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Linkage isomerism of (diamine)platinum(II) complexes of sulfur-containing ylidenemalonate ligands

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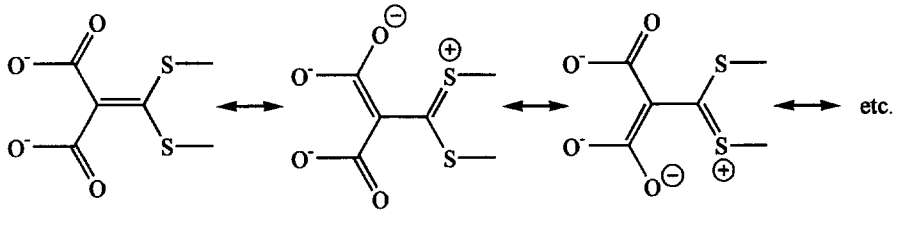
Abstract—A ^{1}H NMR study has been carried out on (diamine)platinum(II) complexes of 1,3-dithian-2-ylidenemalonate (DTAYM) and 1,3-dithiepane-2-ylidenemalonate (DTEYM) ligands as anionic leaving group in aqueous solution. Only the O,S-chelated isomer was observed in solution for all the DTAYM complexes regardless of the kind of carrier ligand amine as was in the solid state. However, both O,S- and S,S′-chelated isomers were observed in solution for DTEYM complexes, which show linkage isomerism from the O,S-chelate to the thermodynamically more stable S,S′-chelate. The rate of linkage isomerism of the DTEYM complexes was found to be dependent on their amine co-ligands. Molecular dynamics of the DTAYM complexes was also discussed based on their temperature-dependent NMR spectra. The crystal structure of the S,S′-isomer of $(NH_3)_2Pt(DTEYM)\cdot H_2O$ was determined whereas that of the O,S-isomer could not be obtained due to its poor crystallinity. © 1997 Elsevier Science Ltd

Keywords: (diamine)platinum(II); 1,3-dithian-2-ylidenemalonate; 1,3-dithiepane-2-ylidenemalonate; O,S-chelate; S,S′-chelate; linkage isomerism.

Coordination chemistry of platinum complexes involving sulfur-containing multidentate ligands [1–10] is currently becoming more important to understanding the biotransformation of cisplatin in human body, since the S,N-chelate of $[Pt(methionine)]^{2+}$ has been found as a metabolite in the urine of patients treated with cisplatin [11,12]. In our previous reports [13–15], all the possible bonding modes of O,O′-, O,S-, or S,S′-chelation were isolated and characterised in the solid state for the (diamine)platinum(II) complexes of ylidenemalonate ligands involving dithioether rings. We have shown that such chelation modes are dependent on the sulfur-containing ring size, which affects the basicity of sulfur atoms due to the different degrees of contribution of the following resonance structures depending on the ring size:



In order to understand further the coordination behavior of such platinum complexes in solution, we have carried out an ^{1}H NMR study on their linkage

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isomerism in aqueous solution and here are reported the results.

EXPERIMENTAL

Materials and instrumentation

Reagent grade potassium tetrachloroplatinate(II) (Kojima), aqueous ammonia (Kanto), *trans*(±)-1,2-diaminocyclohexane(dach)(Aldrich), ethylenediamine(en) (Aldrich) and cyclopropylamine(cpa) (Aldrich) were used as received. Diethylesters of 1,3-dithian-2-ylidenemalonate (DTAYM) and 1,3-dithi epane-2-ylidenemalonate (DTEYM) prepared by the literature method [16–18] were subjected to hydrolysis using equivalent potassium hydroxide in ethanol at boiling temperature. The resultant dipotassium salts of DTAYM and DTEYM ligands were converted to barium salts by treatment with barium chloride. Diaminediiodoplatinum(II) prepared by the literature method [19] were also converted to water soluble (diamine)platinum(II) sulfate [20].

Elemental analysis was performed by the Advanced Analysis Center at KIST. IR spectra in the 4000–400 cm^{-1} region were measured as KBr pellets on a MIDAC model 101025 FT-IR spectrophotometer. ^1H NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer relative to $SiMe_4$ as an external standard.

