thoroughly with water.

Measurements and Instrumentation. Elemental analyses were obtained from Mikroanalytisches Labor Pascher (Remagen, Germany). Infrared spectra were obtained on a Nicolet 510 FT-IR spectrometer as KBr disk at room temperature. Thermogravimetric (TG) and differential thermal analyses (DTA) were simultaneously done using a Seiko SSC 5000 TG/DTA 300 which was temperature programmed at 10.0 °C per minute between 20 and 500 °C under air.

The ^{1}H NMR (399.65 MHz) and ^{13}C NMR (100.40 MHz) were recorded in 5 mm o. d. tubes on a JEOL JNM-EX 400 FT-NMR spectrometer and JEOL EX-400 NMR data processing system at 25 °C. The ^{1}H and ^{13}C{^{1}H} NMR spectra of the complex were measured in D_2O solution of ca. 2 wv% concentration with reference to an internal DSS, at room temperature and 80 °C, and also at room temperature in the presence of 0.5 and 1.0 mol dm^{-3} NaCl. In order to reexamine the ligand-exchange reaction of the complex,[1a,8] both ^{1}H and ^{13}C NMR spectra in D_2O solution at room temperature were measured in the presence of 2 or 3 equivalents of free tma ligand at almost neutral pH. The solution systems examined were 0.55 mL D_2O solutions containing complex : H_3tma : NaOH = 0.05 : 0.10 : 0.25 mmol or 0.05 : 0.15 : 0.30 mmol.

Molecular Weight Determination in Aqueous Solution. Molmass measurement in aqueous solution was done by Mikroanalytisches Labor Pascher (Remagen, Germany) based on the cryoscopic method using 11.46 mg of the prepared Au(I) complex in 0.397027 g H_2O, resulting in 330 (experimental error within ±5%) as the observed molmass value. Control experiments using standard samples, sodium chloride (formula mass: 58) and disodium succinate (formula mass: 162) which have been considered to be strong electrolytes in aqueous solution, gave 29 and 59 as the observed molmass values (experimental error within ±5%), respectively. By multiplying the observed molmass value with the number of species existing in the solution, the formula mass or molecular weight of the complex can be evaluated. The number of species present in equilibrium state solution becomes a function of dissociation degree α for weak electrolytes, which can be experimentally determined by measuring [Na^+] under varied concentrations C_{Na} of the complex. If the plot of observed [Na^+] versus C_{Na} gives a straight line, its slope gives the α value. The [Na^+] measurements were carried out at 25 °C three times each for six different points of C_{Na} under concentration range $C_{Na}=0.914$—182.9 mmol dm^{-3} using a Na^+-ion selective electrode [Horiba 1512A-10C] and a reference electrode [Horiba 2565A-10T] equipped with a pH/Ion meter [Horiba F-23].

Preparation and Purification of Sodium Salt of tma–Au(I) Complex. Method 1. To thiomalic acid (H_3tma) 0.75 g (5 mmol) dissolved in 10 mL water, an aqueous solution of NaOH 0.40 g (10 mmol) in 10 mL water was added. The resulting faint purple solution was dropwise added to the stirred yellow, clear aqueous solution prepared by dissolving $NaAuCl_4\cdot 2H_2O$ 0.50 g (1.25 mmol) in 5 mL water. The initially darkened solution became clear, pale yellow during 20 minute-strring. This solution was once filtered through a fluted filter paper (Whatman #2), followed by rotavaporing the yellow filtrate at 50 °C until it became slightly viscous. This concentrated solution was dropwise added to 250 mL ethanol (stirred). The white precipitate which formed was collected on a fine glass frit, washed with 20 mL ethanol, then with 20 mL ether, and dried at 50 °C in vacuo overnight. A solution of the dried precipitate dissolved in 10 mL water was again filtered through a fluted filter paper (Whatman #2), and the filtrate was added to 250 mL ethanol (stirred). The obtained precipitate was collected on a membrane filter (Millipore, FG 0.2 μm), washed with 20 mL ethanol, then with 20 mL ether, and dried at 50 °C in vacuo overnight. (The white compound at this stage was still crude and highly hygroscopic, its yield was about 1 g. It was shown by ^{1}H NMR and IR spectra that this compound was contaminated with disulfide form of tma^{3-}.)

Purification was carried out as follows. A solution of the crude compound dissolved in 5 mL water was poured into the DE-52 anion-exchange resin column (Cl^--form: Whatman DE-52, 1.5 cmϕ×17 cm height). The absorbate was eluted with 1.0 mol dm^{-3} NaCl aqueous solution and collected using a fraction collector. The eluate was rotavapored to about 5 mL volume at 50 °C. In order to remove contaminated NaCl, the evaporated solution was further passed through a Sephadex G-10 gel filtration column (1.5 cmϕ×90 cm height) and eluted with water. The yellow eluate, collected in a fraction collector, was rotavapored to dryness and then dried at 50 °C in vacuo overnight. Finally obtained with yield of 0.15 g (30%) was yellow or white-yellow powder, which was highly soluble only in water, but insoluble in all organic solvents.

