identified (IR spectrum, melting point) as the original Co cluster catalyst. An immobile green material, which was not identified, always was present on top of the silicic acid pad.

Table I summarizes the experimental details of the catalysis experiments.

Infrared Studies of Hydroformylation Reaction Mixtures. In these experiments, the cooled and depressurized reactor was opened to a nitrogen atmosphere in the drybox, and a sample of the reaction mixture was placed in a 0.1-mm path length NaCl solution cell and sealed from the atmosphere. An IR spectrum was recorded of the $\nu(C{\equiv}O)$ region (2150–1800 cm^{-1}) with a Perkin-Elmer 180 grating infrared spectrophotometer using toluene as the reference solvent. IR spectra also were recorded for pure $PhCCo_3(CO)_9$ and $Co_2(CO)_8$. Table II summarizes these IR data.

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Registry No. **1**, 13682-03-6; **2**, 86846-41-5; **3**, 83835-42-1; **4**, 29890-31-1; **5**, 86853-39-6; **6**, 86846-42-6; **7**, 86846-43-7; **8**, 86846-44-8; **9**, 86846-45-9; **10**, 86846-46-0; $BrCCo_3(CO)_9$, 19439-14-6; p-$CH_3CH(OH)C_6H_4CCo_3(CO)_9$, 86846-47-1; ($p$-$CH_3C(O)C_6H_4C_2C_6H_4C(O)CH_3$-$p$)$Co_2(CO)_6$, 29531-36-0; ($p$-$CH_3C(O)C_6H_4C_2C_6H_5$)$Co_2(CO)_6$, 29531-35-9; $Co_2(CO)_8$, 10210-68-1; $CH_2{=}C(CH_3)C(O)Cl$, 920-46-7; $CH_2{=}C(CH_3)CO_2CH_2CH_2OH$, 868-77-9; 1-hexene, 592-41-6; 1-heptanal, 111-71-7.

Contribution from the Department of Medicinal Chemistry, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101, Department of Chemistry, Birkbeck College, London WC1E 7HX, UK, and Research Institute of Materials, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Gold-197 Mössbauer Studies of Some Gold(I) Thiolates and Their Phosphine Complexes Including Certain Antiarthritic Gold Drugs[1]

DAVID T. HILL,*† BLAINE M. SUTTON,† ANVARHUSEIN A. ISAB,*‖ TAHIR RAZI,‡ PETER J. SADLER,‡ JAN M. TROOSTER,§[2] and GIJS H. M. CALIS§

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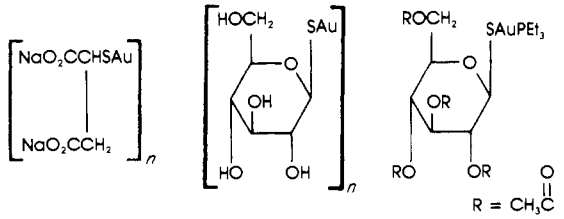
Structural information on 11 gold(I) thiolates and 12 phosphine-coordinated gold(I) thiolates has been collected by using ^{197}Au Mössbauer spectroscopy. The compounds studied include the injectable antiarthritic drugs gold sodium thiomalate (**1**), gold thioglucose (**6**), gold sodium thiosulfate (**11**), and the orally effective (phosphine)gold(I) thiolate auranofin (**15**). Isomer shifts and quadrupole coupling constants indicate that gold atoms in the 1:1 thiolates are sulfur bonded and two-coordinate. These compounds are polymeric in the solid state. This information complements previous solution studies. The Mössbauer spectra of the (phosphine)gold complexes are characteristic and consistent with a monomeric linear SAuP linkage. The spectral parameters (IS, QS) of the phosphine complexes are approximately 2 mm s^{-1} larger than those of the comparable thiolates. The structural and biological significance of these data is discussed.

Introduction

The recent discovery of the antitumor properties of *cis*-diamminedichloroplatinum(II) (*cis*-CDDP) has revived interest in the potential therapeutic applications of metals.[3] Gold compounds, however, have been used successfully, without fanfare, in the treatment of rheumatoid arthritis (RA) for over half a century.[4] Among antirheumatic drugs these chrysotherapeutic agents are unique in that they both relieve symptoms and impede the progressive course of the disease. The two compounds employed most commonly are gold sodium thiomalate (**1**) (Myochrysine) and gold thioglucose (**6**) (Solganal). These water-soluble drugs must be administered by intramuscular injection in order to be effective.



1 **6** **15**

Recently auranofin (**15**) ("Ridaura", Smith Kline & French Laboratories), a triethylphosphine-coordinated gold complex, has been found effective in treating RA when given orally and is presently undergoing extensive clinical investigation.[5] Auranofin's pharmacological[6] and pharmacokinetic[7] profile is distinctly different compared to those of **1** and **6**. Although all three compounds are gold(I) thiolates, these observed biological differences may be due to characteristic physical properties arising from the structural nature of each molecule.

The apparent ligand to gold ratio in **1** and **6** is 1, whereas the gold atom of **15** is two-coordinate as has been shown by X-ray crystallography.[8] Crystals of **1** and **6** suitable for X-ray measurements have remained elusive, so that the molecular structures of these agents are not known in detail despite their extensive clinical use. However, a number of studies (see Discussion) indicate that in solution gold sodium thiomalate (**1**) exists in aggregate form with gold atoms bridging between two sulfur atoms.[9] Similar studies of **6** have been restricted.[10]

† Smith Kline and French Laboratories.
‡ Birkbeck College.
§ University of Nijmegen.
‖ Present address: Department of Chemistry, University of Petroleum and Minerals, Dhahran, Saudi Arabia.

(1) Presented in part at the 179th National Meeting of the American Chemical Society, Houston, TX, March 24, 1980; see Abstracts, MEDI 16.
(2) Deceased Feb 4, 1981.
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^{197}Au Mössbauer spectroscopy has been found useful for characterizing and providing structural information of gold complexes in the solid state. Taken together, the isomer shift (IS) and quadrupole splitting (QS) provide information concerning the type of gold ligand.[11] Viegers,[12] following earlier studies,[13,14] has shown that there is a linear relationship between QS and IS for monovalent gold compounds which differs significantly from that of trivalent gold. Further, the rare three- and four-coordinate gold(I) complexes may be distinguished from the more common two-coordinate gold complexes of the same valence state.[15] Thus, for gold complexes, ^{197}Au Mössbauer spectroscopy is a useful method for determining oxidation state, type of ligand, and degree of coordination. Additional structural information may be derived from Mössbauer data by comparison with data from similar types of compounds whose structures are known, e.g., by X-ray crystallography.