*Synthesis of $A_2Pt(DTAYM)$(A_2 = $2NH_3$(**1**), 2*cpa*(**2**), *en*(**3**), *dach*(**4**))*

Compounds **1** and **4** were prepared by our previous method [15]. Compounds **2** and **3** were prepared by reacting the corresponding (diamine)platinum(II) sulfate with Ba[DTAYM] in aqueous solution, also following the same procedure as described in our previous method, but after the by-product barium sulfate was filtered off, the filtrate was evaporated to dryness, and then the resultant solid product was recrystallized in a solvent pair of water and acetone (1 : 1). Compound **2** was obtained in 59.1% yield. Calcd for $C_{13}H_{20}N_2O_4S_2Pt \cdot 3H_2O$: C,26.8; H,4.50; N,4.81. Found: C, 26.1; H, 4.51; N, 4.61. IR(KBr, cm^{-1}): 3416(m), 3212(m), 2919(w), 1584(s), 1418(w), 1346(s), 1096(m), 822(w), 741(m). **3** was obtained in 72.8% yield. Calcd for $C_9H_{14}N_2O_4S_2Pt \cdot 3H_2O$: C,20.5; H, 3.82; N, 5.31. Found: C, 20.5; H, 3.76; N, 5.68. IR (KBr, cm^{-1}): 3405(m), 3099(m), 1586(s), 1378(s), 1342(s), 1182(m), 1090(m), 1052(m), 888(m), 822(m), 748(m), 586(m).

*Synthesis of $A_2Pt(DTEYM)$ (A_2 = $2NH_3$(**5**), 2*cpa*(**6**), *en*(**7**), *dach*(**8**))*

Compounds **5** and **8** were prepared by our previous method [15]. Compounds **6** and **7** were prepared in the same way as aforementioned. **6** was obtained in 83.4%. Calcd for $C_{14}H_{22}N_2O_4S_2Pt \cdot 3H_2O$: C, 28.2; H, 4.74; N, 4.70. Found: C, 28.2; H, 4.90; N, 4.74. IR (KBr, cm^{-1}): 3405(s), 1618(s), 1366(s), 1156(m), 873(m), 796(m), 723(m). **7** was obtained in 88.5% yield. Calcd for $C_{10}H_{16}N_2O_4S_2Pt \cdot 2H_2O$: C, 22.9, H, 3.85, N, 5.35. Found: C, 23.1; H, 3.67; N, 5.27. IR (KBr, cm^{-1}): 3380(s), 1614(s), 1370(s), 1322(s), 1056(m), 880(m), 728(m), 582(w).

X-ray structure determination for **1**

All the X-ray data were collected on an Enraf–Nonius CAD4 automated diffractometer equipped with a Mo X-ray tube and a graphite crystal monochromator. Details of crystal and intensity data are given in Table 1. The orientation matrix and unit cell dimensions were determined from 25 machine centered reflections. Intensities of three check reflections monitored every 1 h during the data collection period indicated no decay. A direct method (SHELXS-86) [21] was employed to locate platinum atom and subsequent cycle of Fourier map and least square refinements located other atoms (SHELXS-93) [22]. All the non-hydrogen atoms except disordered ones [C(6), C(7)] were refined anisotropically. Hydrogen atoms were included in the structure factor calculation using a riding model.

RESULTS AND DISCUSSION

The crystal structures of **4** and **8** were determined in our previous work [15], which revealed that the six-membered DTAYM ligand chelates to the platinum(II) atom by O,S-bonding mode whereas the seven-membered DTEYM ligand by S,S′-bonding mode. The ^1H NMR spectra of **1**, **2** and **3** exhibit a similar pattern of 1,3-dithian ring proton resonances to that of **4** and also those of **6** and **7** show a similar pattern of 1,3-dithiepane ring proton resonances to that of **8**, as are seen in the Table 2 and Table 3, respectively, and as such is presumed that **1**, **2** and **3** are O,S-chelated products while **6** and **7** are S,S-chelates, which will be discussed later in detail.