The compound in the solid state decomposes at 264 °C without melting. This compound in aqueous solution is sensitive to light and undergoes degradation for several days standing at room temperature, but is stable in the dark. All attempts at crystallization of the complex have been unsuccessful. The data of its characterization are listed in Table 1.

The described preparation has been done using the stoichiometry of $NaAuCl_4\cdot 2H_2O : H_3tma : NaOH = 1:4:8$ molar ratio. From other molar ratios such as 1 : 5 : 10 and 1 : 8 : 16, containing excess amounts of H_3tma and NaOH, the identical product was isolated with slightly lower yields.

Method 2. The preparation described here is based

Table 1. Numerical Data of Elemental Analyses, TG/DTA, Solid FT-IR, and ^{1}H and ^{13}C NMR for the Sodium Salt of tma–Au(I) Complex

(1) Analytical data

Formula	Found (calcd) (%)						
	C	H	O	S	Au	Na	Total
$\{Na_2[Au(OOCCH(S)CH_2COO)]\cdot 1.75H_2O\}_n$	11.49 (11.40)	1.44 (1.55)	21.90 (21.82)	7.64 (7.60)	46.90 (46.72)	10.80 (10.91)	100.17 (100.00)

(2) TG/DTA data

Obserbed weight loss: 6.93% below 250 °C (calcd for $1.75H_2O$: 7.48%)
Decomposition temperature: 264 °C

(3) FT-IR spectrum

Some prominent IR bands in 1700—400 cm^{-1} region measured as KBr disk:
1583 (vs), 1403 (vs), 1311 (vw), 1265 (w), 1185 (w, br), 989 (w), 932 (w), 876 (m), 842 (vw), 693—558 (s, br) cm^{-1}

(4) NMR data

^{1}H and ^{13}C NMR measured in D_2O at 26 °C with an internal DSS
^{1}H NMR $\delta=4.11$ (1H, m, $C\underline{H}$), 2.91 (1H, m, $C\underline{H_a}H_b$), 2.82 (1H, m, $CH_a\underline{H_b}$)
^{13}C NMR $\delta=183.4$ (–$\underline{C}$OO–), 181.0 (–$\underline{C}$OO–), 50.0 (–$\underline{C}H_2$–), 49.7 (–$\underline{C}$H–)

on modifications of the literature method.[16)] Thiodiglycol 0.457 g (3.75 mmol) was slowly added for 45 min to the stirred, *ice-cooled solution* of $NaAuCl_4 \cdot 2H_2O$ 0.497 g (1.25 mmol) dissolved in 10 mL water. To the clear stirred solution, thiomalic acid (H_3tma) 0.333 g (1.25 mmol) dissolved in 20 mL EtOH was dropwise added for 20 min. The obtained pale yellow clear solution was evaporated until it became slightly viscous. 10 mL water was added, then 5 mL of 1.0 $mol\,dm^{-3}$ aqueous NaOH (5 mmol) was added, and the mixture was filtered once through a fluted filter paper (Whatman #2). The filtrate was rotavapored at 50 °C until it became viscous, and then the yellow solution was added to 250 mL EtOH (stirred). The white precipitate was collected on a fine glass-frit, washed with 20 mL EtOH, then with 20 mL ether, and dried in vacuo at 50 °C for 2 h. The yield at this stage was 520 mg. The white powder was redissolved in 10 mL water, filtered through a filter paper (Whatman #2), and the filtrate was rotavapored at 50 °C to form a viscous solution. White precipitate which reprecipitated by adding to 250 mL EtOH was washed with 20 mL EtOH, then with 20 mL ether and dried in vacuo at 50 °C overnight. (The yield was 450 mg. It was also shown by ^1H NMR spectra that the compound at this stage was still crude.)

Purification was carried out as follows. The crude sample (450 mg) dissolved in 5 mL water was added in DE 52 anion-exchange resin column (1.5 cm$\phi \times$15 cm height), unadsorbed materials were washed off with 60 mL water, and the adsorbed complex was eluted with 1.0 $mol\,dm^{-3}$ NaCl aqueous solution with an eluting rate of one drop per 3 seconds. The eluate was rotavapored at 50 °C to dryness. Next, the residue redissolved in a small amount of water was passed through Sephadex G-10 gel filtration column (1.5 cm$\phi \times$97 cm height) and then eluted with water with an eluting rate of one drop per 5 seconds. Yellow powder was obtained with yield of 132 mg (25% with respect to the $NaAuCl_4$ used) by rotavaporing the eluate to dryness at 50 °C.

The FT-IR, ^1H and ^{13}C NMR spectra of this compound were completely identical with those of the tma–Au(I) complex obtained in Method 1.

The solid FT-IR spectrum measured in KBr disk, and ^{13}C and ^1H NMR spectra in D_2O of the sodium salt of tma–Au(I) complex obtained here were compared with those of the commercially available, disodium aurothiomalate monohydrate (Aldrich). They were in good agreement, except that the commercially available sample showed one unknown, intense peak at 2.22 ppm only in the ^1H NMR spectrum.