Previous applications of this technique to measurements of gold(I) thiolates have been limited. Reported here are ^{197}Au Mössbauer data for the antiarthritic drugs **1** and **6** and several related gold(I) thiolates. These data are compared with those of their counterpart phosphine-coordinated complexes including auranofin (**15**). In addition, the ^{197}Au Mössbauer parameters of another gold antiarthritic drug $Na_3[Au(S_2O_3)_2]$ (**11**, Sanochrysine) reported previously[14] have been remeasured. These studies constitute an application of the use of ^{197}Au Mössbauer spectroscopy to acquire comparative data about gold compounds that have similar apparent molecular structures but exhibit dissimilar physical and biological properties. This information may lead to a better understanding of the bioinorganic chemistry of these compounds.

Experimental Section

Materials. Gold sodium thiomalate monohydrate (**1**) was obtained from Aldrich Chemical Co., and the dihydrate glycerate (**2**) was supplied by May and Baker (Dagenham) Ltd. Gold thioglucose (**6**) was purchased from Sigma Chemical Co., and gold thioglucose monohydrate (**7**) was obtained from Schering Corp. Gold sodium thiosulfate (**11**, Sanochrysine) was purchased from the Life Sciences Group, ICN Pharmaceuticals, Inc. Sodium tetrachloroaurate dihydrate was brought from Alfa Division of Ventron, Inc. Compounds **8**,[16] **13**,[17] **14**,[18] **15**,[19] **16**[19], **20**,[17] and **21**[20] were prepared as described in the literature, as were chloro(triethylphosphine)gold[19] and chloro(triphenylphosphine)gold[21] used as starting materials.

Gold Sodium Thiomalate–Sodium Chloride (3). Compound **2** (0.1135 g, 0.25 mmol) was dissolved in water (1 mL), and a solution of sodium chloride (0.0585 g, 1 mmol) in water was added. A light yellow product was obtained after lyophilization.

Gold Sodium Thiomalate–Thiomalic Acid (4). Compound **2** (0.1135 g, 0.25 mmol) was dissolved in water (1 mL), and thiomalic acid (0.0188 g, 0.125 mmol) was added. Sodium hydroxide solution (10 M) was added until pH 7 and the solution lyophilized to give a colorless solid.

Gold Sodium Thiomalate–Dithiomalic Acid (5). Compound **2** (0.1135 g, 0.25 mmol) was dissolved in water (1 mL), and thiomalic acid (0.0755 g, 0.5 mmol) was added. Sodium hydroxide solution (10 M) was added until pH 7 and the solution lyophilized to give a colorless solid.

Gold Sodium *N*-Acetylcysteine Dihydrate (9). A solution of 2,2′-thiobis[ethanol] (0.976 g, 8 mmol) in water (20 mL) was added dropwise to a constantly stirred solution of sodium tetrachloroaurate dihydrate (1.6 g, 4 mmol) in water (40 mL) maintained at 0 °C. After the mixture became colorless (indicating complete reduction of Au(III) to Au(I)), a solution of *N*-acetylcysteine (0.652 g, 4 mmol) in water (15 mL) was added. A colorless gelatinous precipitate was formed, which was removed by filtration, washed with water, and dried in vacuo.

The material was redissolved in water (10 mL) containing sodium hydroxide (0.16 g, 4 mmol) to give a yellow solution. Ethanol was added to the solution and the resulting pale yellow precipitate collected, washed with aqueous ethanol (1:3), and dried in vacuo.

Anal. Calcd for $C_5H_7AuNNaO_3S\cdot H_2O$: C, 14.40; H, 2.66; N, 3.36; S, 7.69. Found: C, 14.79; H, 2.27; N, 3.45; S, 7.18.

Gold Penicillamine Hydrobromide (10). The preparation of **10** is similar to that of **9**. However, the initial precipitate was obtained as the hydrochloride salt only after addition of acetone. The pale yellow solid was used without reprecipitation.

Anal. Calcd for $C_5H_{11}AuClNO_2S$: C, 14.87; H, 2.48; N, 3.47; S, 7.53. Found: C, 14.68; H, 2.24; N, 3.08; S, 7.16.

(2-Thiopseudoureato)(triethylphosphine)gold Hydrochloride (12). A mixture of chloro(triethylphosphine)gold (4.0 g, 11.4 mmol) and thiourea (0.86 g, 11.4 mmol) in acetone (80 mL) was stirred 18 h at 25 °C. The precipitate that formed was removed by filtration, washed with acetone, and dried to give 4.2 g (99%) of a white solid, mp 140–143 °C.

Anal. Calcd for $C_7H_{19}AuClN_2PS$: C, 19.70; H, 4.49; N, 6.56. Found: C, 20.37; H, 4.40; N, 6.77.

(2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*)(triphenylphosphine)gold (17). Chloro(triphenylphosphine)gold (2.0 g, 4 mmol) in ethanol (150 mL)/methylene chloride (100 mL) was added dropwise to a solution of potassium carbonate (0.57 g, 4 mmol) and β-D-thioglucose tetraacetate (1.46 g, 4 mmol) (Aldrich Chemical Co.) in 60% ethanol (65 mL) maintained at −5 °C. After standing 18 h, the reaction mixture was concentrated under reduced pressure and the residue taken up in chloroform. The chloroform solution was extracted with water, dried ($MgSO_4$), and filtered, and the chloroform was removed under vacuum. Dry-column chromatography (ether/silica gel) gave 2.33 g (70%) of a white solid: mp 78–82 °C; $[\alpha]^{25}_D$ = −70.6° (1.0% in CH_3OH).

Anal. Calcd for $C_{32}H_{34}AuO_9PS$: C, 46.72; H, 4.17; P, 3.77. Found: C, 46.76; H, 4.14; P, 3.83.