Complexes **1**–**4** show temperature-dependent ^1H NMR spectra, reflecting molecular dynamics. Variable temperature ^1H NMR spectra of **1** are displayed in Fig. 1. The spectrum recorded at 10°C shows the 1,3-dithian ring proton resonances at 3.75(1H), 3.37(1H), 3.25(1H), 3.05(1H), and 2.40(2H) ppm. The peaks at 3.25 and 3.05 ppm are due to the protons on the carbon next to the uncoordinated sulfur. Considering the Karplus equation, the upfield peak is assigned to the equatorial proton because it shows narrower band shape than the downfield one which is assigned to, accordingly the axial proton. Two peaks at 3.75 and 3.37 ppm are due the protons on the carbon next to the Pt-coordinated sulfur. The peak at 3.75 ppm may be assigned to the axial proton res-

Table 1. Crystallographic data for **1**

Formula	$C_8H_{14}N_2O_4Pt\,S_2 \cdot H_2O$
F.w.	479.44
Space group	C2/c (No.15)
a (Å)	22.527(4)
b (Å)	12.035(2)
c (Å)	12.136(3)
β (°)	121.33(2)
V (Å^3)	2810.5(10)
Z	8
D_{calc} (gmc^{-3})	2.266
Abs. coef. (mm^{-1})	10.295
Crystal size (mm)	0.05 × 0.25 × 0.35
Scan range (θ, deg)	2.00–24.96
Reflections collected	2237
Independent reflections ($I > 2\sigma(I)$)	2181 [R(int) = 0.0162]
No. of parameters	176
GOF	1.017
final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0525^a$, $wR_2 = 0.1528^b$
largest diff. (eÅ^{-3})	2.438 and −3.196

[a] $R_1 = \Sigma\|F_o\| - |F_c\|/\Sigma|F_o|$

[b] $wR_2 = \{\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4\}^{1/2}$, where $w = 1/\{\sigma^2 F_o^2 + (0.1344P)^2 + 34.64P\}$, where $P = \{\text{Max}(F_o^2, 0) + 2F_c^2\}/3$

Table 2. 1,3-Dithian ring proton resonances (δ)[a] for Pt(DTAYM) complexes[b]

Compound	Ha	Hb	Hc	Hd	He,f
1	3.75	3.42	3.21	3.12	2.40
2	3.85–3.55		3.18		2.40
3	3.75	3.35	3.22	3.12	2.43
4	3.74	3.34	3.28	3.15	2.40
Ba[DTAYM]	3.00(t)	—	—	—	2.15(q)

[a] H NMR data were recorded in D_2O at 20°C.

[b] Proton labelling scheme is shown in Fig. 2. All the peaks are broad.

Table 3. 1,3-Dithiepane ring proton resonances (δ)[a] for Pt(DTEYM) complexes[b]

	S,S isomer		O,S isomer			
Compound	Ha	Hb,c	Hd	He	Hf	Hg
5	3.32(t)	2.93(m),2.31(m)	3.54(t)	3.23(t)	2.17(t)	2.10(t)
6	3.31(t)	2.92(m),2.33(m)	—			
7	3.34(t)	2.85(m),2.30(m)	—			
8	3.32(t)	2.85(m),2.26(m)	—			
Ba[DTEYM]	3.12(br)	2.08(br)				

[a] ^{1}H-NMR data were recorded in D_2O at 20°C.

[b] The proton labelling scheme is given in Scheme 1.