Results and Discussion

Complex Formation Reaction. The stoichiometry of this synthetic reaction in Method 1 can be represented by Eqs. 1 and 2, where the finally obtained compound is actually an oligomer, or $\{Na_2[Au(tma)]\}_n$ with polymerization degree n=3—10 as described later.

$$\begin{aligned}&NaAuCl_4 + 3H_3tma + (9-x)NaOH \rightarrow\\ &\quad Na_2[Au(tma)] + 4NaCl + (9-x)H_2O\\ &\qquad + Na_{4-x}H_x[\{tma\}_2^{4-}] \quad (x = 0\text{—}4), \quad (1)\end{aligned}$$

$$Na_2[Au(tma)] \rightarrow 1/n\{Na_2[Au(tma)]\}_n, \qquad (2)$$

where H_3tma is $HOOCCH_2CH(SH)COOH(RSH)$ and $[\{tma\}_2^{4-}]$ is a disulfide form (RS–SR) of H_3tma. The net reaction (1) in aqueous solution consists of a reduction of Au(III) by thiols of two tma^{3-} ions which is coupled with an oxidative formation of disulfide species RS–SR of tma^{3-}, and a following complexation of Au(I) with one remaining tma^{3-} ion. The tma^{3-} : Au(I)=1 : 1 composition in the complex formed according to Eq. 1 is conserved, even if excess amounts of H_3tma ligand and NaOH are initially used (See Experimental). These results support the previously reported papers; neither Au(I) nor Ag(I) has a tendency to form the 1 : 2 complex with tma^{3-} ligand in aqueous solution.[8a,8b,18)] The disulfide species $Na_{4-x}H_x[\{tma\}_2^{4-}]$ are removed by an anion-exchange resin column, and both NaCl used in the eluent and that formed in the reaction (1) are removed off by a gel filtration column. It has been previously pointed by spectrophotometric methods that the reaction of Au(III) by tma^{3-} ions more readily proceeds in aqueous solution than in organic solutions such as eth-

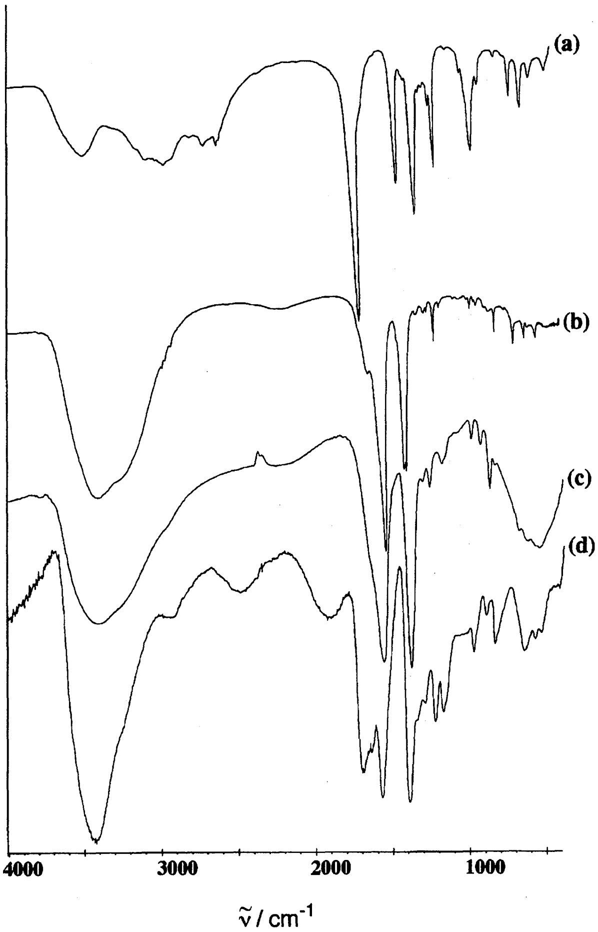

Fig. 1. Solid FT-IR spectra in 4000—400 cm^{-1} region measured in KBr disk: (a) free H_3tma, (b) the sodium salt of tma, prepared by rotavaporing the aqueous solution containing H_3tma and 3 equiv of NaOH, (c) the sodium salt of tma–Au(I) complex, $\{Na_2[Au(tma)] \cdot 1.75H_2O\}_n$ and (d) the sodium salt of tma–Ag(I) complex, $\{Na[Ag(Htma)] \cdot 0.5H_2O\}_n$.[5)]

anol and acetonitrile.[17)]

On the other hand, the preparation in Method 2 is based on the ligand-exchange reaction between an intermediate complex Au(I)Cl(thiodiglycol) and the tma^{3-} ligand.[16)] Although this method needs the reduction of Au(III) with thiodiglycol *under ice-cooled conditions*, otherwise the starting Au(III) is completely reduced to metallic gold, it also gives the sodium salt of tma–Au(I) complex identical with that obtained in Method 1 with the same purity and with almost the same yield, after the purifications using anion-exchange resin and gel filtration columns.