[Mercaptobutanedioato(1−)-*S*](triethylphosphine)gold (18). Chloro(triethylphosphine)gold (3.5 g, 10 mmol) in ethanol (30 mL) was added to a solution of sodium hydroxide (1.2 g, 30 mmol) and thiomalic acid (1.5 g, 10 mmol) in water (30 mL) at 0 °C. After the mixture warmed to room temperature, the solvent was removed under vacuum and the residual wet solid was dissolved in water (10 mL). Adjustment of pH to 3.5 resulted in the separation of an oil, which was removed by ethyl acetate extraction (6 × 50 mL). The extracts were dried ($MgSO_4$) and filtered, and the solvent was removed at reduced pressure to give 2.0 g of a white solid. Recrystallization (acetonitrile) gave 1.3 g (28%), mp 136–138 °C.

Anal. Calcd for $C_{10}H_{20}AuO_4PS$: C, 25.87, H, 4.34. Found: C, 26.36; H, 4.16.

(2-Acetamido-3-mercaptopropanoato-*S*)(triethylphosphine)gold (19). Chloro(triethylphosphine)gold (3.5 g, 10 mmol) in ethanol (18 mL)/methylene chloride (2 mL) was added to a mixture of *N*-acetylcysteine (1.36 g, 10 mmol) and sodium hydroxide (0.8 g, 20 mmol) in 70% ethanol (35 mL) at −5 °C. After 30 min the solvent was removed under reduced pressure; the residue was dissolved in water (20 mL) and neutralized with dilute hydrochloric acid. The product was extracted with ethyl acetate, the organic phase dried ($MgSO_4$) and filtered, and the solvent removed under pressure to give 4.1 g of crude material (colorless oil). Treatment of this oil with acetone gave 0.9 g (19%) of crystalline **19**, mp 130–131.5 °C.

Anal. Calcd for $C_{11}H_{33}AuNO_3PS$: C, 27.68; H, 4.86; N, 2.93; P, 6.49. Found: C, 27.62; H, 4.93; N, 2.92; P, 6.76.

[9*H*-Imidazo[4,5-*d*]pyrimidine-6-thionato-*S*](triethylphosphine)gold (22). Chloro(triethylphosphine)gold (4.7 g, 13.4 mmol) in ethanol (22 mL)/methylene chloride (3 mL) was added to a solution of 6-mercaptopurine (2.0 g, 13.1 mmol) (Aldrich Chemical Co.) and potassium hydroxide (0.73 g, 13.1 mmol) in ethanol (30 mL) at −5 °C. After 30 min the reaction mixture was concentrated under reduced pressure and the residue dissolved in acetone. The precipitate that

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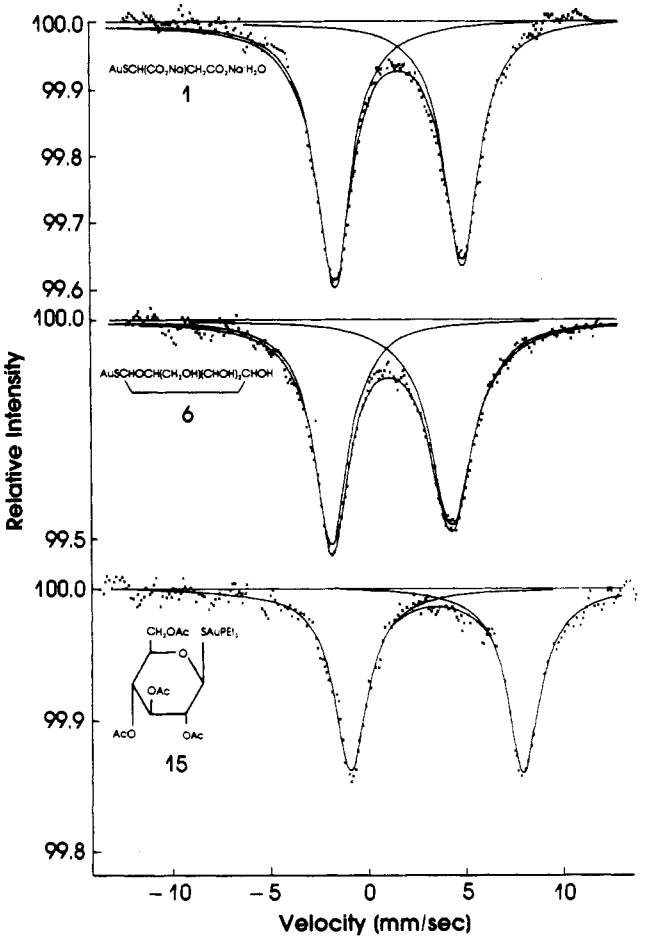

Figure 1. Mössbauer spectra of **1**, **6**, and **15**, recorded with respect to ^{197}Pt at 4.2 K. The solid lines represent the Lorentzian lines, and the total spectrum was calculated with the parameters given in Table I.

formed was removed by filtration, and the filtrate was concentrated under reduced pressure. The residual oil was subjected to chromatography (silica gel/acetone). An acetone-soluble oil was obtained that crystallized out of the solvent after several days to give, as the hemihydrate, 2.0 g (32%) of **22**, mp 100–102 °C.

Anal. Calcd for $C_{11}H_{18}AuN_4PS\cdot0.5H_2O$: C, 27.80; H, 4.03; N, 11.79; P, 6.52. Found: C, 27.72; H, 4.16; N, 11.62; P, 6.21.

[2(3*H*)-Benzoxazolethionato-*S*](triethylphosphine)gold (23). Chloro(triethylphosphine)gold (5.25 g, 15 mmol) in 1:1 chloroform/ethanol (40 mL) was added to a solution of sodium hydroxide (0.6 g, 15 mmol) and 2-mercaptobenzoxazole (2.28 g, 15 mmol) in 50% ethanol (40 mL) at 25 °C. After 1 h the reaction mixture was filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was dissolved in methanol, treated with activated charcoal, and cooled to give 4.9 g (70%) of **23** as white crystals, mp 100–102 °C.

Anal. Calcd for $C_{13}H_{19}AuNOPS$: C, 33.65; H, 4.12; N, 3.01. Found: C, 33.65; H, 4.14; N, 2.91.

^{197}Au Mössbauer Measurements. All measurements were taken directly on carefully ground powdered crystals at liquid-helium temperature (4.2 K). The compounds were pressed in lucite containers with an inner diameter of 12 mm and a thickness up to 5 mm, depending on the amount of material available (0.3–0.5 g) and the density.