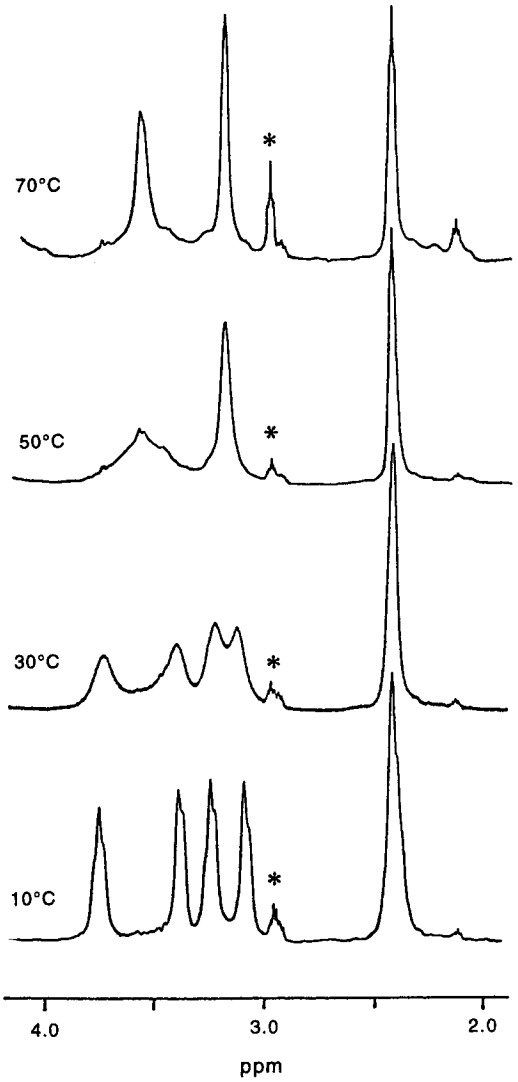


Fig. 1. Temperature dependent ^{1}H NMR spectra of **1**. Growing peaks (*) are possibly due to O,O-coordinated species. Chemical shifts were referenced to TSPSA (sodium 3-trimethylsilylpropane sulfonate; $\delta = 0.015$ ppm)

onance and the peak at 3.37 ppm to the equatorial proton for the same reason. The 1,3-dithian ring shows a pseudo-boat conformation having Pt atom in its equatorial position in the crystal structure of **4** as shown in our previous work [15]. We assume this conformation to be retained also in solution. Higher temperature ^{1}H NMR spectra in the figure indicate molecular dynamics of sulfur-inversion (S.I) and ring reversal (R.R.) [23,24] as shown in Fig. 2. The protons exchange their magnetic environments as the temperature is raised. The rapid exchange of their magnetic environments gives rise to an average peak of A and B and another of C and D. Coalescent temperatures of the Pt(DTAYM) complexes (approximately 50°C for **1**, 20°C for **2**, 50°C for **3** and over 70°C for **4**) are remarkably different depending on their amine ligands.

Time dependent ^{1}H NMR spectra of **5** are displayed in Fig. 3, and the chemical shifts of its fresh solution are listed along with those of other DTEYM complexes in Table 3. Their peak assignments were made according to the following labeling Scheme 1.

The ^{1}H NMR spectrum of **5** in fresh aqueous solution clearly indicates the presence of two different species. The peaks at 3.32, 2.29 and 2.31 ppm are certainly assignable to the 1,3-dithiepane ring proton resonances of the S,S-chelated complexes because they exhibit the same pattern as those of fully characterized S,S-chelated DTEYM complexes whereas the peaks at 3.54, 3.23, 2.17 and 2.10 ppm are due to the proton resonances of the O,S-chelated 1,3-dithiepane ring. It can be seen in the figure, that the peaks assigned to the O,S-chelated complexes disappear after 1 day, which indicates linkage isomerism from O,S-chelate to S,S′-chelate. Other DTEYM complexes **6**, **7** and **8** also show minor peaks corresponding to the O,S-isomers in fresh aqueous solution, which, however, disappear in less than a few hours. The different stability of the O,S-isomers of the DTEYM complexes seems to be ascribed to the different electronic effects of the different carrier amine groups. When we attempted to grow single crystals from the aqueous solution of **5**, we could isolate two different forms of crystals, that is, one needle shape and another parallelepiped shape. The crystals of needle shape are presumed to be the O,S-coordinated isomer, but their crystal structure could not be determined because of its poor crystallinity. Only the crystal structure of the latter shape could be obtained, and its ORTEP drawing and selected bond lengths and angles are shown in Fig. 4 and Table 4, respectively. The anionic DTEYM ligand is coordinated to the platinum atom through two sulfur atoms with two uncoordinated carboxylate groups. Two ammines occupy *cis* position in a regular square plane with the N1–Pt–N2 angle of 89.5(4) while the two sulfur donor atoms deviate from the regular positions with the S1–Pt–S2 angle of 76.82(10). The two counterpart angles of **8** previously published [15] are 81.8(4) and 76.6(1), respectively. The smaller N1–Pt–N2 angle of **8** is probably due to the bite angle of the DACH ligand. The distances Pt–N(1) [2.063(10)], Pt–N(2) [2.064(10)], Pt–S(1) [2.265(3)] and Pt-S(2) [2.268(3)] are in the range observed for other similar compounds [1,2,25]. Three bond angles around S(1) are 100.9(6) [C(1)–S(1)–C(5)], 88.6(4) [C(1)–S(1)–C(5)] and 105.8(5) [C(5)–S(1)–Pt]. Thus the pyramidal geometry around the sulfur atom is largely distorted due to the ring strain. The distortion of DTEYM ligand in the S,S-coordinated Pt complexes may make their synthesis more difficult kinetically even though they are more stable thermodynamically than the O,S-coordinated isomers.