Characterization of Sodium Salt of tma–Au(I) Complex. All of characterization (Table 1) described here is based on the complex obtained by Method 1. The complete elemental analyses of C, H, S, O, Au, and Na for the sodium salt of tma–Au(I) complex show that this complex is highly pure, its composition consists of $tma^{3-}:Au(I):Na^{+}=1:1:2$ and 1.75 hydrated waters are present. For a triply charged form of thiomalate tma^{3-}, this complex is unprotonated and its formula can be written as $\{Na_2[Au(tma)]\cdot 1.75H_2O\}_n$ (formula weight: $421.5n$). The presence of 1.75 hydrated waters is also supported by TG/DTA measurement: 6.93% weight loss observed under 250 °C (calcd 7.48%), and further supported by a very strong, broad IR absorption band at ca. 3450 cm^{-1} observed in solid FT-IR spectra.

For the dissociating complex in aqueous solution, $\{Na_2[Au(tma)]\}_n \rightarrow 2nNa^{+}+\{[Au(tma)]^{2-}\}_n$, the observed molmass value has been cryoscopically determined to be 330 (experimental error within ±5%) using 11.46 mg of the complex dissolved in 0.397027 g water. In concentration range $C_{Na}=0.914$—182.86 $mmol\,dm^{-3}$, the $[Na^{+}]$ values measured using a Na^{+} ion selective electrode were plotted for six different points of C_{Na} to give *a straight line* with a correlation coefficient 1.00—0.996. Its slope, i.e., dissociation degree α, was determined as 0.44—0.54. Since the molar number of species present in the solution becomes $(1+2n\alpha)$, the formula mass is described as $390n=330(1+2n\alpha)$. Thus, the polymerization degree was derived as $n=3$—10 and the molecular weight as 1260—4220. The validity of this method has been confirmed for several recent measurements in the oligomeric tma–Ag(I) and tsa–Ag(I) complexes,[5,6)] as well as control experiments using standard NaCl and disodium succinate. This is