The instrumentation employed has been described elsewhere.[12,22] The integrating counting technique was used,[23] allowing an average measuring time of 15 min for each sample. The recorded spectra have been folded and subsequently fitted to a set of Lorentzian lines, without

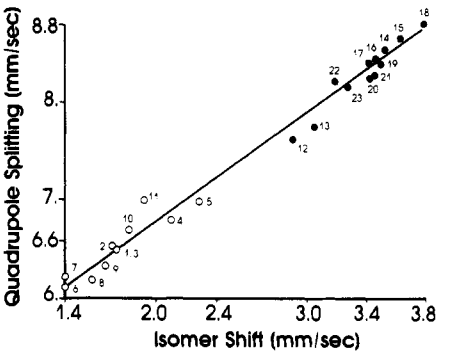

Figure 2. Mössbauer data plot for gold(I) thiolates (○) and phosphine-coordinated gold(I) thiolates (●). The numbering corresponds to Table I. The least-squares line: QS = (1.11 ± 0.03)IS + (4.55 ± 0.09); r^2 = 0.984.

further constraints. The intensity and the line width of each peak of a quadrupole doublet agree within the 5% except where noted. However, the areas of the Lorentzian lines are equal within 2%. In the fitting procedure for compounds **1** and **6**, we assumed identical line widths for both lines.

Results

The compounds used in this study (see Table I) were obtained from commerical sources or prepared according to standard procedures (see Experimental Section). Compounds **1** and **2** are the same chemically as are **6** and **7**, the latter in each case being the actual therapeutic formulation. These were obtained for comparison and for discussion will be referred to as **1** and **6**, respectively. In a number of compounds, the gold ligands such as cysteine (**8**) were of biological significance. Compounds **12**, **13**, and **21** were examined for comparison.

The Mössbauer fitting parameters are presented in Table I. All of the spectra are quadrupole doublets of varying symmetry. The spectra of the chrysotherapeutic agents **1**, **6**, and **15** are illustrated in Figure 1. A plot of the QS vs. IS for compounds **1–23** is shown in Figure 2. A computer-generated least-squares line has been fitted to the plot in Figure 2. The resulting linear relationship between QS and IS is given in eq 1. This relationship is similar to that found by Viegers[24]

$$QS = 1.11IS + 4.55 \text{ mm/s} \quad (1)$$

$$QS(Au^{+}) = 1.06IS + 5.05 \text{ mm/s} \quad (2)$$

$$QS(Au^{3+}) = 1.79IS - 0.22 \text{ mm/s} \quad (3)$$

for aurous compounds (eq 2) and differs from his expression for auric complexes (eq 3). The slope of the line in Figure 2 (1.11) matches the slope (1.06) determined for known two-coordinate gold(I) complexes. Thus, the +1 oxidation state assigned to these compounds on a chemical basis is supported by Mössbauer spectroscopy. The plot in Figure 2 is especially noteworthy with regard to the thiolates **1–10** that fall in the lower region. Their close fit to the two-coordinate line indicates that in the solid state the gold atom is bound by two ligands and is not monocoordinate as expected on the basis of stoichiometry. Since the ^{197}Au Mössbauer parameters (see Discussion) are similar to those of a number of complexes where the gold is known from crystal structure determinations to be coordinated by two sulfur ligands, the 1:1 gold(I) thiolates must be oligomeric with the gold atoms bridged by sulfur atoms. Therefore, the injectable gold drugs **1** and **6** are polymeric in the solid form.

The spectra of **1** and **6** (Figure 1), typical of the gold(I) thiolates **1–9**, are asymmetric, with the high-velocity line being broader and being of reduced intensity relative to the low-

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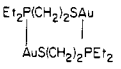
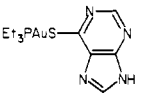
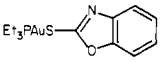
Table I.[a] Gold-197 Mössbauer Data

no.	complex	IS[b]	QS	Γ_1	Γ_2
1[c]	$AuSCH(CO_2^-Na^+)CH_2CO_2^-Na^+\cdot H_2O$	1.74 (2)	6.5 (1)	2.2 (1)	2.2 (1)
2[d]	$AuSCH(CO_2^-Na^+)CH_2CO_2^-Na^+\cdot 2H_2O\cdot 0.3C_3H_8O_3$	1.72 (1)	6.50 (2)	2.0 (1)	2.4 (1)
3[i]	$AuSCH(CO_2^-Na^+)CH_2CO_2^-Na^+\cdot NaCl$	1.74 (2)	6.48 (3)	2.3 (1)	2.5 (1)
4[i]	$AuSCH(CO_2^-Na^+)CH_2CO_2^-Na^+\cdot 0.5C_4H_6O_4S$	2.10 (2)	6.78 (3)	2.3 (1)	2.8 (1)
5[i]	$AuSCH(CO_2^-Na^+)CH_2CO_2^-Na^+\cdot 2C_4H_6O_4S$	2.23 (1)	7.03 (2)	1.90 (5)	2.78 (6)
6[e]	$AuSCHOCH(CH_2OH)(CHOH)_2CHOH$	1.4 (1)	6.1 (1)	2.4 (1)	2.4 (1)
7[f]	$AuSCHOCH(CH_2OH(CHOH)_2CHOH\cdot H_2O$	1.40 (1)	6.20 (2)	2.0 (1)	2.4 (1)
8	$AuSCH_2CH(NH_2)CO_2H$	1.58 (1)	6.18 (2)	1.9 (1)	2.3 (1)
9	$AuSCH_2CH(NHAc)CO_2Na$	1.67 (1)	6.33 (2)	2.1 (1)	2.4 (1)
10	$AuSC(CH_3)_2CH(NH_2)CO_2H\cdot HCl$	1.82 (1)	6.68 (2)	1.9 (1)	2.1 (1)
11[g]	$[Au(S_2O_3)_2]Na_3$	1.92 (1)	6.98 (1)	1.96 (2)	1.97 (2)
12	$Et_3PAuSCH(NH_2)_2^+Cl^-$	2.9 (1)	7.6 (1)	2.2 (1)	2.2 (1)
13	$Et_3PAuSCN$	3.04 (1)	7.73 (1)	1.96 (2)	1.98 (2)
14	$Et_3PAuSCOC_6H_5$	3.51 (1)	8.53 (1)	1.87 (2)	1.96 (3)
15[h]	$Et_3PAuSCHOCH(CH_2OAc)(CHOAc)_2CHOAc$	3.55 (2)	8.64 (3)	1.9 (1)	2.2 (1)
16	$Et_3PAuSCHOCH(CH_2OH)(CHOH)_2CHOH$	3.44 (2)	8.43 (5)	1.93 (5)	2.37 (5)
17	$(C_6H_5)_3PAuSCHOCH(CH_2OAc)(CHOAc)_2CHOAc$	3.4 (1)	8.4 (1)	2.0 (1)	2.2 (1)
18	$Et_3PAuSCH(CO_2H)CH_2CO_2H$	3.76 (2)	8.79 (2)	1.96 (5)	2.00 (5)
19	$Et_3PAuSCH_2CH(NHAc)CO_2H$	3.48 (2)	8.39 (2)	1.88 (5)	2.02 (5)
20	$Et_3PAuSCH_3$	3.41 (2)	8.23 (2)	2.10 (5)	2.06 (5)
21		3.42 (2)	8.25 (2)	2.08 (5)	2.07 (5)
22		3.18 (2)	8.2 (1)	2.0 (1)	2.2 (1)
23		3.26 (2)	8.15 (2)	2.10 (5)	1.97 (5)