In conclusion, the ^{1}H NMR studies of the (diamine)platinum(II) complexes of the DTAYM and DTEYM ligands show that not only different bonding modes of O,S- or S,S-chelation could be obtained in

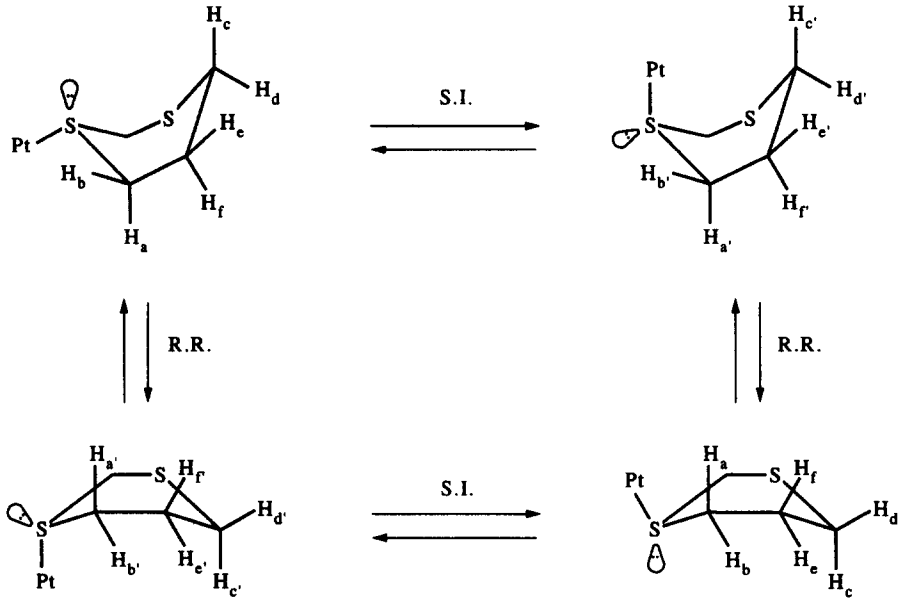
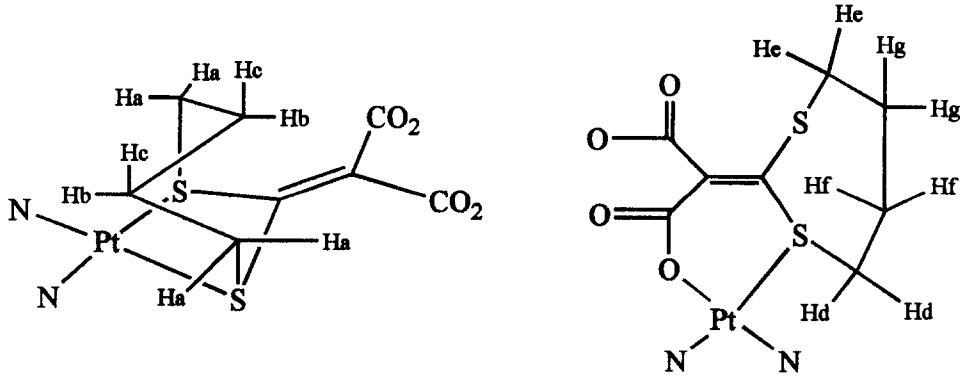


Fig. 2. Molecular dynamics of Pt(DTAYM) complexes including S-inversion and ring reversal.

Table 4. Selected bond length (Å) and Angles (°) for **1**

Pt—S(1)	2.265(3)	Pt—S(2)	2.268(3)
Pt—N(1)	2.063(10)	Pt—N(2)	2.064(10)
S(1)—C(1)	1.797(11)	S(1)—C(5)	1.84(2)
S(2)—C(1)	1.779(11)	S(2)—C(8)	1.824(13)
C(1)—C(2)	1.33(2)		
S(1)—Pt—S(2)	76.82(10)	N(1)—Pt—N(2)	89.5(4)
N(2)—Pt—S(1)	97.2(3)	N(1)—Pt—S(1)	172.8(3)
N(1)—Pt—S(2)	96.3(3)	S(2)—C(1)—S(1)	103.9(6)
C(1)—S(1)—Pt	88.6(4)	C(1)—S(1)—C(5)	100.9(6)
C(5)—S(1)—Pt	105.8(5)	C(8)—S(2)—Pt	106.5(4)
C(1)—S(2)—C(8)	100.2(6)	C(1)—S(2)—Pt	89.0(4)