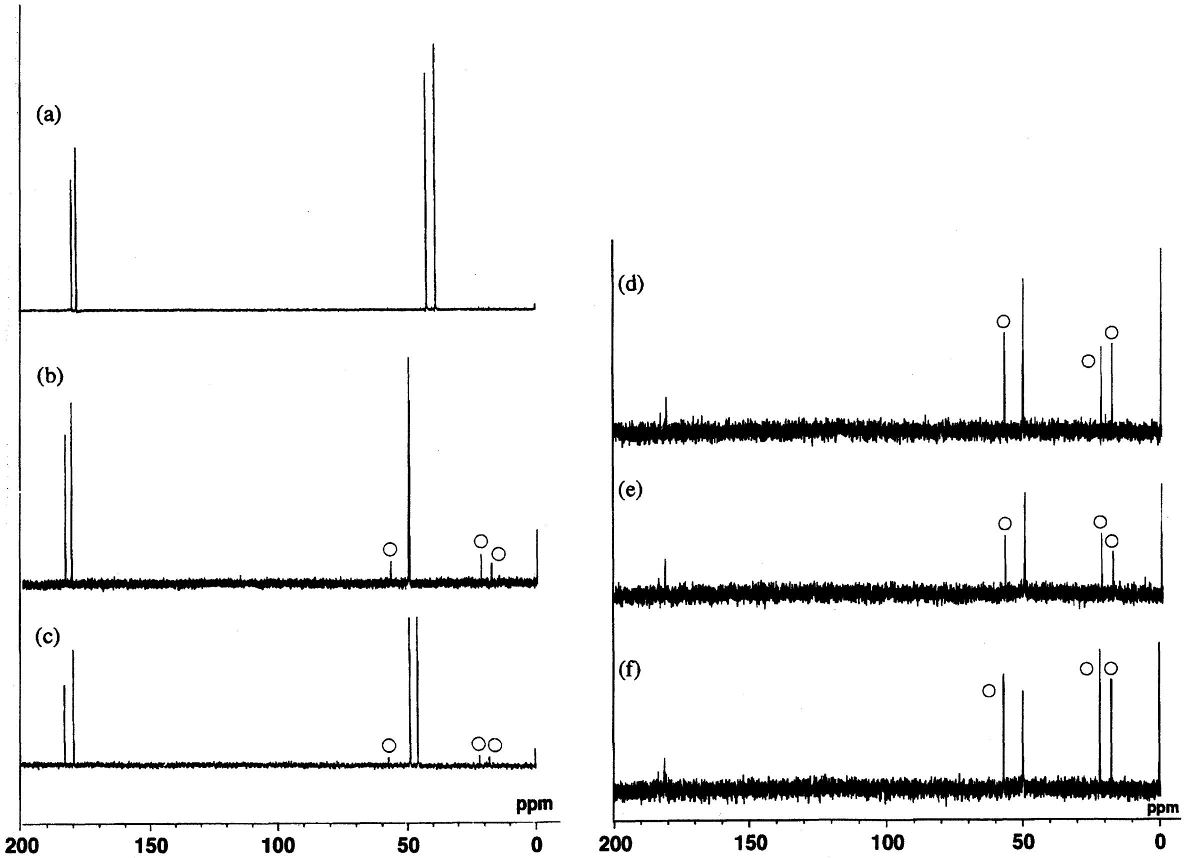

Fig. 2. ^{13}C NMR spectra measured in D_2O with reference to an internal DSS: (a) free H_3tma at room temperature, (b) the sodium salt of tma–Au(I) complex, $\{Na_2[Au(tma)]\cdot 1.75H_2O\}_n$ at room temperature, (c) the sodium salt of tma–Ag(I) complex, $\{Na[Ag(Htma)]\cdot 0.5H_2O\}_n$ at room temperature,[5)] (d) the tma–Au(I) complex at 80 °C, (e) the tma–Au(I) complex at room temperature in the presence of 0.5 $mol\,dm^{-3}$ NaCl, and (f) in the presence of 1.0 $mol\,dm^{-3}$ NaCl, where carbon signals denoted by (○) are from methylene groups of the DSS.

the case if there is no significant difference between the first and second dissociation constants of two sodium ions. On the other hand, when the first dissociation constant is much more larger than the second one and the actual dissociation can be represented as $\{Na_2[Au(tma)]\}_n \rightarrow nNa^+ + [\{Na[Au(tma)]\}^-]_n$, the molar number of species present in the solution becomes $(1+n\alpha)$ and the formula mass is rewritten as $390n=330(1+n\alpha)$. In this case if experimentally obtained $\alpha=0.44$—0.54 are used, unreasonably small values $n=1.35$—1.56 are derived.

The sodium salt of tma–Au(I) complex in aqueous solution has been considered to be a polymeric species with high molecular weight by the ultracentrifuge and Sephadex chromatography measurements.[1a,12,14] However, its polymerization degree significantly depends upon the experimental conditions. The present method based on the molmass value and the dissociation degree shows that the tma–Au(I) complex in the aqueous solution without any other electrolytes is not a polymeric species, but only an oligomeric with the polymerization degree of $n=3$—10.