[a] All data are in mm s^{-1}. [b] Relative to ^{197}Pt source at 4.2 K. [c] Aldrich Chemical Co. [d] May and Baker ("Myocrisin"). [e] Sigma Chemical Co. [f] Schering ("Solganol"). [g] ICN Pharmaceuticals Inc. (Sanochrysine). [h] "Ridaura" (Smith Kline & French Laboratories, auranofin). [i] 3, 4, and 5 are powders obtained by lyophilizing a solution containing two reagents in various ratios.

Table II. Matched-Pair Mössbauer Parameter Differences (mm s^{-1})

	ΔIS	ΔQS
17-1	2.02	2.29
15-5	2.04	2.23
18-7	1.81	2.06

velocity line although the peaks are approximately of equal area. This phenomenon is attributed to small variations in the environment surrounding the gold atom such as bond lengths or bond angles. Because of the linear relationship between QS and IS, the high-velocity line is expected to be broader under these circumstances. The spectrum of auranofin (**15**) (Figure 1) is typical of the phosphine-coordinated gold(I) thiolates **12–23**. As a group, the spectra are more symmetrical than those of the simple thiolates. However, their IS and QS values are considerably larger, and consequently, they fall into the upper region of the plot in Figure 1. Where possible, the comparison of the (phosphine)gold(I) thiolates with their monocoordinate thiolate counterparts (Table II) indicates an increase in both IS and QS of about 2 mm s^{-1}. The magnitude of this increase is greater than expected on the basis of an average-environment rule, i.e. by averaging data from $(R'S)_2Au^-$ and $(R_3P)_2Au^+$.[11] Nevertheless, their relative position with respect to the spectrochemical series remains intact. Despite the variety of substituents on sulfur, the range of IS and QS parameters for compounds **12–23** is relatively narrow. Notable are **12** and **13**, which have electronegative groups attached to sulfur and consequently have smaller Mössbauer parameters.

No significant differences were observed between **15** and the $(C_6H_5)_3P$ analogue **17**. The spectrum of the large-ring digold compound **21** is identical with the corresponding monogold compound **20** so that Au–Au interactions are unlikely, contrary to the expectations based on its mass spectrum[20] and X-ray crystal structure determination.[25]

Discussion

Gold(I) Thiolates. Gold is unique in that it is the only metal that does not react directly with sulfur. Nevertheless gold–sulfur compounds and particularly the 1:1 gold(I) thiolates (AuSR) represent an interesting and important class of gold compounds with diverse practical uses. The most important of these applications is in the treatment of disease. Both gold sodium thiomalate (**1**) and gold thioglucose (**6**) are used in treating bronchial asthma,[26] pemphigus,[27] and, most importantly, rheumatoid arthritis.[4] Gold(I) thiolates are potential metabolites of gold drugs.[16] Certain sulfhydryl derivatives such as 2,3-dimercaptopropanol (BAL),[28] 2,3-dimercaptosuccinic acid, and penicillamine[29] have been recommended for use as gold-detoxifying agents. Despite their biological importance, little is known of the structures of these thiolates nor gold(I) thiolates in general. This is due in large part to their poor crystallinity and solubility, which hinder X-ray and solution measurements. The chrysotherapeutic agents **1** and **6**, however, are water soluble, and a number of solution studies have been carried out on gold sodium thiomalate (**1**).

Conductivity and cryoscopic measurements indicate gold thiomalic acid, and by implication its sodium salt **1**, to be an aggregate of at least 8 formula units.[30] Electronic and circular

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dichroism spectra of solutions of **1** were interpreted as being consistent with polymer formation.[31] In an ^1H and ^{13}C NMR study Isab and Sadler concluded that **1** exists as a low molecular weight polymer with only sulfur coordination at gold. The degree of polymerization was dependent on ionic strength and pH.[32] Shaw has reported that **1** elutes from Sephadex G-100 as though it is a polymeric species.[16] In a sodium phosphate buffer at pH 7.3, ultracentrifuge sedimentation molecular weight measurements determined **1** to be an oligomer of 6 formula units.[32] Osmometry in water indicated **1** to be at least dimeric.[33] Thus, data from a variety of physical methods lead to the conclusion that in solution **1** exists in aggregate form. At the time the studies described here were initiated, information concerning the structures of **1** and **6** in the solid state was not available.

Since ^{197}Au Mössbauer spectroscopic measurements are carried out at 4.2 K usually on finely ground powders, this technique is ideal for studying gold(I) thiolates. Previously, the only gold–sulfur compounds to be examined by this method were certain gold complexes of BAL,[34] penicillamine,[35] and gold sodium thiosulfate (**11**), Sanochrysine).[14] These measurements established the gold oxidation state but did not generate general structural information. Structural information may be deduced from the study of a series of compounds by comparing the data with that from compounds of a similar type of known structure.