Scheme 1

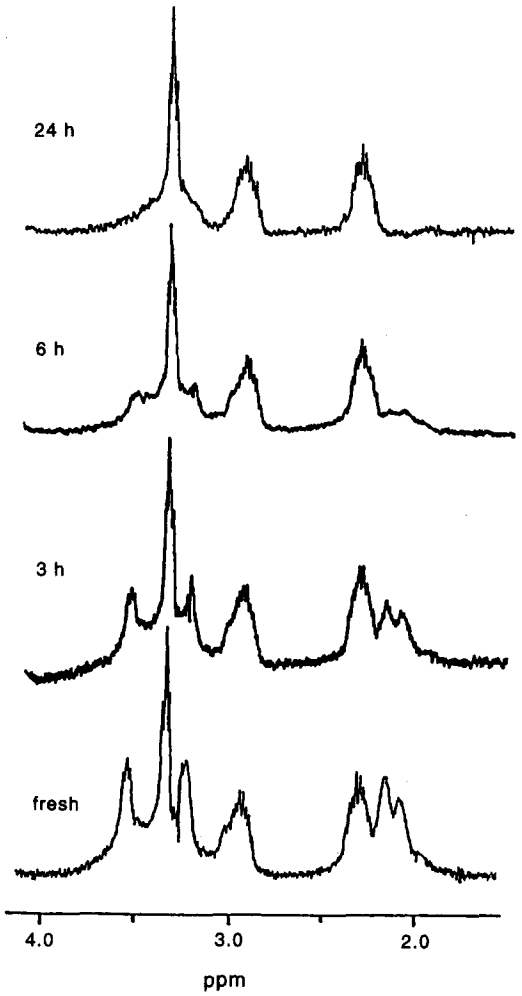


Fig. 3. Time dependent ^{1}H NMR spectra for **5**.

solution depending on the ring size of the anionic leaving groups, but also different rates of linkage isomerism were observed for the same leaving group depending on their carrier amine ligands.

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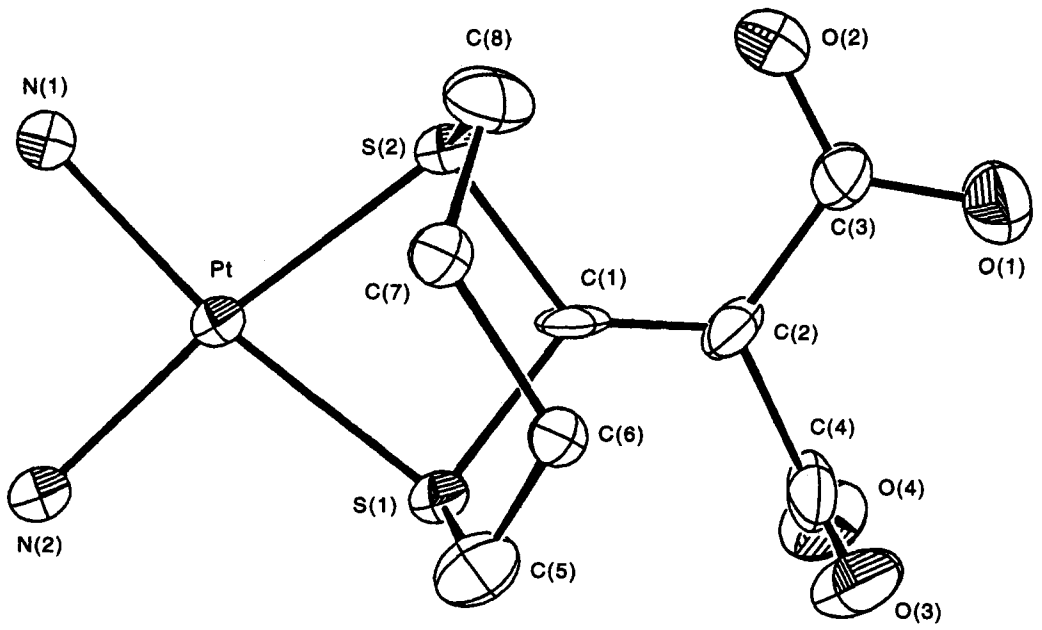

Fig. 4. ORTEP drawing of S,S-coordinated complex of **5** with labelling scheme.

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