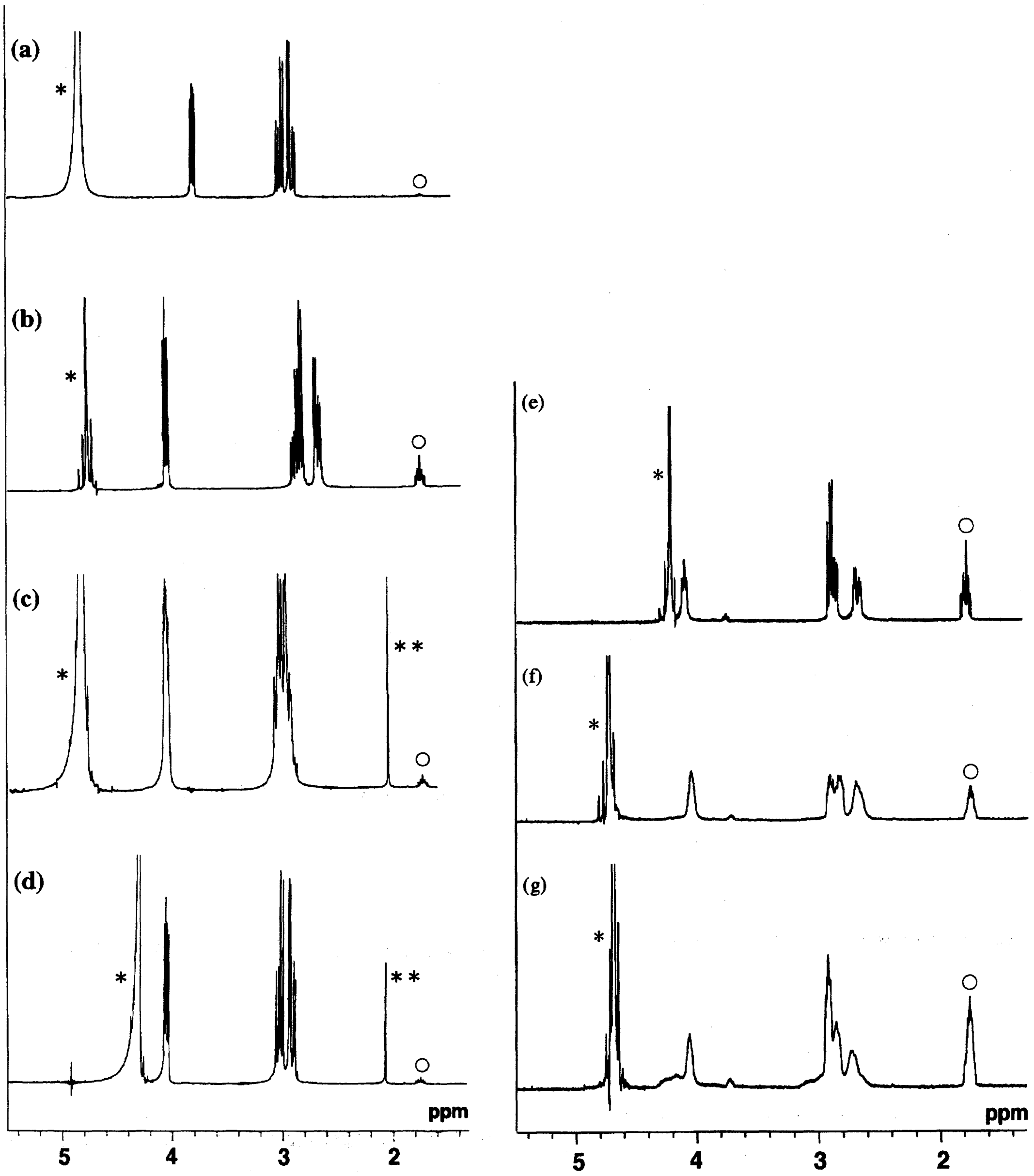

Fig. 3. ^{1}H NMR spectra measured in D_2O with reference to an internal DSS: (a) free H_3tma at room temperature, (b) the sodium salt of tma–Au(I) complex, $\{Na_2[Au(tma)]\cdot 1.75H_2O\}_n$ at room temperature, (c) the sodium salt of tma–Ag(I) complex, $\{Na[Ag(Htma)]\cdot 0.5H_2O\}_n$ at room temperature,[5] (d) the tma–Ag(I) complex at 80 °C,[5] (e) the tma–Au(I) complex at 80 °C, (f) the tma–Au(I) complex at room temperature in the presence of 0.5 mol dm^{-3} NaCl, and (g) in the presence of 1.0 mol dm^{-3} NaCl, where proton signals denoted by (*), (**), and (○) are from water, contaminated CH_3CN, and some methylene groups of the DSS, respectively.

The solid FT-IR spectrum (Fig. 1) of the tma–Au(I) complex showed (1) one strong broad band at ca. 3450 cm^{-1} due to the hydrated waters, (2) a disappearance by complex formation of S–H stretching band at ca. 2560 cm^{-1} due to the SH group in free H$_3$tma ligand, suggesting the Au–S bond formation, and (3) the shift of one very strong carbonyl stretching band at ca. 1690 cm^{-1} in the carbonyl group of the free H$_3$tma to a strong band at ca. 1590 cm^{-1}, suggesting that two carboxyl groups of the complex are not protonated, but attached to Na$^+$ ions in the solid state. As also shown in IR spectra of the analogous tma–Ag(I) and tsa–Ag(I) complexes,[5,6] these IR spectra indicate that carboxylic, hard oxygen atoms do not participate in the coordination to soft, Au(I) atoms in this oligomeric complex. The suggested geometry is compatible with the previously proposed one.[12]

When compared with the free H$_3$tma ligand, the ^{13}C NMR spectrum (Figs. 2a and 2b) of the tma–Au(I) complex measured in D$_2$O at room temperature showed (1) all of carbon resonances of coordinating tma^{3-} ligands were down-field shifted; the methylene and methyne carbon signals were remarkably shifted, (2) methylene and methyne carbon resonances appeared to be very close (at $\delta = 50.0$ and 49.7), and (3) all of tma^{3-} ligands coordinating to Au(I) ions in this

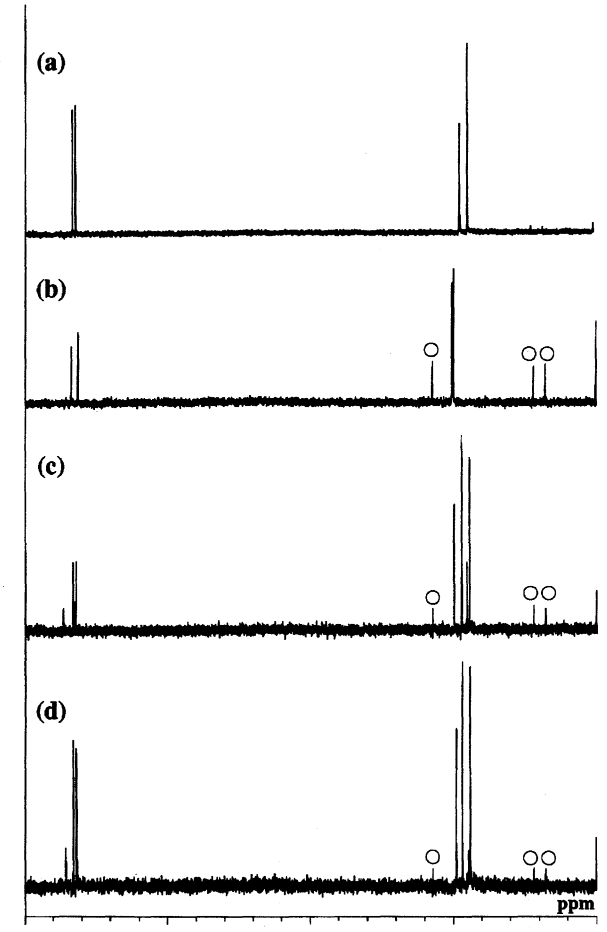

Fig. 4. ^{13}C NMR spectra of the sodium salt of tma–Au(I) complex in the presence of free tma^{3-} ligand, measured at room temperature in almost neutral pH solution with reference to an internal DSS: (a) free H$_3$tma ligand in the presence of 2 equiv of NaOH in D$_2$O solution, (b) the tma–Au(I) complex in D$_2$O, (c) the tma–Au(I) complex in the presence of 2 equiv of free tma^{3-} in D$_2$O solution and (d) in the presence of 3 equiv of free tma^{3-} (See the Experimental for the preparation of the solutions (c) and (d)). Carbon signals denoted by (O) are from some methylene groups of the DSS.