As indicated in Figure 2, the ^{197}Au Mössbauer data (Table I) for the 1:1 gold(I) thiolates **1–9** fall very close to the two-coordinate line. This close fit is consistent with two-coordinate gold with both ligands being sulfur. Comparison (below) with ^{197}Au Mössbauer data obtained from gold–sulfur compounds of known structure provides additional support for these conclusions.

The X-ray structure of bis(ethylenethiouronium)gold(I) chloride monohydrate (**24**) reveals the gold atom bound by two sulfur ligands although with considerable deviation from linearity (SAuS = 167°) due possibly to the water of hydration.[36] The IS and QS values of **24** (1.52 and 7.22 mm s^{-1}) however fall within the range observed for the 1:1 gold(I) thiolates, e.g., **1** (Table I). It should be noted that the gold atom of **24** is part of a cationic complex.

In contrast, the gold portion of **11** is anionic. X-ray crystallography shows the gold atom of **11** bound to two sulfur atoms in a nearly linear array (SAuS = 176.5°).[37] The ^{197}Au Mössbauer parameters of **11** had earlier been reported by Faltens and Shirley.[14] However, the value they list for the IS (7.22 mm s^{-1}) is quite large and differs from the value obtained directly from their published spectrum (1.92 mm s^{-1} with respect to ^{197}Pt). Subsequently, we remeasured the ^{197}Au Mössbauer parameters of this material and found the IS and QS (1.92 and 6.98 mm s^{-1}) to be in closer agreement with those derived from their spectrum. The magnitudes of these parameters also lie within the range observed for the thiolates **1–11**. It is noteworthy that the IS and QS of **11** and **24** are similar despite the charge differences on the gold residues.

An example of a neutral complex is provided by the dimer of gold(I) dipropyldithiocarbamate: $[Pr_2NCS_2Au]_2$ (**25**). Again, the X-ray crystal structure of **25** shows two linear SAuS linkages (178°),[38] and the reported IS and QS (1.80 and 6.39 mm s^{-1})[39] are also similar to those observed in compounds **1–11**. Two additional examples reported by Viegers are a tetrathiotungstate $[(C_6H_5)_4P]_2[Au_2(WS_4)_2]$ (**26**) and a diisopropyl dithiophosphate $[(i\text{-}PrO)_2PS_2Au]_2$ (**27**). In both **26** and **27**,[41] linear SAuS arrays have been determined by X-ray crystallography. The ^{197}Au Mössbauer data (IS and QS for **26**[40] 0.86 and 5.58 mm s^{-1} and for **27** 0.96 and 6.09 mm s^{-1} [42]) for these compounds were interpreted as being consistent with a linear two-coordinate sulfur–gold–sulfur linkage. Comparison of these ^{197}Au Mössbauer fitting parameters with those from the 1:1 thiolates is consistent with gold being coordinated by two sulfur atoms in compounds **1–11**.

Confirmation of these findings by an alternate spectroscopic technique is reported in a recently described EXAFS study of **1** and **6** in comparison with **11**.[43] Analysis of the extended X-ray absorption fine structure of the L_{III} absorption edge of Au showed the environment of the Au(I) atom to be similar in all three compounds. Since gold in **11** is known to be bound by two sulfur atoms, then **1** and **6** must also be structurally similar. Interpretation of the EXAFS data gave AuS bond distances of 237 pm in **1** and **6**, slightly longer than in **11** (AuS = 228 pm). The degree of polymerization of various gold(I) thiolates is not known, but most likely these materials exist as chains of varying length with considerable folding and possibly ring formation. Consequently, all the gold coordination geometries may not be identical. This is consistent with the interpretation of the asymmetric doublets observed in the Mössbauer spectra. The degree of aggregation of **1** in solution seems to vary with solution conditions and method of molecular weight determination as noted earlier. Using ^1H and ^{13}C NMR and electronic absorption spectroscopy, Isab and Sadler have shown that the aqueous solution structure of **1** is highly dependent on ionic strength.[32] For example, a ^{13}C NMR spectrum of a 0.8 M solution of **1** in the presence of 1 M NaCl shows six carboxyl resonances, suggesting three types of coordinate thiomalate. To determine if similar behavior occurs in the solid state, a lyophilized sample **3** was prepared from the above solution and its ^{197}Au Mössbauer spectrum obtained. The IS and QS values of **3** (Table I) are virtually identical with those of **1** and **2**, indicating no change in gold coordination upon sodium chloride addition although there is a slight increase in line widths. Thus, the ^{13}C NMR and ^{197}Au Mössbauer data, taken together, are consistent with the presence of oligomeric or polymeric species derived from **1** with up to three different environments for thiomalate. In solution at pH 7 the gold atom of **1** has the capacity to bind added thiols and form species of the type $Au(SR)_n$ where n is betwen 1 and 2. Since the nature of these species in the solid state is unknown, two additional complexes derived from **1**, i.e. **4** and **5**, were prepared, both of which had ligand to gold ratios greater than 1. Samples **4** and **5** were made by addition of the appropriate quantity of thiomalic acid to a solution of **1** adjusted to pH 7 followed by lyophilization. The resulting products were examined by ^{197}Au Mössbauer spectroscopy.

The spectra of **4** and **5** show a marked increase, in each case, in both IS and QS (Table I) compared to that of **1**. The magnitude of these increases is directly proportional to the number of thiomalate ligands; i.e., the IS and QS of **5** with

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a stoichiometric Au:thiomalate ratio of 1:3 is greater than those of **4** with half as much thiomalate present. These higher values are due to increased electron donation by the thiomalate ligands into both the 6s and 6p orbitals of gold(I). Although the data for **4** and **5** suggest that changes have occurred in the environment surrounding the gold atom, they lie close to the line in the QS–IS plot (Figure 2) and it is most likely that they contain two-coordinate gold. Although structural details remain speculative, the increases in IS and QS indicate that the nature of the sulfur to gold bond in **4** and **5** has changed toward something more reminiscent of that found in aurate complexes of the type $(RS)_2Au^-$. The Au–S bond lengths of complexes of this type, e.g. **11** (Au–S = 228 pm),[14] are shorter compared to those of the gold monothiolates **1** and **6** (237 pm).[43] This decrease in bond length would result in increased electron donation and also account for the increase in IS and QS values. Although speculative, **4** and **5** could be mixtures, of varying proportions, comprised of the bis(thiomalato)aurate(I) complex above plus 1:1 polymer or smaller oligomers. Support for this is seen in the asymmetry of the quadrupole doublets with the high-velocity line considerably broader than the low-velocity line (Table I). This apparent asymmetry indicates that the environment surrounding the gold atom is not uniform.

Cysteine, a sulfhydryl-containing amino acid, is a constituent of a number of proteins and is known to bind metals. Albumin's cysteine residue has been implicated in gold transport,[44] and a bis(cysteinato)aurate(I) complex has been found in the kidney cytosol of rats dosed with **1**.[16] The CD spectrum of a (cysteine)gold(I) complex suggested polymer formation in solution.[35] Subsequently, the gold(I)–cysteinato complex **8** was prepared and its ^{197}Au Mössbauer parameters measured. Both the IS and QS values (1.67 and 6.33 mm s^{-1}) are typical of gold(I) thiolates (Table I), indicating that this potential gold-drug metabolite also exists in a polymeric form.

Penicillamine, besides its suggested utility as a gold-detoxifying agent, is also used in the treatment of rheumatoid arthritis and Wilson's disease.[45] Two penicillamine–gold complexes have been reported previously, together with their UV–visible and CD spectra.[35] One, a yellow compound, was stable only under a nitrogen atmosphere. The other was an orange solid containing gold, which ^{197}Au Mössbauer spectroscopy showed to be in the +3 oxidation state (IS and QS = 3.01 and 3.74 mm s^{-1}). The electronic spectrum of the orange solid was also consistent with the presence of Au(III) as was the spectrum of the unstable material. However, the latter was prepared originally as a sodium salt, which may have contributed to its instability, preventing Mössbauer measurements. Therefore **9**, a pale yellow gold-penicillamine complex was prepared, under acid conditions, and its ^{197}Au Mössbauer spectrum measured. The IS and QS (1.82 and 6.68 mm s^{-1}) show clearly that the gold valence state is +1. This appears to be the first example of a gold(I)–penicillamine complex.

(Phosphine)gold(I) Thiolates. Previous ^{197}Au Mössbauer studies of phosphine-coordinated gold(I) thiolates have been limited mainly to measurements of a few (triphenylphosphine)gold(I) dithiocarbamates and several related compounds.[11,12] Among the latter is a triphenylphosphine complex of gold 1,8-dithionaphthalene (**28**). The IS and QS for **28** (3.74 and 8.42 mm s^{-1}) are well within the range observed by us for compounds of a similar type, i.e., **14–23** (Table I). As expected, coordination of a 1:1 gold(I) thiolate by an additional phosphine ligand increases substantially the magnitude of both the isomer shift and quadrupole splitting. This is seen directly in three specific examples where the gold(I) thiolate, in each case, has been complexed with Et_3P (Table II). Comparison of the IS and QS for each pair shows an increase of approximately 2 mm s^{-1} on complexation with the phosphine.

These increases are due to the strong σ-donor–π-acceptor properties of phosphorus, which lead to higher 6s-electron density at the gold nucleus relative to sulfur.[11] However, the values observed are somewhat higher than might be expected on the basis of an average-environment rule, particularly for auranofin. The IS and QS values of auranofin (**15**) (3.55 and 8.64 mm s^{-1}) are closer to the values observed for chlorobis(triethylphosphine)gold (**29**) (3.06 and 8.93 mm s^{-1})[46] than those observed for the polymeric gold(I) thiomalate (**1**). Again this can be explained partly by the fact that the gold–sulfur bond distances in the polymeric gold(I) thiomalates are probably longer than those in the monomeric gold–sulfur species, resulting in the loss of σ-donor capacity of the sulfur ligand and a corresponding reduction in the Mössbauer parameters. The increasing IS and QS values of those compounds with a thiomalate to gold ratio higher than 1 (**4** and **5**) are further evidence for this effect. In some cases, the solid state bis(phosphine)gold complexes are three-coordinate, but the hyperfine parameters of these compounds clearly lie above the line for linear gold(I) compounds in the QS–IS plot.[46] On the basis of the plot in Figure 2, the complexes **12–23** appear to have linear SAuP coordination. This is confirmed in **15** by X-ray crystallographic studies that show the gold atom to have a marked preferential orientation toward the pyranose-ring oxygen, suggesting a possible influence of the thioglucose ligand. However, the SAuP bond angle (176°) and the AuO distance (341 pm) both indicate that any gold–oxygen interaction must be negligible.

Compound **17** possesses the triphenylphosphine ligand, which, because of its larger size, would reduce or preclude Au–O interaction. However, the Mössbauer parameters of **17** do not differ significantly from those of **15**. This is consistent with the published observation that Ph_3P and Et_3P appear to be similar ligands so far as gold is concerned.[46] Further, comparison with **20**, which has no oxygen atoms, again indicates little difference. Thus, the magnitude of the Mössbauer parameters in compounds **14–23** must be intrinsic to the SAuP linkage.

The decrease in the Mössbauer parameters of the thiouronium salt **12** and the thiocyanate **13** relative to the other two-coordinate (phosphine)gold(I) thiolates is noteworthy. In both compounds the sulfur atom is bound directly to an electronegative group that withdraws electrons from sulfur, reducing its donor capability. Consequently, the density of 6s electrons at the gold nucleus is diminished, resulting in smaller IS and QS values (Table I). In **14**, the *S*-benzoyl compound, the electronegative effect of the carbonyl is compensated by the phenyl, which, by virtue of its π system, apparently donates electrons to the carbonyl preferential to sulfur. Aromatic groups tend to be slightly electronegative, and this is seen in the Mössbauer measurements of **22** and **23**, where the magnitudes of the IS and QS are reduced compared to those of **15–21**. The effect of various substituents on the ^{197}Au Mössbauer parameters in this class of compounds deserves further investigation.

The large-ring digold compound **21** was of special interest to us because it contains two SAuP linkages and its x-ray structure has been reported.[25] The SAuP bonds are slightly bent (173.5°), and the gold atoms are directed in toward each other. The Au–Au distance of 310 pm is considered within the range for Au–Au bonds but is somewhat weak at the distance cited. Because of the increased electronic charge perpendicular to the coordination axis arising from a Au–Au

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bond, the magnitude of the QS should be reduced compared to that of other compounds in its class.[47] However, both the IS and QS of **21** are typical for phosphine-coordinated gold(I) thiolates and differ little from those of **20**. Therefore, within the sensitivity of the Mössbauer experiment no evidence for Au–Au bonding is observed.