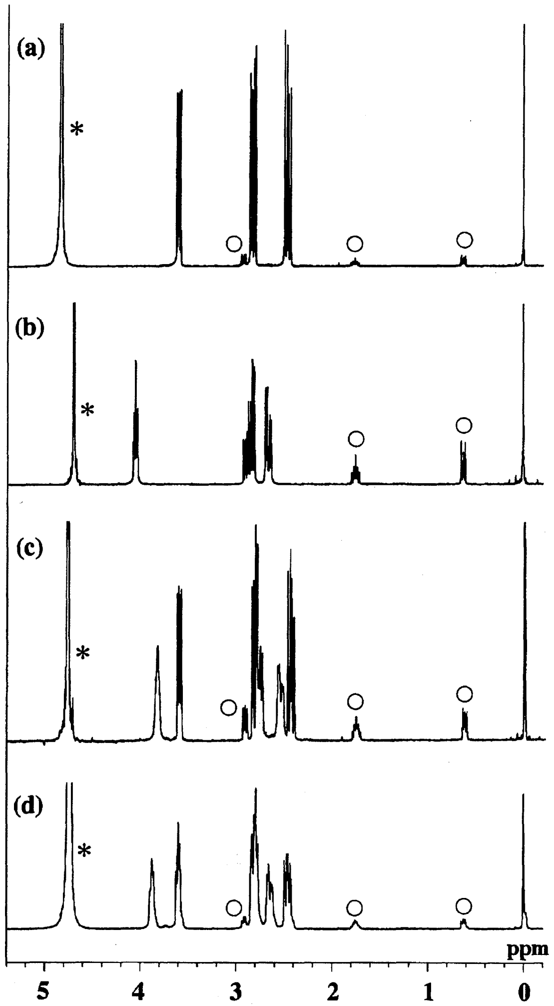

Fig. 5. ^{1}H NMR spectra of the sodium salt of tma–Au(I) complex in the presence of free tma^{3-} ligand, measured at room temperature in almost neutral pH solution with reference to an internal DSS: (a) free H$_3$tma ligand in the presence of 2 equiv of NaOH in D$_2$O solution, (b) the tma–Au(I) complex in D$_2$O, (c) the tma–Au(I) complex in the presence of 2 equiv of free tma^{3-} in D$_2$O solution and (d) in the presence of 3 equiv of free tma^{3-} (See the Experimental for the preparation of the solutions (c) and (d)). Proton signals denoted by (*) and (O) are from water and some methylene groups of the DSS, respectively.

oligomeric complex were quite equivalent. The simple four-line ^{13}C NMR spectrum in the tma–Au(I) complex indicates that carboxylic, hard oxygens of the tma ligand do not participate in coordination to soft metal ions, just as demonstrated in the tma–Ag(I) complex.[5] On the other hand, in comparison with the free H_3tma, the 400 MHz ^{1}H NMR spectrum (Figs. 3a and 3b) of the complex in D_2O at room temperature showed that methyne proton resonance was down-field shifted by about 0.3 ppm, whereas the methylene proton resonances were up-field shifted by about 0.1 ppm.

Isab and Sadler have reported that thiolate exchange reactions in aqueous solution of the disodium aurothiomalate are facile.[1a,8] Indeed, ^{1}H and ^{13}C NMR spectral changes due to the ligand-exchange reaction between tma–Au(I) complex and free tma ligand were evidently observed at room temperature in D_2O under the conditions; at pH ca. 7 aqueous solution in the presence of 2 or 3 equiv of free tma ligand for the tma–Au(I) complex, where all of chemical shifts depended upon the concentration of free tma ligand added as shown in Figs. 4 and 5. However, both in the ^{1}H and ^{13}C NMR, all of chemical shifts for the tma–Au(I) complex measured both at room temperature and at 80 °C with no addition of free tma ligand, were unchanged (Figs. 2d and 3e), suggesting that there were no further aggregation of this oligomeric complex and no ligand-dissociation from the complex in aqueous solution, and rather indicating that this ligand-exchange reaction was due to the S_N2 type mechanism.