Summary and Conclusion

The ^{197}Au Mössbauer fitting parameters derived from the spectra of the PAuS compounds (**12–23**) are unique to this type and are not explained totally by an average-environment rule although their magnitude appears to be influenced by contiguous electron-withdrawing groups. The values for IS and QS for the simple gold(I) thiolates, besides being of lower magnitude compared to those of their phosphine-coordinated counterparts, appear to be affected by the ratio of sulfur ligand to gold; that is, as the ratio of ligand to gold increases, so also do the values of IS and QS, reflecting increased electron density around the gold nucleus.

The ^{197}Au Mössbauer data obtained from the injectable gold drugs **1** and **6** are compatible with a two-coordinate, nearly linear SAuS linkage. Therefore, these gold drugs (**1** and **6**), as well as other 1:1 gold(I) thiol derivatives, must, in the solid phase, be polymeric, i.e., $[-(R)S-Au(R)S-Au-]_n$. This conclusion, based on the ^{197}Au Mössbauer data, is supported by recent EXAFS measurements[43] and is consistent with what is known about the stoichiometry, coordination number, and stereochemistry of gold(I) complexes. Further, studies using a variety of physical methods have invariably determined that **1** behaves as an oligomer in solution. Thus, the overwhelming body of evidence indicates that gold sodium thiomalate (**1**) and therefore **6** and other 1:1 gold(I) thiolates are polymers. The degree of polymerization has not been determined, but most likely, on the basis of solution measurements of **1**, it is low. **1** and **6**, which are polymeric, contrast with auranofin (**15**), which ^{197}Au Mössbauer suggests and X-ray crystallography confirms is monomeric. Though speculative, these differences, polymer vs. monomer, may be invoked to explain, at least in part, the cited biological variances (see Introduction).

For example, it is reasonable to suppose that large molecules, even though water soluble, would be less likely to penetrate membranes and be absorbed compared to smaller lipophilic molecules. This might account partly for the oral absorption of **15** vs. the nonabsorption of **1** and **6**. Walz et al., in a pharmacokinetic study of **1** vs. **15**, observed that **15** associates readily with the cellular elements of the blood whereas **1** is found mainly in the serum.[48] Similar findings were reported by Herrlinger, who noted that 40% of the gold in blood from **15** was localized within the erythrocytes compared to none for **1**.[49] These observations are compatible with the notion that large molecular species are less likely to penetrate membranes than smaller molecules although **1** may have a higher protein-binding affinity than **15**.

Conversely, high molecular weight metal species are more likely to be engulfed by macrophages and therefore effect lysosomal enzyme activity, as seen with **1**.[6] It is also reasonable to suppose that thiol-exchange reactions, which may play a key role in the biology of gold, would be affected differently by a polymeric gold thiolate than by a monomeric species and would explain the differences in pharmacokinetics between **1** and **15**. Additionally, a comparison of blood gold levels revealed that gold from **15** was approximately 4 times more effective in stimulating cell-mediated immunity than was gold from **1**,[50] again suggesting that the physical form in which gold is presented to a biological system has a major effect on that system's response. These points deserve further attention and should be the subject of future investigations.

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Registry No. **1**, 12244-57-4; **6**, 74610-70-1; **8**, 65286-35-3; **9**, 86421-40-1; **10**, 86421-41-2; **11**, 10233-88-2; **12**, 52621-55-3; **13**, 14243-46-0; **14**, 54720-68-2; **15**, 34031-32-8; **16**, 34031-29-3; **17**, 85528-72-9; **18**, 41581-85-5; **19**, 86421-42-3; **20**, 15685-02-6; **21**, 51365-22-1; **22**, 86421-43-4; **23**, 55927-98-5; 2,2′-thiobis(ethanol), 111-48-8; *N*-acetylcysteine, 616-91-1; sodium tetrachloroaurate, 15189-51-2; chloro(triethylphosphine)gold, 15529-90-5; thiourea, 62-56-6; chloro(triphenylphosphine)gold, 14243-64-2; β-D-thioglucose, 19879-84-6; thiomalic acid, 70-49-5; 6-mercaptopurine, 50-44-2; 2-mercaptobenzoxazole, 2382-96-9.

(47) Reference 12, p 82.

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Contribution from the Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Acid Hydrolysis of the (μ-Oxo)bis(pentaaquochromium(III)) Ion

RANDY F. JOHNSTON and ROBERT A. HOLWERDA*

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In acid solution, the (μ-oxo)bis(pentaaquochromium(III)) ion decays to give $Cr(H_2O)_6^{3+}$ as the sole product: $(H_2O)_5CrOCr(H_2O)_5^{4+} + 2H^+ + H_2O \rightarrow 2Cr(H_2O)_6^{3+}$. The rate law for this reaction in a $HClO_4/LiClO_4$ medium, I = 1.0 M, is $-d[((H_2O)_5Cr)_2O^{4+}]/dt = (k_0 + k_1[H^+])[((H_2O)_5Cr)_2O^{4+}]$ where k_0(25 °C) = 5×10^{-5} s^{-1} ($\Delta H^* = 22$ kcal/mol, $\Delta S^* = -5$ eu) and k_1(25 °C) = 1.61×10^{-3} M^{-1} s^{-1} ($\Delta H^* = 12.9$ kcal/mol, $\Delta S^* = -28$ eu). The k_0 pathway corresponds to rate-limiting cleavage of a Cr–bridging oxygen bond, with probable associative assistance from the incoming H_2O ligand. Rapid preequilibrium protonation of the weakly basic bridging oxygen atom, followed by a rate-determining structural change, is proposed to account for the predominant k_1 hydrolysis pathway.

Introduction

The rhodo and erythro oxo- and hydroxo-bridged series of amminechromium(III) ions were reported in 1882.[1] In contrast, the (μ-oxo)bis(pentaaquochromium(III)) ion, prepared through the oxidation of chromous ion by 1,4-benzoquinone, was reported only recently.[2] The "basic rhodo"

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