To examine the effect of an added electrolyte on aqueous solution of the tma–Au(I) complex, the ^{1}H and ^{13}C NMR spectra of this complex were also measured at room temperature in the presence of 0.5 and 1.0 mol dm^{-3} NaCl (Figs. 2e, 2f, 3f, and 3g). In comparison with the ^{1}H NMR spectra in the absence of NaCl, all of ^{1}H signals were much more broadened in the ^{1}H NMR spectra with the higher NaCl concentrations, where the fine structures of the signals due to the coupling were not seen. In the ^{13}C NMR spectra, methylene and methyne carbon resonances appeared to be completely coalesced at 49.8 ppm, probably due to the broadening of two very close ^{13}C signals. These are attributed to the motional broadening due to the inhibited motion of the oligomeric, electrolyte-complex in the presence of higher NaCl concentrations. In these NMR measurements, we were not able to find any evidence for the further aggregation or polymerization of the oligomeric tma–Au(I) complex in aqueous solution, although an increase in intensity of the ^{13}C NMR bands due to polymeric forms on addition of NaCl has been previously reported.[1a,8]

Consequently, the present NMR measurements show that the tma–Au(I) complex itself exists in an oligomeric form both in the solid and in aqueous solution, which does not further polymerize in aqueous solution.

Comparison with Recently Obtained tma–Ag(I) Complex. Many known complexes of Ag(I) or Au(I) with thiol ligands have been reported as polymeric or oligomeric, but not monomeric.[1a,5—8,12,14] In fact, some phosphine ligands have been recently utilized in order to limit such polymerizations in the coordination chemistry of Ag(I) and Au(I).[19,20] The one exception is the monomeric 2 : 1 tsa–Au(I) complex, which has been recently isolated as colorless needle crystals of $Na_3[Au(tsa)_2]\cdot 5H_2O$.[7] In the present oligomeric, 1 : 1 tma–Au(I) complex, it has been shown that the Au(I) atom exists in the Au(I) S_2 unit with two bridged

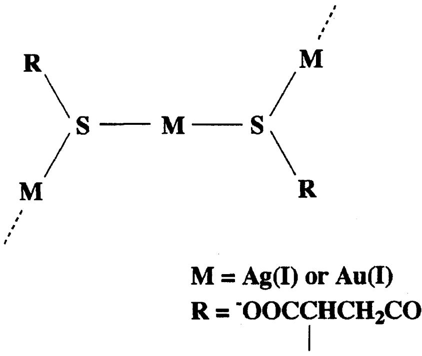

Fig. 6. Suggested structure of sodium salts of tma–metal (I) complexes.

Table 2. Comparison of the tma–Au(I) Complex with the tma–Ag(I) Complex

	tma–Ag(I) Complex	tma–Au(I) Complex
1) Formula	$\{Na[Ag(Htma)]\cdot 0.5H_2O\}_n$	$\{Na_2[Au(tma)]\cdot 1.75H_2O\}_n$
2) Polymerization degree	n=24—34	n=3—10
3) Molecular weight	6910—9790	1260—4220
4) Biological activity	Antimicrobial activity Life-prolongation effect for some cut flowers	Antiarthritic activity
5) Color/solid state	Intense yellow/powder	Pale yellow/powder
6) Decomposition temperature	180 °C	246 °C
7) Stability in solution in the light	Stable	Less stable
8) Dissolving solvent	Only water	Only water
9) A ratio of metal ion : tma	1 : 1	1 : 1
10) Coordination donor atom of tma	Sulfur (thiol)	Sulfur (thiol)
11) Geometry around metal ion	Linear $Ag(I)S_2$	Linear $Au(I)S_2$

S atoms, without coordination of carboxylic oxygens. The structure of its monomeric unit (Fig. 6) will be similar to that of the oligomeric, tma–Ag(I) complex.[5a)] Very recently, the tetrameric anion species $\{Na_3[Ag(Htma)]_4\}^-$ has been detected with negative-ion electrospray ionization (ESI) mass spectra as a stable, constituent unit derived from an aqueous solution of the $\{Na[Ag(Htma)]\cdot 0.5H_2O\}_n$.[5b)] Thus, the oligomeric Ag(I) complex can be represented as $\{Na_4[Ag(Htma)]_4\}_{n'}$ ($n'=6$—8) which results from a coupling of n' cyclic tetramers, probably through an interaction with undissociated Na^+ ions.

Some properties of the tma–Au(I) complex, in comparison with those of the recently prepared tma–Ag(I) complex,[5)] are summarized in Table 2. Both tma complexes are biologically or medicinally active and oligomeric, but not monomeric. The degrees of oligomerization are much less in the Au(I) complex than in the Ag(I) complex. The Au(I) complex in the solid state is much more stable than the Ag(I) complex, whereas the Au(I) complex in aqueous solution is more sensitive to light and undergoes degradation more than the Ag(I) complex. Both complexes cannot be isolated as crystals suitable for X-ray crystallography so that their molecular structures are not known in detail, although their coordination geometries around metal(I) ions have been considered very similar. The ^{1}H NMR spectrum of the tma–Au(I) complex measured at room temperature (Fig. 3b) was highly resolved, whereas that of the tma–Ag(I) complex at room temperature (Fig. 3c) was less. The latter spectrum became highly resolved at 80 °C (Fig. 3d), although the chemical shifts were essentially unchanged. The ^{1}H NMR spectral changes of the tma–Ag(I) complex stem from the decreased degree of oligomerization at an elevated temperature, or the enhanced molecular motion. Thus, the ^{1}H NMR spectrum of the tma–Au(I) complex reflects the fact that its degree of oligomerization is much less than that of the tma–Ag(I) complex.

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